Autoimmune Thyroid Disease in Primary Sjögren's Syndrome

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PURPOSE: To evaluate the prevalence of autoimmune thyroid disease and thyroid dysfunction in patients with primary Sjögren's syndrome.

PATIENTS AND METHODS: Thyroid function of 33 patients with primary Sjögren's syndrome was clinically and biochemically evaluated. Thyroid hormones and autoantibodies against thyroid peroxidase, thyroglobulin, and thyroid hormones were measured.

RESULTS: Autoimmune thyroid disease and thyroid dysfunction were found in 15 cases (45%): autoimmune thyroiditis in 8 (24%); autoimmune hyperthyroidism in 2 (6%); and reversible iodine-induced hypothyroidism in the remaining 5 (15%). One or more of the evaluated autoantibodies were detected in 8 euthyroid patients (24%). Overall, the prevalence of autoantibodies against thyroid peroxidase, thyroglobulin, thyroxine, and triiodothyronine was 45%, 18%, 42%, and 36%, respectively.

CONCLUSIONS: The high prevalence of autoimmune thyroid disease and thyroid dysfunction found in primary Sjögren's syndrome, using sensitive immunologic and thyroid function tests, suggest that both diseases are more frequently associated than it was previously thought, and should be sought clinically and by laboratory tests in all patients with primary Sjögren's syndrome.

Although primary Sjögren's syndrome and autoimmune thyroid disease (ATD) have been considered to result from different immunopathogenic mechanisms,[1,2] they share several histologic and genetic features.[3-5] In spite of these similarities, Bloch et al[6] and Whaley et al[7] concluded that clinical thyroid disease was not common in Sjögren's syndrome (whether primary or secondary), since they found the association of both diseases in only 10% and 14% of their patients, respectively. In support of these findings, Loviselli et al[8] reported a 12% prevalence of hypothyroidism in a prospective study of 32 patients with primary Sjögren's syndrome (pSS) or secondary Sjögren's syndrome (sSS). In contrast, Karsh et al[9] found that clinical and subclinical thyroid disease occurred in almost 50% of patients with pSS. In these series, thyroid antibodies were more frequently detected in Sjögren's syndrome than was clinical thyroid disease.

It is of interest that Graves' disease has not been described in pSS. To our knowledge, only 3 patients with hyperthyroidism and sSS were reported by Whaley et al,[7] while Mitani et al[10] described a woman with sicca syndrome, thyrotoxicosis due to silent thyroiditis, and symptoms suggestive of lupus erythematosus.

Finally, Foster et al[11] studied the prevalence of thyroid disease and antithyroid antibodies in family members of patients with pSS and found it high in first- and second-degree relatives and in patients with pSS, with a significant relationship among thyroid peroxidase autoantibodies, hypothyroidism, antinuclear antibodies (ANA), and HLA-DR3 phenotype.

The high prevalence of antibodies against thyroglobulin and thyroid peroxidase as well as the presence of thyroid hormone antibodies in Sjögren's syndrome could indicate that subclinical ATD disease is frequent in this disease.[12,13] On the other hand, the presence of significant grades of focal sialadenitis of the labial glands in 25% of patients with ATD suggests that subclinical Sjögren's syndrome may also occur frequently in individuals with ATD.[14]

To evaluate the former possibility, we carried out a complete clinical and biochemical evaluation of thyroid function, including serological detection of autoantibodies (AuAb) against thyroglobulin (Tg), thyroid peroxidase (TPO), thyroxine (T_4), and triiodothyronine (T_3), in patients with pSS.

PATIENTS AND METHODS

Patients

Thirty-three Mexican patients with pSS and similar ethnic background attending our Sjögren's syndrome clinic as outpatients, but otherwise unselected, were included in this study. Most of them (72%) live in Mexico City and each of the remaining patients (28%) live in different cities. The make-up of this clinic has been described previously.[15-17] The mean age of the patients was 50.3 years (standard deviation 12.9, range 39 to 62). Thirty-one were women. The diagnosis of pSS was established when the patients met the following three criteria: keratoconjunctivitis sicca, demonstrated by an unanesthetized Schirmer's test (<5 mm after 5 minutes) or

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characteristic corneal and conjunctival epithelial staining with rose bengal observed through a slit lamp; focal sialadenitis in a labial salivary gland biopsy specimen with a focus score >1 according to Daniels[18]; exclusion of primary connective tissue disease or autoimmune liver disease by pertinent clinical and serological studies.

