Thyroid Disease in Primary Sjogren Syndrome: Study in a Series of 160 Patients

Ramos-Casals, Manuel M.D.; Garcia-Carrasco, Mario M.D., Ph.D.; Cervera, Ricard M.D., Ph.D.; Gaya, Joan M.D., Ph.D.; Halperin, Irene M.D., Ph.D.; Ubieto, Irene M.D.; Aymami, Ana M.D.; Morla, Rosa M. M.D.; Font, Josep M.D., Ph.D.; Ingelmo, Miguel M.D., Ph.D.

From Systemic Autoimmune Diseases Unit (MR-C, MG-C, RC, RMM, JF, MI), Hormonal Laboratory (JG), and Department of Endocrinology (IH), Department of Medicine, Institut d'Investigacions Biomediques August Pi i Sunyer (IDIBAPS), Hospital Clinic, School of Medicine, University of Barcelona; CAP Molins de Rei (IU, AA), Molins de Rei, Barcelona, Catalonia, Spain; and Rheumatology Department (MG-C), Benemerita University School of Medicine, Puebla, Mexico.

Supported by Grants SAF96-0120 from the Comisión Interministerial de Ciencia y Tecnología, FIS 97/0669 and FIS 99/0280 from the Fondo de Investigaciones Sanitarias. M. Ramos-Casals is a Research Fellow sponsored by a grant from the Hospital Clinic.

Address reprint requests to: Dr. Ricard Cervera, Unitat de Malalties Autoimmune, Hospital Clinic, C/Villarroel, 170, 08036-Barcelona, Catalonia, Spain. Fax: 34-93-451 52 72; e-mail: cervera@medicina.ub.es.

Abbreviations used in this article: ANA, antinuclear antibodies; ATD, autoimmune thyroid disease; CI, confidence interval; NATD, nonautoimmune thyroid disease; OR, odds ratio; SS, Sjogren syndrome; TgAb, antithyroglobulin antibodies; TPOAb, antithyroid peroxidase antibodies; TSH, thyroid-stimulating hormone.

Outline

Introduction
Methods
Patients
Control group patients
Hormonal studies
Immunologic studies
Statistical analysis
Iodine Sjogrens Med Baltimore 2000_79_2.txt

Results

Thyroid disease in patients with primary SS

Relationship between thyroid disease and other features of SS

Comparison of thyroid disease in patients with primary SS and controls

Discussion

Summary

References

Graphics

Table 1
Table 2
Table 3
Table 4
Table 5

Introduction

Sjogren syndrome (SS) is an autoimmune disease that mainly affects exocrine glands and usually presents as a persistent dryness of the mouth and eyes due to functional impairment of the salivary and lacrimal glands (6). In the absence of an associated systemic autoimmune disease, patients with this condition are classified as having primary SS. The histologic hallmark is a focal lymphocytic infiltration of the exocrine glands, and the spectrum of the disease extends from an organ-specific autoimmune disease (autoimmune exocrinopathy) (28) to a systemic process (musculoskeletal, pulmonary, gastric, hematologic, vascular, dermatologic, renal, nervous system involvement, and lymphoproliferation) (1, 4, 8, 10, 22, 23). Because of this heterogeneity, some researchers have attempted to identify subsets of patients that would permit more reliable prediction of the course of primary SS in the affected individuals (11, 24, 25).

Considering the developmental, functional, and pathologic similarities of the thyroid and salivary glands (18), of particular interest is the association of thyroid disease and SS, which may have not only clinical but also etiopathogenic significance. The first studies of this association were included in general descriptions of the clinical picture of SS, whether primary or secondary (2, 31). These studies found the association of both diseases in 10%-14% of patients and showed that clinical thyroid disease was not common in SS, although similar studies (14) have shown a higher prevalence (50%). Since these initial reports, studies on the prevalence and clinical significance of thyroid disease in patients with primary SS have been scarce and generally performed in small series of patients without an age/gender-matched control group (9, 12, 14, 16, 20). We conducted the present study to determine the prevalence and clinical significance of thyroid disease in a large series of patients with primary SS.
Methods

Patients

We investigated 160 consecutive patients (147 women and 13 men; mean age, 60 yr; range, 23-87 yr) seen in the Systemic Autoimmune Disease Unit. All patients fulfilled 4 or more of the preliminary diagnostic criteria for SS proposed by the European Community Study Group in 1993 (30). Moreover, presence of a positive minor salivary gland biopsy result (lymphocytic infiltrates grade 3 or 4 according to Chisholm-Mason's classification [5]) or a positive immunologic test (antinuclear antibodies [ANA] with a titer > 1/40, rheumatoid factor, anti-Ro/SS-A or anti-La/SS-B antibodies) was required for the diagnosis of SS. None of these patients presented clinical or immunologic evidence of other systemic autoimmune disease, and all were classified as having primary SS.

