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ORIGINAL ARTICLE

Thyroid Dysfunction in Primary Sjögren's Syndrome: A Long-Term Followup Study

FRÉDÉRIQUE D'ARBONNEAU, SÉVERINE ANSART, ROZENN LE BERRE, MARYVONNE DUEYMES, PIERRE YOUINOU, AND YVON-LOUIS PENNEC

Objective. **To evaluate the prevalence of thyroid dysfunction and related autoantibodies in patients with primary Sjögren's syndrome (pSS), and to determine whether these abnormalities develop over time.**
Methods. **pSS patients (n = 137) and controls (n = 120) were investigated for thyroid dysfunction and for the presence of anti–thyroid peroxidase antibody (anti-TPO) and antithyroglobulin antibody (ATG). Followup time for patients was 1–16 years, and 72 of the 120 controls were reevaluated 3 years after initial evaluation.**
Results. **Thyroid disease was more frequent in the pSS patients than in the controls (30% versus 4%; $P < 10^{-4}$), as were anti-TPO and ATG (11% versus 3%; $P < 0.02$, and 3% versus 1%, not significant). Ten of 107 euthyroid pSS patients dropped out of the study, and thyroid dysfunction became apparent at followup in 12 of the remaining 97. Most of the patients with thyroid-related autoantibodies at entry developed autoimmune thyroid disease thereafter.**
Conclusion. **Thyroid dysfunction is frequent in pSS patients, and those prone to develop thyroid disorders are identified by thyroid-related autoantibodies, or by rheumatoid factor and anti-Ro/SSA activity.**

KEY WORDS. Sjögren's syndrome; Thyroid dysfunction.

INTRODUCTION

Sjögren's syndrome (SS) is a chronic autoimmune epithelitis of which the hallmarks are a disruption of epithelial cells, the ensuing lymphoplasmocytic infiltration of exocrine glands, and the subsequent dryness of the mouth and the eyes (1). A number of nonexocrine sites may be involved during the disease process. It may occur alone as primary SS (pSS) or be associated with other connective tissue diseases as secondary SS (sSS) (2).

Several inflammatory thyroid diseases are also considered to be autoimmune in origin. In this respect, it is interesting that the histopathologic picture of pSS exocrine glands and autoimmune thyroid glands show great similarities, such as infiltration by activated T lymphocytes (3,4), epithelial expression of HLA class II molecules (5,6), and clonal B cell expansion (7). Furthermore, antithyroid antibodies have been detected in a proportion of patients with nonorgan-specific autoimmune conditions, including pSS, systemic lupus erythematosus (SLE), or rheumatoid arthritis (RA) (8,9). The question thus arises as to whether patients with pSS are at risk of developing autoimmune thyroid disease (AT). This has never been evaluated over a long period of time.

Yet, controversy exists over the prevalence of these complications, given striking differences in the results. Pioneering works by Bertram et al (8), Whaley et al (10), and Hansen et al (11) found that both conditions were associated in as few as 10%, 14%, and 18 % of the cases, respectively, leading to the conclusion that AT was rather uncommon in pSS. These results are at variance with the reports of Karsh et al (12) and Pérez-E et al (13), where AT occurred in as many as 50% of the patients. However, the absence of controls is a limitation that questions the significance of such important results. This reservation is supported by the recent finding that there were no significant differences in the prevalence of AT between patients with pSS and appropriate controls (14). Moreover, because the above investigators did the tests on a single occasion, there is still a need for information on the long-term outcome of thyroid function in pSS, where dysfunction might be delayed along with other autoimmune abnormalities. In these cross-sectional surveys, it is indeed impossible to know if positivity of autoantibodies precedes the clinical manifestations, and for how long.

The present study was, therefore, undertaken to 1) de-

Frédérique d'Arbonneau, Odont D, Séverine Ansart, MB, Rozenn Le Berre, MD, Maryvonne Dueymes, MD , PhD, Pierre Youinou, MD, PhD, Yvon-Louis Pennec, MD: Brest University Medical School, Brest, France.
Address correspondence to Dr. Pierre Youinou, Laboratory of Immunology, Brest University Medical School Hospital, BP 824, F 29609 Brest Cedex, France. E-mail: youinou@univ-brest.fr.
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termine thyroid dysfunction when first examined and during followup in a cohort of 137 patients with definite pSS, compared with 120 sex- and age-matched controls; 2) evaluate the frequency of thyroid autoantibodies in pSS patients and their relationship to ongoing or delayed AT; and 3) identify in advance those pSS patients prone to the development of thyroid complications.