Thyroid Function Tests

Total T_3 and T_4 were measured in serum by a double-antibody radioimmunoassay (RIA) kit (DPC Inc., Los Angeles, California). The normal ranges were 1.16 to 3.86 nmol/L for T_3 and 77.20 to 154.40 nmol/L for T_4. The intra-assay and interassay coefficient of variation (CV) was 2.5%, respectively, for both thyroid hormones.

Serum thyrotropin (TSH) was measured by a sensitive second-generation immunoradiometric assay kit (DPC Inc.), with intra-assay and interassay CV of 1.5%. The normal range for TSH was 0.3 to 3.5 mU/L.

Serum Tg and thyroxine-binding globulin (TBG) were also measured by RIA kits (DPC Inc. and Clinical Assays, Stillwater, Minnesota, respectively). The normal range for Tg was 0 to 60 µg/L, and for TBG it was 15 to 30 mg/L. The intra-assay and interassay CVs were 5% and 7.5%, respectively, for Tg and 4% and 7%, respectively, for TBG.

Thyroid radioactive iodine uptake (normal range at 24 hours, 10% to 25%) and thyroid scans were performed when clinically indicated.

Autoantibody Assays

Antithyroglobulin (TgAb) and antithyroid peroxidase (TPOAb) antibodies were tested by gelatin particle agglutination (Fujirebio Inc., Tokyo, Japan). Antibody titers of 1:800 were considered positive. We have previously determined that titers of (≥ 1:12,800 are diagnostic of autoimmune thyroiditis.[19]

Autoantibodies to T_3 and T_4 (T_3-T_4 AuAb) were detected by a modification of Nakamura's method.[13,20] In brief, we treated 0.1 mL of the patient's serum with 0.4 mL of tris[hydroxymethyl]aminomethane hydrochloride (TRIS-HCl) buffer, 0.05 M, pH 2.2 instead of glycine-HCl buffer; free thyroid hormones were adsorbed with dextran-coated charcoal (25 mg/mL). Serum was incubated (1 hour at 4°C) and centrifuged (3,000 rpm, 20 minutes at 4°C). An aliquot of 0.2 mL of the supernatant was obtained, and the serum was neutralized with 0.7 mL of 0.06 M barbital buffer, pH 8.6, containing 8-anilino-1-naphthalene-sulfonic acid. We added 0.1 mL of ^{125}I-T_3 (10 pg) or 0.1 mL of ^{125}I-T_4 (1.0 pg). The mixture was incubated 20 hours at 4°C, and then we added 1.0 mL of polyethylene glycol solution (250 mg/mL). The mixture was centrifuged (3,000 rpm, 20 minutes at 4°C) and the pellet counted. Serum from normal volunteers was used as a control.

Antibody cross-reactivity was assessed with purified human TPO and Tg obtained in our laboratory. The sera from 12 patients with high-to-low titers of rheumatoid factor (RF), ANA, SSA, and SSB antibodies were absorbed with both thyroid antigens. In brief, 100 µL of serum with a previously known titer of the above-mentioned antibodies was treated with 1 µg of purified human TPO and 2 µg of purified human Tg. Sera were incubated 20 hours at room temperature and then centrifuged (3,000 rpm, 20 minutes at 4°C). Antithyroid antibodies were detected in the supernatant of treated sera. The RF, ANA, SSA, and SSB were also tested and the titers were compared with untreated sera. We did not find cross-reactivity between the antibodies assessed.

RESULTS

Twenty-three of the 33 patients (70%) with pSS had ATD or thyroid dysfunction, or at least the presence of one of the evaluated AuAb.

Prevalence of Thyroid Disease

Fifteen patients had thyroid disease. Six of these were hypothyroid due to autoimmune thyroiditis. All 6 had significant titers of TPOAb (1:12,800 to 1:51,200) whereas only 2 of them also had significant titers of TgAb (1:12,800 and 1:25,600). Moreover, in 3 patients T_3 AuAb and T_4 AuAb were also detected.