All patients underwent a complete history and physical examination, as well as diagnostic tests for SS applied according to the recommendations of the European Community Study Group (30). All patients were specifically questioned on the presence of a past history of thyroid disease as well as on the current presence of clinical manifestations suggestive of hyper- or hypothyroidism. A careful examination of the neck was performed in all patients and thyroid echography and/or scintigraphy was performed in those patients in whom a goiter or a thyroid nodule was suspected clinically.

Control group patients

To ensure that age and gender were similarly distributed in primary SS and control groups, we sorted the 160 SS patients in ascending order according to age and alternatively selected the odd cases. Each odd case was individually matched with a control subject of the same age and sex, consecutively selected from a primary care center in our geographic area. Thus, we selected 80 control subjects, but 5 refused to participate in the study and we finally obtained a control group of 75 individuals (66 women and 9 men; mean age, 61 yr; range, 23-80 yr) with a demographic profile similar to the 160 SS patients. Control subjects were selected if they did not have referred clinical manifestations of SS and did not receive medications that might alter the thyroidal profile (lithium, iodine, amiodarone, phenylbutazone, sulfonamides, glucocorticoids, fenclofenac, or furosemide).

Hormonal studies

The following hormonal studies were performed in all patients and controls at the time of the study. Triiodothyronine (T3) and free thyroxine (FT4) were determined using a heterogeneous competitive magnetic separation assay (Technicon Immuno 1 System, Bayer Corporation, Tarrytown, NY). The normal ranges were 0.6-1.6 ng/dL for T3 and 0.8-2.0 ng/dL for FT4. Thyroid-stimulating hormone (TSH) was determined using a sandwich immunoassay format (Technicon Immuno 1 System, Bayer Corporation, Tarrytown, NY) with a sensitivity of 0.03 mIU/L. The normal range for TSH was 0.4-4.0 mIU/L. Clinical hypothyroidism is defined by the finding of a decreased serum concentration of FT4 with an increase in
Iodine Sjogrens Med Baltimore 2000_79_2.txt

Serum TSH. Subclinical hypothyroidism is defined by the finding of an increase in serum TSH concentration with normal serum FT4 and T3 concentrations. Clinical hyperthyroidism is defined by the finding of an increased serum concentration of FT4 or T3, or both, but decreased serum TSH. Finally, subclinical hyperthyroidism is defined by normal serum FT4 and T3 concentrations but decreased serum TSH in an asymptomatic individual.

Immunologic studies

Serum autoantibodies against thyroglobulin (TgAb) and thyroid peroxidase (TPOAb) were determined by an automatic ELISA system in which the autoantibodies react with specific antigen linked to a solid phase and to Protein-A labeled with enzyme (Enzymun-Test, Roche-Boehringer, Manheim, RFA). The existence of an autoimmune thyroid disease (ATD) was based on the presence of TgAb and/or TPOAb in high titer (>136 IU/mL for TgAb and >36 IU/mL for TPOAb). Other immunologic tests included determination of ANA (indirect immunofluorescence using mouse liver as substrate), precipitating antibodies to the extractable nuclear antigens Ro/SS-A and La/SS-B (counterimmunoelectrophoresis), and rheumatoid factor (ELISA).

Statistical analysis

We used conventional chi-square and Fisher exact tests to analyze qualitative differences, the Student test for comparison of means in large samples of similar variance, and the nonparametric Mann-Whitney U test for small samples. The odds ratio (OR) was calculated for assessing the risk of appearance of each variable, with a confidence interval (CI) of 95%. Values of quantitative variables are expressed as mean +/- standard error of the mean. A value of p Results

Thyroid disease in patients with primary SS

Fifty-eight (36%) of the 160 patients with primary SS had evidence of thyroid disease (Table 1). Fifty-seven were female and 1, male. At the time of protocol, the mean age of the patients was 60 years (range, 24-80 yr) and the mean disease duration of SS was 81 months (range, 12-180 mo). None of these patients was treated with medications that might alter the thyroidal profile (lithium, iodine, amiodarone, phenylbutazone, sulfonamides, glucocorticoids, fenclofenac, or furosemide).

TABLE 1. Thyroid disease in 160 patients with primary Sjogren syndrome
Autoimmune thyroid disease: Autoimmune thyroid disease (ATD) was diagnosed in 32 (20%) of the 160 patients with primary SS. Twenty patients showed an altered hormonal profile: 18 showed hypothyroidism (15 subclinical hypothyroidism and 3 clinical hypothyroidism) and 2 hyperthyroidism (both subclinical hyperthyroidism). The remaining 12 patients were euthyroidal (6 of them previously had hypothyroidism and received substitutive treatment).