PATIENTS AND METHODS

Initial evaluation. This project was approved by the Brest University Medical School Hospital institutional review board. From 1985 through 2000, 164 unselected patients referred to us for assessment of inflammation and/or oral and/or ocular dryness, and then classified as having definite pSS were prospectively enrolled in this study. All met at least 4 of the 1993 preliminary European community classification criteria for the disease (15) with slight modifications introduced in 1996 (16). All these pSS patients had at least 1 salivary gland biopsy performed. Therefore, to establish diagnosis, we required a positive labial salivary gland biopsy result (17), or any 1 positive among the following immunologic tests: rheumatoid factor (RF; 103/164 positive, 63%), antinuclear antibodies (ANA; 144/164 positive, 88%), or anti-Ro/SSA and anti-La/SSB antibodies (100/164 and 96/164 positive, 61% and 59%, respectively). The labial salivary gland biopsy done at first evaluation was positive in 117 patients, and 12 of the 47 initially negative biopsies became positive on second samples taken at least 1 year later (18). Altogether, the histopathologic approach was considered as diagnostic in 129 patients (79%). None of them presented clinical or immunologic evidence of other systemic autoimmune disease. Fifteen pSS patients who had been given treatments known to cause thyroid dysfunction, including beta-blockers, lithium, amiodarone, phenylbutazone, glucocorticoids, furosemide, and carbamazepine, were excluded from the study. Furthermore, because all individuals with sciatica or osteoarthritis (OA) who served as controls without pSS (and whose sera originally collected had then been stored for another study dedicated to steroids) were female, 12 men among the remaining 149 pSS patients were excluded to match the patients to the controls. It follows that the 137 pSS patients included in the present study were all female and their age ranged from 19 to 73 years (53.6 $\pm$ 11.9 years) on first referral.

None of the control subjects had clinical manifestations of pSS; nor did they have RF, ANA, or anti-Ro/SSA and anti-La/SSB antibodies. The sciatica and OA controls were age-matched to the pSS patients. Samples were taken from the serum collection for determination of free thyroxine (T4), triiodothyronine (T3), thyroid-stimulating hormone (TSH), anti–thyroid peroxidase antibody (anti-TPO), and antithyroglobulin antibody (ATG), RF, ANA, and anti-Ro/SS-A and anti-La/SS-B antibodies. One of several aliquots was systematically left at −80°C until use, so that all sera could be reevaluated using the latest more sensitive methods.

All pSS patients and consenting controls were carefully questioned on the use of medications that might have altered thyroid activity, and 24 of them who were taking 1 or several of such medications were excluded from this particular study. The remaining 120 ranged from 20 to 82 years in age (56.0 $\pm$ 15.6 years; difference nonsignificant with the pSS patients). A past or present history of thyroid disease was substantiated by medical records or by contacting the physicians who made the diagnosis. Hashimoto's thyroiditis (HT) was defined by past or present hypothyroidism with elevated TSH levels, high anti-TPO titers, and typical cytologic or histologic findings when available (19). The disease was classified as nonautoimmune hypothyroidism when the cause of hypothyroidism could not be ascertained by past or current history, and when the results of the anti-TPO test at the very onset of thyroid dysfunction were not available.

Laboratory tests. Free T4, free T3, and TSH were measured using third-generation chemiluminometric commercial kits (Ortho Clinical Diagnostics, Raritan, NJ). RF was determined using previously described in-house class-specific enzyme-linked immunosorbent assays (ELISAs) (20); and ANA was assayed by indirect immunofluorescence with HEp-2 cells as substrate. Commercial ELISA kits were used to measure anti-TPO and ATG antibodies (Sanofi Pasteur-Biorad, Paris, France), as well as anti-Ro/SSA and anti-La/SSB antibodies (The Binding Site, Birmingham, UK). HLA typing on peripheral blood lymphocytes was performed by standard serologic techniques (France-Transplant, Paris, France).