Five other patients (mean age 49 years) with similar ethnic background but without history of thyroid disease, who live in iodine-sufficient cities (4 in Mexico City and the fifth lives in Guadalajara, Jalisco) developed iodine-induced hypothyroidism. They did not use drugs that modify thyroid function or any other medications containing iodides, but they had dyed their hair with iodine-containing compounds. Hypothyroidism disappeared once they stopped the hair dyeing (**Figure 1**). Low titers of TPOAb and TgAb (1:6,400) and T_3 AuAb and T_4 AuAb were detected in 1 of these patients. Another patient also had low titers of TPOAb (1:6,400), and in another patient we found both T_3 and T_4 AuAb.

Two additional patients had autoimmune hyperthyroidism characterized by elevated serum levels of thyroid hormones and thyroid radioactive iodine uptake, suppressed TSH, and diffuse goiter. Thyroid-associated ophthalmopathy was not apparent in either. Both patients were treated with methimazole and 1 received radioiodine therapy followed by thyroid-hormone replacement. Significant titers of TPOAb (1:12,800 and 1:102,400) were found in both after they became euthyroid. One of these patients also had T_3 AuAb while the other had T_4 AuAb.

Two other euthyroid patients also had significant titers of TPOAb (1:12,800 and 1:102,400) although

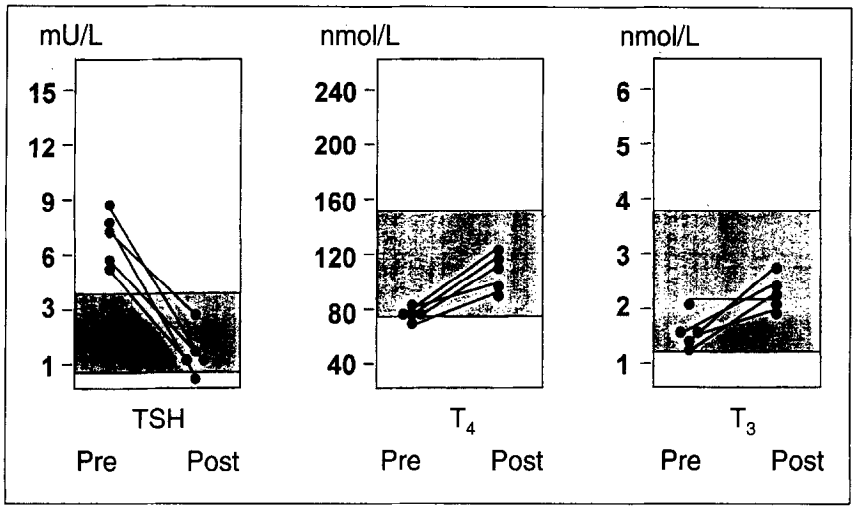

Figure 1. Serum concentration of thyroid hormones in patients with reversible iodine-induced hypothyroidism during the use of hair colorants (PRE) and 6 to 8 weeks after hair dyeing stopped (POST). Normal ranges are depicted as **shaded** areas. TSH = serum thyrotropin; T_3 = triiodothyronine; T_4 = thyroxine.