Nonautoimmune thyroid disease: Nonautoimmune thyroid disease (NATD) was diagnosed in 26 (16%) of the 160 patients with primary SS. Seventeen patients showed an altered hormonal profile: 7 showed hypothyroidism (4 subclinical hypothyroidism and 3 clinical hypothyroidism) and 10 showed hyperthyroidism (3 subclinical hyperthyroidism and 7 clinical hyperthyroidism). The remaining 9 patients showed a morphologic thyroid disease with euthyroidism. The diagnoses in these patients were multinodular goiter in 5, diffuse goiter in 3, and thyroid adenoma in 1.

Considering those patients with altered hormonal profiles, a different hormonal pattern was observed when ATD patients were compared with NATD patients. Patients with ATD showed mainly hypothyroidism (18/20, 90% versus 7/17, 41% in patients with NATD, p = 0.001, OR 12.86, CI 1.87-138.09), and those with NATD showed mainly hyperthyroidism (10/17, 59% versus 2/20, 10% in patients with ATD, p = 0.001, OR 12.86, CI 1.87-138.09).

Relationship between thyroid disease and other features of SS

Clinical and immunologic manifestations of primary SS in patients with and without thyroid disease are shown in Table 2. A higher frequency of female patients was found in patients with thyroid disease than in those without (57/58, 98% versus 90/102, 88%, p = 0.03, OR 7.60, CI 1.06-330.47), but no statistical differences were found between the groups concerning age at protocol or mean disease duration. The prevalences of glandular and extraglandular manifestations during the course of the disease were also similar in both groups, but when immunologic profiles were compared, patients with thyroid disease showed a higher prevalence, compared with those without thyroid disease, of antiparietal cell autoantibodies (33% versus 12%, p = 0.002, OR 3.65, CI 1.50-9.05), TgAb (30% versus 5%, p

TABLE 2. Clinical and immunologic manifestations of primary SS in patients with and without thyroid disease

Comparison of thyroid disease in patients with primary SS and controls

Page 5
Table 3 shows the prevalences of the different types of thyroid disease in patients with primary SS and in controls of similar age and gender. No significant differences were found when comparing the prevalences of both ATD and NATD in patients with primary SS and in controls, respectively (32/160, 20% versus 13/75, 17% for ATD and 26/160, 16% versus 7/75, 9% for NATD).

TABLE 3. Epidemiologic characteristics and prevalence of thyroid disease in patients with primary SS and in control group

Discussion

In our study, we found a similar prevalence of thyroid disease in patients with primary SS and in a control group of similar age and gender. Although thyroid disease was more common in patients with SS than in the control group, the difference (36% versus 27%, respectively) did not reach statistical significance.

Patients with primary SS and thyroid disease were preferentially women, and showed the same glandular and extraglandular manifestations of SS as those without thyroid disease, but we found a higher prevalence of several autoantibodies (antiparietal cell-Ab, TgAb, and TPOAb) in patients with thyroid disease.

The thyroid and salivary glands have a number of interesting functional similarities, including the uptake and concentration of iodine by both glands (18). Histopathologically, the lymphocytic infiltrates of lacrimal and salivary glands that are found in SS are similar to those of the thyroid gland in Hashimoto thyroiditis (13, 17). These observations may suggest a common pathogenetic mechanism for thyroid and salivary gland disease in SS (3). It is possible that antigens shared by the salivary and thyroid glands are responsible for the apparent association of autoimmune disease directed to each organ. In addition, a similar genetic background could predispose individuals to both diseases (26). Foster et al (9) studied the prevalences of thyroid disease and antithyroid antibodies in family members of patients with primary SS and found that they were increased in first- and second-degree relatives and in patients with primary SS, with a significant relationship among TPOAb, hypothyroidism, ANA, and HLA-DR3 phenotype.

The prevalence and characteristics of thyroid disease in patients with primary SS have been evaluated by several uncontrolled studies (9, 12, 14, 15, 16, 20, 21) (Tables 4 and 5). These studies showed percentages of thyroid dysfunction ranging from 10% to 45%, but at least 90% of the patients studied were women whose average age was about 50 years. Thus, that thyroid disease is more common in patients with primary SS than in the general population of similar age and gender.
gender could not be ascertained from these studies because of the high expected rate of thyroid disease in this population (middle-aged individuals, mainly women) (7, 29). It is noteworthy that our study shows that patients with primary SS have a prevalence of thyroid disease similar to that of a control group of similar age and gender (36% versus 27%, respectively). Moreover, the prevalences of both ATD and NATD were similar in SS patients and controls.