Followup study. Of the 137 pSS patients, 127 were reevaluated for thyroid function and antibodies on a regular basis over an average of 6 years (range 1–16 years). Seventy-two sciatica and OA controls were also investigated again, but only once, 3 years after the outset. A particular note of the presence of symptoms and physical signs of hypo- or hyperthyroidism was made in the pSS patients and the controls. Any thyroid dysfunction was recorded when there was clinically overt disease requiring treatment, despite the fact that subclinical hypothyroidism is not exceptional (21). Our approach was justified by the recent report (22) that pSS patients demonstrate elevated levels of basal TSH with evidence of mild hypothyroidism, suggesting a central deficiency in neuroendocrine axes.

Statistics. The data were expressed as arithmetic means $\pm$ standard deviation and the 95% confidence intervals (95% CIs) were calculated. Comparisons were made using the chi-square test with Yates' correction when required, the Fisher exact test, and the Mann-Whitney U test.

RESULTS

Initial findings. When the patients were first referred for assessment of inflammation or dryness (Table 1), clinical evidence for thyroid disease was significantly ($P < 10^{-4}$) more frequent in those with pSS (30/137, 21.8%; 95% CI 14–27) than in the sciatica and OA controls (5/120, 4.2%; 95% CI 2–11). Twenty-one pSS patients had AT (20 cases of HT and 1 case of Graves' disease [GD]) and 9 had

Table 1. Frequency of thyroid disease in patients with primary Sjögren's syndrome (SS) and matched controls at first examination*

Type of thyroid disease	Number positive (%)		*P*
	Primary SS (n = 137)	Controls (n = 120)	
Autoimmune thyroid diseases			
Hashimoto's thyroiditis	20 (14.6)	2 (1.7)	<0.001
Graves' disease	1 (0.7)	0 (0.0)	NS
Total	21 (15.3)	2 (1.7)	<0.001
Nonautoimmune thyroid diseases			
Hypothyroidism	2 (1.5)	1 (0.8)	NS
Thyroid adenoma	6 (4.4)	0 (0.0)	NS
Multinodular goiter	1 (0.7)	3 (2.5)	NS
Total	9 (6.6)	3 (2.5)	NS

* NS = not significant.

nonautoimmune thyroid disease (2 cases of hypothyroidism, 6 of adenoma, and 1 of multinodular goiter). In the control group, 2 presented with HT ($P < 0.01$ compared with the pSS patients), 3 had adenoma, and 1 had hypothyroidism. Forty random patients (54.1 ± 7.8 years) and 40 random controls (52.8 ± 15.9 years) were then selected. There were 9 with HT in the former group, compared with 1 in the latter ($P < 0.01$). In all patients, the thyroid disease antidated the diagnosis of pSS by a mean of 4.5 years (range 3–9 years). The mean age at diagnosis of thyroid dysfunction in the 21 patients with AT was 51.3 years (range 37–67 years). Although sensitive testing was used, no new thyroid disease was detected in patients at the time they were examined for pSS.

Thyroid serologic abnormalities. Fifteen pSS patients (10.9%; 95% CI 6–16) compared with 4 controls (2.9%; 95% CI 2–11) had anti-TPO antibodies only ($P < 0.02$). Of these (Table 2), 6 pSS and 1 OA control had AT. Four pSS patients (2.9%; 95% CI 2–16) compared with 1 OA control (0.8%; 95% CI 2–16) had ATG antibodies only (not significant), but neither group presented with thyroid disease. Twenty pSS patients (14.6%; 95% CI 10–22) compared with 3 controls (2.5%; 95% CI 2–10) had both ($P < 0.001$). Of these, 15 pSS and 1 control had AT. Overall, there were 39 pSS patients with 1 autoantibody or both, compared with 11 controls ($P < 10^{-4}$).