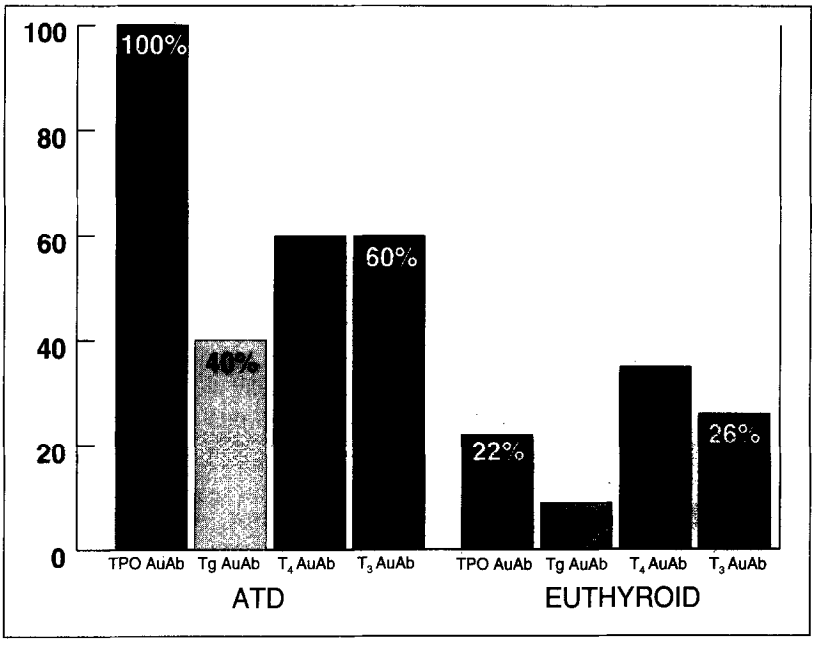

Figure 2. Prevalence of thyroid and thyroid hormone autoantibodies among patients with autoimmune thyroid disease (ATD) and thyroid dysfunction (**left panel**) and euthyroid patients (**right panel**), including those who were euthyroid after iodine-containing compounds were stopped. TPO = thyroid peroxidase; AuAb = autoantibodies; Tg = thyroglobulin; T_3 = triiodothyronine; T_4 = thyroxine.

TgAb titers were significant in only 1 of them (1:800 and 1:51,200, respectively). T_3 AuAb and T_4 AuAb were detected in both patients. We believe that both patients had autoimmune thyroiditis,[19] but thyroid biopsy was not performed.

Prevalence of Antithyroid and Thyroid Hormone AuAb in Euthyroid Patients

Among the remaining 18 euthyroid patients, 8 had one or more of the evaluated AuAb. Three had both T_3 AuAb and T_4 AuAb. Another 3 had T_4 AuAb, whereas in 1 additional case only, T_3 AuAb was detected. Low titers of TPOAb (1:800 to 1:6,400) were found in 2 of these 7 cases. The remaining patient also had low titers of both TPOAb and TgAb (1:1,600). This group of 8 euthyroid patients with AuAb represents 24% of all patients studied. The remaining 10 euthyroid patients did not have any of the evaluated AuAb. This group represents 30% of all our patients.

Overall Prevalence of Autoantibodies

In this report, the overall prevalence of antithyroid and thyroid hormone AuAb in pSS was TPO 45%, Tg 18%, T_4 42%, and T_3 36%. Patients with ATD and thyroid dysfunction had a higher prevalence of thyroid and thyroid hormone AuAb than euthyroid patients (**Figure 2**).

DISCUSSION

Thyroid disease in Sjögren's syndrome was formerly considered infrequent due to the lack of sensitive immunologic and thyroid function tests. Karsh et al,[9] however, have recently shown that when thyroid reserve is assessed with sensitive tests, thyroid failure in pSS is a clinical problem of greater magnitude than previously thought. The prevalence of 45% of thyroid dysfunction and ATD demonstrated in this report in patients with pSS is in agreement with their findings and indicates that ATD in pSS is more frequent than previously thought. The prevalence of TPOAb

and TgAb found in our study was also similar to that found in previous reports of patients with Sjögren's syndrome.[7,9,11] Therefore, ATD should be sought clinically and by laboratory tests in all patients with pSS.

To our knowledge, this is the first report on the association of autoimmune hyperthyroidism and pSS[7,11] and the largest one in which the prevalence of T_3 AuAb and T_4 AuAb in pSS has been assessed.[12,13] It has been shown that thyroid hormone AuAb in patient's serum may interfere with RIA technique for T_3 and T_4. If both hormones are assayed by a double- or single-antibody RIA method, serum concentrations of these hormones will be overestimated or underestimated, respectively.[13] Therefore, the high prevalence of thyroid hormone AuAb found in pSS should be kept in mind in order to avoid misdiagnosis and unnecessary therapy. Nevertheless, Karlsson et al[21] and Trimarchi et al[12] have reported 2 cases of hypothyroidism without histological evidence of thyroid disease, apparently caused by thyroid hormone AuAb. Although we believe that our hypothyroid patients had autoimmune thyroiditis, in 3 of them we could not exclude that T_3 AuAb and T_4 AuAb may have caused hypothyroidism in the absence of thyroiditis.

