

EXTENDED REPORT

Autoimmune thyroiditis and anti-thyroid antibodies in primary Sjögren's syndrome: a case-control study

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Objective: To determine the frequency of antithyroid antibodies and the presence of autoimmune thyroiditis among patients with primary Sjögren's syndrome.**Design:** A case-control study.**Methods:** 53 consecutive patients with primary Sjögren's syndrome, 30 with rheumatoid arthritis, 12 with secondary Sjögren's syndrome associated with rheumatoid arthritis, 17 with autoimmune thyroiditis, and 53 apparently healthy controls were studied for anti-TG and anti-TPO antibodies as well as serum thyroid hormones and TSH levels.**Results:** The overall frequencies of thyroid antibodies were 6/53 (11%) in primary Sjögren's syndrome, 2/30 (7%) in rheumatoid arthritis, 2/12 (17%) in secondary Sjögren's syndrome, 4/53 (8%) in healthy controls, and 16/17 (94%) in autoimmune thyroiditis. There was no difference in the frequency of the thyroid antibodies among the groups if patients with autoimmune thyroiditis were excluded ($p=0.415$ for anti-TPO; $p=0.275$ for anti-TG; $p=0.696$ for either anti-TG and/or anti-TPO). Only two patients with primary Sjögren's syndrome had clinical hypothyroidism associated with autoimmune thyroiditis.**Conclusions:** In this Turkish population, no association between primary Sjögren's syndrome and autoimmune thyroiditis was found.

Chronic autoimmune thyroiditis is an organ specific autoimmune disorder characterised by disturbed thyroid function and organ specific autoantibodies against thyroglobulin (anti-TG) and thyroid peroxidase (anti-TPO). Sjögren's syndrome, on the other hand, is a non-organ-specific systemic autoimmune disease with diverse clinical manifestations such as Raynaud's phenomenon, arthritis, and vasculitis.

An association between primary Sjögren's syndrome with autoimmune thyroiditis has been reported.¹⁻⁸ However, controlled studies looking at this association have been few and the results have not been uniform.⁹⁻¹⁰ We therefore addressed this issue in a case-control protocol.

METHODS

Patients

We studied 53 consecutive patients with primary Sjögren's syndrome, 30 patients with rheumatoid arthritis, and 12 patients with secondary Sjögren's syndrome associated with rheumatoid arthritis in the rheumatology outpatients clinic at the Cerrahpaşa Medical Faculty in Istanbul, Turkey.

We also recruited as positive and negative controls 17 patients with autoimmune thyroiditis currently attending the endocrinology outpatients clinic of the same institution and 53 healthy controls from among hospital staff and their relatives, age and sex matched for the patients with primary Sjögren's syndrome. None of the healthy controls had sicca symptoms or were receiving drugs that might affect thyroid function. The patients and controls were advised about the investigational nature of the study. None refused to participate.

The patients with primary Sjögren's syndrome all had definite disease according to the European criteria.¹¹ All patients had the clinical symptoms of dry eyes and mouth, a positive Schirmer's test (less than 5 mm wetting of a strip of filter paper per five minutes), and Rose Bengal staining (increased uptake of Rose Bengal dye in devitalised areas in the conjunctiva and cornea) along with the presence of at

least one of the following autoantibodies: anti-Ro, anti-La, antinuclear antibodies (ANA), rheumatoid factor (RF). All patients had clinically dry mouth, but formal salivary flow studies were not done. Their diagnoses had all been confirmed by lip biopsies showing clusters of at least 50 lymphocytes (foci). All primary Sjögren's syndrome patients reported here had at least a foci score of 1,¹² and only patients with primary Sjögren's syndrome had lip biopsies.

Eight of the 53 patients with primary Sjögren's syndrome (15%) had arthritis; among these four had a symmetrical arthritis. None, however, had erosions. The frequencies for positivity for ANA, RF, anti-Ro, and anti-La were 43/50 (86%), 33/47 (70%), 28/44 (63%), and 25/44 (57%), respectively.

The control patients with a diagnosis of rheumatoid arthritis or secondary Sjögren's syndrome were classified according to the revised criteria of the American College of Rheumatology (ACR)¹³ and the European criteria,¹¹ respectively.

Antithyroid antibodies

Anti-thyroglobulin (anti-TG) and anti-thyroid peroxidase (anti-TPO) antibodies were measured using Immulite anti-TG and TPO kits (Euro/DPC, UK). These kits use the chemiluminescent immunometric assay method with the respective normal ranges of 0 to 40 and 0 to 60 IU/ml.