Followup study. Ten of the 107 pSS patients with normal thyroid function at the outset dropped out of the study at followup. All were thyroid-related antibody negative at entry. The remaining 97 pSS patients were reassessed at least once 1 year later (mean followup 5.3 years; range 1–16 years). Fifty-one patients were reexamined at least 5 years later (mean 9.3 years; range 5–16 years). In parallel, 72 of the 120 controls were investigated again 3 years after initial evaluation, on average. Thyroid dysfunction became clinically apparent during followup in 12 patients: HT in 10 (3.3 years after initial evaluation; range 2–8), and GD in the remaining 2 (after 2 and 5 years of followup). One control with OA developed HT during followup. Six of the 40 random patients and none of the 40 random controls developed HT ($P < 0.04$). Of the 10 pSS patients with delayed HT (Table 3), 8 had high titers of anti-TPO antibodies, and 4 also had significant ATG antibody titers when first tested. The remaining 2 had both antibodies, but they were only detected at the second evaluation. The 2 patients with delayed GD had anti-TPO antibodies at first evaluation and 1 also had ATG antibodies. Fine-needle aspiration and thyroid biopsy were not performed during the followup. The predictive values of these autoantibodies are depicted in Table 3. Of the 39 pSS patients with thyroid-related autoantibodies at first evaluation, 21 were afflicted with AT at entry, and another 10 developed these conditions over time.

Table 2. Antithyroid autoantibodies in patients with primary SS and matched controls at first examination*

Individuals	Number positive (%)			
	Anti-TPO only	Anti-TG only	Anti-TPO + anti-TG	Total
Primary SS (n = 137)	15 (10.9)	4 (2.9)	20 (14.6)	39 (28.5)
Controls (n = 120)	4 (3.3)	1 (0.8)	3 (2.5)	8 (6.7)
P	<0.02	NS	<0.001	$<10^{-4}$

* SS = Sjögren's syndrome; TPO = thyroid peroxidase; TG = thyroglobulin; NS = not significant.

Table 3. Predictive value of antithyroid antibody at entry*

Autoantibody at first evaluation	AT disease, n		
	At entry	At followup	No AT
Anti-TPO only, n = 15	6	5	4
Anti-TG only, n = 4	0	0	4
Anti-TPO + anti-TG, n = 20	15	5	0
Total†	21/137	10/97	

* AT = autoimmune thyroid disease; TPO = thyroid peroxidase; TG = thyroglobulin.
† Total number of positive/number tested.

Relationship between pSS and thyroid disease. Clinical and immunologic characteristics of pSS patients were analyzed (Table 4) based on the presence or the absence of thyroid disease on first referral. RF (mainly of the IgA isotype) and anti-Ro/SSA antibodies appeared to be significantly more frequent ($P < 0.03$ and $P < 0.05$, respectively) in pSS patients with overt thyroid disease at entry than in those without. The HLA-DR3 phenotype was more frequent in the former than in the latter group of pSS patients, although it was not significant. It is of considerable interest that, among nonorgan-specific autoantibodies present at first evaluation, anti-Ro/SSA reactivity was found significantly more often ($P < 0.04$) in pSS patients who then developed thyroid dysfunction than in those who did not.

DISCUSSION

The alteration in thyroid function in our patients with pSS, although at a higher level than in earlier studies (8,23), is consistent with an early report by Karsh et al (12) and a recent study by Pérez-E et al (13) who found similar abnormalities in nearly half of their patients at the time they were tested for pSS. These findings are at variance with those of the only controlled study available thus far (19). Ramos-Casals et al (14) found no association between pSS and AT, and thus casted doubt on the relationship between these 2 conditions. However, although our controls without pSS did not have RF, ANA, or anti-Ro/SSA and anti-La/SSB antibodies, the Ramos-Casals controls were selected if they did not have referred clinical manifestations of SS, so that some of them might have been afflicted with asymptomatic pSS (24). This study and ours differ also in that these investigators examined 147 women and 13 men, while we selected only female patients. AT is indeed predominantly a female disease, particularly in pSS. Such an interpretation is supported by the virtual absence of AT in our population of men with pSS who had been excluded from analysis (1 case of HT in 12 individuals). Likewise, the incidence of lymphocytic infiltration in females was 3 times that in males in a postmortem examination of the thyroid gland in 70 patients without overt thyroid disease (25). Another argument for this difference comes from the study of Foster et al (26), which showed a high prevalence of thyroid disease and antithyroid antibodies in female relatives of 42 patients with pSS (13.7% compared with 3.3% in the female controls), but not in their male relatives (1.4% compared with 0.2% in the male controls). Furthermore, due to disease duration at initial evaluation of pSS, delayed AT might have developed over time in the present series of patients.