Increasing evidence from epidemiological and experimental studies has suggested that iodine may exacerbate or induce autoimmune thyroiditis in predisposed individuals. Conversely, low iodine intake may delay or decrease the expression of ATD and clinical hypothyroidism.[22] Supporting this, there are reports of patients with spontaneous hypothyroidism due to excessive iodine intake that reverted after iodine restriction.[23-25] Almost one third of the patients described by Tajiri et al[24] had no goiter, and one third to two thirds of patients also had antithyroid AuAb in these series.[23-25] Tajiri et al[24] found lymphocytic thyroiditis in those in whom thyroid biopsy was done, and Mizukami et al[25] found it in about half of their patients. It has been shown that iodine-induced hypothyroidism is due to an organification defect caused by a persistent Wolff-Chaikoff effect from which escape does not occur.[24]

The persistent Wolff-Chaikoff effect (inhibition of iodine organification) has also been described in persons with thyroid disease or an underlying, albeit subclinical, reduction in thyroid reserve. These studies included patients with autoimmune (Hashimoto's disease) thyroiditis, patients treated with radioiodine or thyroid surgery, and euthyroid subjects with a previous episode of subacute or postpartum thyroiditis and amiodarone-induced thyrotoxicosis.[26-30] In contrast, hypothyroidism has not been demonstrated in normal persons exposed to pharmacological doses of iodine coming from oral supplements,[26,31] douching,[32] and mouth rinsing.[33] Although some of these studies showed small decreases in serum T_3 and T_4 concentration as well as a slight compensatory increase in serum TSH concentration, and some of them demonstrated an increase in TSH response to thyrotropin-releasing hormone, the basal values of thyroid hormones and TSH during chronic exposure to iodine excess remained within normal range.[31-33]

Five of our 33 pSS patients, who live in iodine-sufficient cities and who used hair dye with iodine-containing compounds, developed reversible iodine-induced hypothyroidism. None had previous thyroid disease, and they were not using drugs or other local medications containing iodides. All of them became euthyroid once they discontinued the use of hair colorants, and they shared the same ethnic origin of our remaining patients with pSS. None had goiter, but 3 of them had serum antithyroid and thyroid hormone AuAb. Although thyroid biopsy was not performed, they may have had incipient lymphocytic thyroiditis that became evident by iodine excess coming from hair colorants.

The reversible iodine-induced hypothyroidism is not restricted to a particular ethnic group. It had also been reported in some euthyroid individuals living in Japan, the United States, and Italy. The individuals described in these reports had a history of thyroid disease or they had subclinical lymphocytic thyroiditis and became hypothyroid due to excessive iodine intake.[23-30] In contrast, our 5 patients with pSS who developed reversible iodine-induced hypothyroidism had dermal exposure from iodine-containing hair colorants. Therefore, dermal exposure could be another route of significant iodine absorption.

The recognition of reversible iodine-induced hypothyroidism in pSS could avoid lifelong thyroid hormone therapy in these patients. Nevertheless, prospective studies on the natural course of thyroid function in iodine-induced hypothyroidism are needed to determine the incidence of permanent hypothyroidism once iodine excess is removed.

It is of particular interest that thyroid hormones AuAb were more frequently found than TPOAb and TgAb in 8 of the euthyroid patients. An explanation could be that appearance of T_3 AuAb and T_4 AuAb precedes the development of the ATD in some patients with pSS. Prospective follow-up of these patients will permit us to test this hypothesis. The prevalence of thyroid hormone AuAb found in euthyroid patients with pSS is more than 100-fold that of the general population in ethnically similar individuals (G. López and B. Pérez-E, unpublished data).

On the other hand, the findings of sialadenitis in subjects with autoimmune thyroiditis[14] could relate to salivary gland enlargement found in hypothyroid patients,[34] as well as the effects of iodine on the natural course of autoimmune thyroiditis and its potential to induce salivary gland enlargement.[22,35] In a

recent study involving 176 patients with ATD, 24% were found to have keratoconjunctivitis sicca, and 36% had xerostomia. Forty-three of the 176 had a definite Sjögren's syndrome, and this prevalence was equally divided among patients with Graves' disease, Hashimoto's thyroiditis, and primary hypothyroidism.[36] These could be related through similarities in the genetic background of patients with pSS and ATD. Linkage of biological modulation between immune and neuroendocrine systems[37,38] should be considered in future investigations into the etiopathogenic and immunopathogenic mechanisms of ATD in pSS.

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