Thyroid hormones and TSH

The T3 and T4 levels were measured using Ciba Corning Diagnostics Corporation kits (Madfield, Massachusetts, USA) employing a competitive immunoassay method, with normal

Abbreviations: ACR, American College of Rheumatology; ANA, antinuclear antibodies; anti-TG and anti-TPO, autoantibodies against thyroglobulin and thyroid peroxidase; RF, rheumatoid factor; TSH, thyroid stimulating hormone

ranges of 82 to 179 ng/dl and 4.5 to 12.5 mg/dl, respectively. TSH levels were also measured using a Ciba Corning kit, employing a two site chemiluminometric immunoassay method, with a normal range of 0.4 to 4.0 mIU/ml.

Statistical analysis

Age, thyroid hormones, and TSH levels among the groups were analysed by one way analysis of variance (ANOVA). Pearson's χ^2 test was used to compare the sex distribution and antithyroid antibody positivity among the groups.

RESULTS

Demographic characteristics are summarised in table 1. The patients with autoimmune thyroiditis were about a decade younger ($F = 2.412$, $p = 0.051$) than the rest of the group, while the sex distribution was similar in all groups ($p = 0.889$).

The distribution of antithyroid antibodies in all groups is also shown in table 1. The frequencies of anti-TPO and anti-TG were, as expected, significantly increased (both $p < 0.001$) among the patients with autoimmune thyroiditis, while again, as expected, all patients but one with autoimmune thyroiditis tested positive for one or other thyroid autoantibody at the time of the study ($p < 0.001$). Excluding the patients with autoimmune thyroiditis, the levels of the same antibodies were not significantly different among the remaining two groups of patients and the healthy controls ($p = 0.415$ for anti-TPO; $p = 0.275$ for anti-TG; $p = 0.696$ for either anti-TG and/or anti-TPO).

Two (4%) of the patients with primary Sjögren's syndrome were identified as having clinically definite autoimmune thyroiditis during our survey. One was being followed at the endocrinology outpatient clinic and was receiving thyroid replacement therapy. The second patient was diagnosed for the first time during this study as having autoimmune thyroiditis. She had an enlarged thyroid gland with hypothyroidism. She also had antithyroid antibodies and abnormal thyroid hormone levels. One further patient had slightly raised TSH (7.74 mIU/ml; normal = 0.4 to 4.0 mIU/ml) with no clinical hypothyroidism or antithyroid antibodies. Fine needle aspiration biopsy of the thyroid of this patient showed a mononuclear cell infiltration. She was diagnosed as having a seronegative autoimmune thyroiditis. All other patients and controls with or without thyroid antibodies had normal TSH and thyroid hormones.

The medical histories and thyroid gland examinations of other patients with thyroid antibodies but normal TSH and thyroid hormone levels were all normal or negative for thyroid disease.

Finally, if the patients with autoimmune thyroiditis were excluded there were no statistically significant differences in serum T3, T4, and TSH levels among the study groups ($F = 0.163$, $p = 0.84$ for serum T3; $F = 1.512$, $p = 0.21$ for serum T4; and $F = 0.152$, $p = 0.85$ for serum TSH) (table 2).

Table 1 Age and sex distribution and frequency of antithyroid antibodies among the groups

Group	n	F/M	Age (years)	Anti-TPO (%)	Anti-TG (%)	Both (%)	Total (%)
PSS	53	51/2	51.8 (14.8)	5 (9)	5 (9)	4 (8)	6 (11)
RA	30	28/2	51.1 (12.2)	2 (7)	0 (0)	0 (0)	2 (7)
SSS	12	12/0	57.3 (11.6)	2 (17)	1 (8)	1 (8)	2 (17)
Healthy	53	51/2	52.0 (15.4)	2 (4)	2 (4)	0 (0)	4 (8)
AIT	17	16/1	41.8 (15.8)	14 (83)	6 (35)	4 (24)	16 (94)

Values are n (%) or, for age, mean (SD).

Anti-TG, autoantibodies against thyroglobulin; anti-TPO, autoantibodies against thyroid peroxidase; AIT, autoimmune thyroiditis; F, female; M, male; PSS, primary Sjögren's syndrome; RA, rheumatoid arthritis; SSS, secondary Sjögren's syndrome.

Table 2 Mean serum T3, T4, and TSH among the groups

Groups	n	T3 (ng/ml)	T4 (mg/dl)	TSH (mIU/ml)
PSS	53	130 (24)	9.7 (2.5)	1.48 (1.14)
RA	30	130 (38)	9.8 (1.8)	1.61 (1.10)
SSS	12	136 (28)	10.1 (2.3)	1.48 (1.14)
Healthy	53	135 (22)	9.4 (1.7)	1.56 (0.68)

Values are mean (SD).

F, female; M, male; PSS, primary Sjögren's syndrome; RA, rheumatoid arthritis; SSS, secondary Sjögren's syndrome, TSH, thyroid stimulating hormone; T3, tri-iodothyronine; T4, thyroxine.