TABLE 4. Prevalence of thyroid disease in patients with primary Sjögren syndrome, present report and previous studies

<table>
<thead>
<tr>
<th>Prevalence of thyroid disease</th>
<th>Present Report</th>
<th>Previous Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subclinical hypothyroidism</td>
<td>19 (51%)</td>
<td></td>
</tr>
<tr>
<td>Clinical hypothyroidism</td>
<td>2 (5%)</td>
<td></td>
</tr>
</tbody>
</table>

The most frequent hormonal profile observed in our SS patients with thyroid disease was subclinical hypothyroidism, detected in 19 (51%) of the 37 patients with altered hormonal values. Subclinical hypothyroidism is a relatively common disorder caused by the same disorders that result in overt hypothyroidism. The most common cause, responsible for about 50% of cases, is autoimmune or Hashimoto thyroiditis (27). The overall prevalence of these findings in the general population is 2%-8% (2.8% in men and 7.5% in women) with a particularly high prevalence, up to 16%, in women older than 60 years of age (27). In our control group (mainly women, with a mean age of 60 years) we found a similar prevalence (17%). Early investigators believed that these findings characterized a stage of hypothyroidism that preceded the clinical presentation of disease. We also believe that, in most of our SS patients, an increase in serum TSH represents the earliest detectable stage of hypothyroidism. When patients with subclinical hypothyroidism are studied over a period of years, 20%-50% of individuals appears to develop overt clinical hypothyroidism within 4-8 years. Furthermore, those patients who also have higher titers of antithyroid antibodies have a higher risk of developing clinical hypothyroidism. In patients older than 65 years of age, the presence of an increase in serum TSH and antithyroid antibodies predicts that about 80% of individuals will develop clinical hypothyroidism within 4 years (27). A prospective follow-up of our clinical study showed that the prevalence of hypothyroidism increased significantly over the study period, with an estimated prevalence of 20% after 5 years of follow-up.
Iodine Sjogrens Med Baltimore 2000_79_2.txt

Subclinical SS patients is required to confirm the development of overt clinical thyroid disease.

Subclinical hyperthyroidism occurs less frequently than subclinical hypothyroidism. The reported prevalence in the general population ranges from 1% to 12%, and the most common causes of hyperthyroidism are Graves disease, nodular goiter, and thyroiditis (27). To our knowledge, the association between primary SS and Graves disease has been described anecdotally (15), and hyperthyroidism has been scarcely described in SS patients (19, 20, 21, 31). In this study, we found hyperthyroidism in 12 (8%) of 160 SS patients, thus hyperthyroidism in primary SS is more frequent than previously thought. Furthermore, only 2 of our patients showed autoimmune hyperthyroidism, a rare association previously described by Perez-E et al (20). Most of our hyperthyroidal patients had NATD, while hypothyroidal patients had mainly ATD.

In conclusion, a high prevalence of thyroid disease was found in a large series of patients with primary SS, although no significant differences were demonstrated when we compared this prevalence with that of a control group of similar age and gender. Subclinical hypothyroidism is the most frequent thyroidal profile found in patients with ATD, while patients with NATD had mainly hyperthyroidism. Our results indicate that middle-aged women (with or without SS) should be screened periodically for thyroid function.

Summary

We studied 160 consecutive patients (147 female and 13 male) with primary Sjogren syndrome (SS) to determine the prevalence and clinical significance of thyroid disease in a large series of patients with primary SS from our unit and to compare the prevalence and significance with those in 75 individuals without SS from a primary care center. Serum levels of thyroid hormones (free thyroxine, triiodothyronine, and thyroid-stimulating hormone) and autoantibodies against thyroglobulin (TgAb) and thyroid peroxidase (TPOAb) were measured in all SS patients and in 75 control patients.

Fifty-eight (36%) of the 160 patients with primary SS had evidence of thyroid disease. Autoimmune thyroid disease (ATD) was diagnosed in 32 (20%) patients and nonautoimmune thyroid disease (NATD) in 26 (16%). No significant differences were found when these prevalences were compared with those in control patients. On the other hand, comparing those patients with altered hormonal profiles, patients with NATD showed mainly hyperthyroidism (10/17, 59% versus 2/20, 10% in patients with ATD, p = 0.001). Finally, when clinical and immunologic manifestations of SS were analyzed in patients with and without thyroid disease, respectively, 


we found that patients with thyroid disease had a higher prevalence of female gender (98% versus 88%, p = 0.03), antiparietal cell autoantibodies (33% versus 12%, p = 0.002), TgAb (30% versus 5%, p

In conclusion, thyroid disease occurred in more than one-third of patients with primary SS; the main cause was ATD, which was present in 20% of the patients studied. We note that no significant differences were observed when the prevalence of thyroid disease (either ATD or NATD) was compared with that in a control group of similar age and gender. Our results indicate that middle-aged women (with or without SS) should be screened periodically for thyroid function.

References


other autoimmune phenomena in a family study of primary Sjo


----------------------------------------------
Accession Number: 00005792-200003000-00004