DISCUSSION

In this study, we found that the frequency of thyroid antibodies was 11% among the patients with primary Sjögren's syndrome. This was not different than that observed among our healthy controls (8%).

In a family study of primary Sjögren's syndrome, Foster *et al* reported that index cases and first degree relatives of patients with primary Sjögren's syndrome had more frequent thyroid disease ($p < 0.001$) and thyroid antibodies ($p < 0.001$ both for anti-TPO and anti-TG) when compared with historical controls.⁶ In support of this, Punzi *et al* reported an increase in the frequency of anti-TPO (17.6% *v* 9%; $p < 0.05$) and anti-TG (13.4% *v* 1%; $p < 0.001$) in 119 female patients with primary Sjögren's syndrome compared with 199 female controls.⁹ In contrast, Ramos-Casals *et al* reported 32 cases of autoimmune thyroiditis among 160 patients with primary Sjögren's syndrome (20%), a frequency not different than that observed among their controls (17%; $p = 0.628$) who were age and sex matched subjects from a primary care centre with no symptoms of Sjögren's syndrome and who had not received drugs that might have altered thyroid function.¹⁰ Finally, Petri *et al*, looking at the reverse association, reported that there was no increase in the frequency of rheumatological symptoms, including dry eyes and mouth, and systemic autoantibodies, except ANA but including anti-Ro and anti-La, in patients with autoimmune thyroiditis compared with patients with thyroid disease other than autoimmune thyroiditis.¹⁴

The cross sectional design and the fact that the patients were not stratified according to disease activity can be considered limitations of our study. In future studies the effects of the course and activity of the disease on the frequency and the titre of the antithyroid antibodies should also be explored.

Another potential drawback of our study was the rather limited number of patients with secondary Sjögren's syndrome and autoimmune thyroiditis who could be studied. This also needs to be taken into account in future studies. Notwithstanding the importance of sample size, however, there were no clear cut trends in the frequency of the antibodies we were studying, and this gives us confidence in our data.

Table 3 Frequency of antithyroid antibodies and autoimmune thyroiditis in association with primary Sjögren's syndrome: summary of previous publications and a comparison of their results with our findings

Country	n	TPO (%)	TG (%)	Both (%)	Total (%)	AIT (%)	Criteria
USA ¹	24	10 (42)**	5 (21)	5 (21)	10 (42)**	13 (54)**	NA
Italy ²	8	NA	NA	NA	6 (75)**	2 (25)*	NA
UK ³	100	40 (40)**	NA	NA	40 (40)**	14 (14)	Fox's criteria
France ⁴	26	NA	26 (100)**	NA	26 (100)**	8 (31)**	Fox's criteria
Sweden ⁵	28	10 (36)**	10 (36)**	10 (36)**	10 (36)**	5 (18)*	Copenhagen ¹⁸
UK ^{6†}	42	14 (33)**	6 (14)	NA	NA	NA	Fox's criteria
Mexico ⁷	33	15 (45)**	6 (18)	NA	16 (48)**	11 (33)*	NA
UK ⁸	74	17 (23)*	NA	NA	NA	NA	Fox's criteria
Italy ^{9†}	119	21 (18)	16 (13)	NA	22 (19)	16 (13)	ECSG
Spain ^{10†}	160	25 (16)	20 (13)	NA	NA	32 (20)**	ECSG
Turkey (CS)†	53	5 (9)	5 (9)	4 (8)	6 (11)	2 (4)	ECSG

*p<0.05, **p<0.01: results of current study v those of previous studies.

†Controlled studies.

AIT, autoimmune thyroiditis; CS, current study; ECSG, European Community Study Group; NA, not available; TG, thyroglobulin; TPO, thyroid peroxidase.

An interesting finding of our study was the observation that the frequency of antithyroid antibodies among our patients with primary Sjögren's syndrome tended to be lower than that reported from other countries (table 3). It is known that some autoimmune diseases show geographical differences. The prevalence of pericardial disease is low in Turkish patients with rheumatoid arthritis,¹⁵ and systemic lupus erythematosus is more common in certain Asian populations and may be more severe among hispanics and native Americans than among whites in the United States.¹⁶ Moreover the frequency of certain antibodies, such as anti-Sm, also differs in patients with systemic lupus erythematosus reported from different geographical regions.¹⁷ Our finding of a lower frequency of autoantibodies among our patients with primary Sjögren's syndrome may indicate yet another geographical difference in autoantibody production, the reasons for which need to be elucidated. We remain cautious in our conclusions, in that a proper assessment of these differences would require matched comparisons of demography, disease severity, and disease duration, which were not available in the present study.

In conclusion, in a case-control study we have not been able to show an association between primary Sjögren's syndrome and autoimmune thyroiditis in a Turkish population.

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