Discrepancies in the results are also partly accounted for by 2 facts: on the 1 hand, the criteria for diagnosing pSS were markedly varied (15,27,28) from 1 study to another, given that the Copenhagen (11,27), the Fox (28,29), and the European criteria (14,15) have been used; on the other hand, the sensitivity of the thyroid tests has consistently been improved. In our study, particular care was taken to include only patients with definite pSS, but also to determine thyroid function on stored sera using the latest sensitive techniques. To explain the high frequency of thyroid dysfunction at initial evaluation, we cannot formally exclude a Berksonian bias—that is patients seen in a medical center are more likely to have more than 1 disease than community patients (30). This bias is, however, unlikely, because the controls were not normal volunteers but individuals with sciatica or OA, and because the course of thyroid disease and autoimmune traits were characterized over time.

We did not determine the presence of antibodies to T3 and T4 as did Pérez-E et al (13), who showed that such autoantibodies are common and can interfere with radioimmunoassays for T3 and T4 and result in misdiagnosis of thyroid function. This cannot be argued here because thyroid dysfunction was clinically overt, and chemilumines-

Table 4. Clinical and immunologic characteristics of primary Sjögren's syndrome patients when first investigated*

	Thyroid disease present (n = 30)	Thyroid disease absent (n = 107)	*P*
Age, years, mean ± SD	55.2 ± 11.4	59.3 ± 8.3	NS
Disease duration, years, mean ±SD	8.1 ± 5.4	5.7 ± 3.3	NS
Rheumatoid factor, % positive	79	58	<0.03
Antinuclear antibody, % positive	93	86	NS
Anti-Ro/SSA, % positive	75	57	<0.05
Anti-La/SSB, % positive	67	64	NS
HLA-DR3 phenotype, % positive	71	53	NS

* NS = not significant.

cence-based assays were used to measure thyroid parameters.

The present study is 1 of 2 addressing the question of the relevance of serial thyroid antibody determination and thyroid dysfunction in SS patients. However, in the pilot study by Loviselli et al (31), only 16 patients were followed, the survey was rather short (2 years), and there were only 6 patients with pSS in their cohort. Despite the limited size of this group of patients, the authors were able to show that the rate of AT development was higher in pSS than in sSS, indicating that pSS and sSS must be analyzed separately. In this respect, it is noteworthy that pSS and sSS patients were studied together in some reports, but not in others. Davidson et al (32) followed for 10 years 100 patients diagnosed as having SS. At entry to their study, hypothyroidism was noted in 12 patients, and antimicrosomal antibodies were detected in 17. These autoantibodies were found again later and, of the 83 autoantibody-negative patients, only 1 became positive at followup. Of note is that, whereas thyroid function was not evaluated over time in this study, 9 of the pSS patients developed an additional connective tissue disease at the time of the survey.

One study focused on hyperthyroidism (13), which was previously believed to be relatively infrequent in pSS, and found that 2 of their 33 patients presented with hyperthyroidism. Punzi et al (29) and Ramos-Casals et al (14) described hyperthyroidism in 10% and 8% of the pSS patients, respectively. We have also seen patients with hyperthyroidism, of whom the majority had antithyroid antibodies at first evaluation.

In fact, the link between pSS and AT has not been unequivocally substantiated to date. It is, however, relevant that primary biliary cirrhosis is frequently associated not only with pSS, but also with AT in individuals and family members of pSS patients (32,33). A family thyroid history had already been noticed in some pSS patients by Karsh et al (12). Conversely, numerous studies have mentioned a high prevalence of subclinical features of pSS in patients selected as having AT. For example, Coll et al (34) found as high as 24% of the features of SS in a large study of 176 patients with AT. Similarly, Hansen et al (11) reported a log increase in prevalence of pSS in patients with AT, and a 9-time higher prevalence of AT in pSS.

Overlaps between pSS and AT can, at least in part, be explained by common genetic factors, inasmuch as both diseases are associated with HLA-DR3 (35,36). It is interesting that thyroid dysfunction occurs at a higher frequency in patients with SLE than in controls (37) and people with RA (38), although the HLA-DR3 phenotype is associated with the first condition in patients of northern Europe origin (39), but not with the second (40), suggesting a multifactorial susceptibility.

An interesting result emerging from our study is that there were only 4 patients with anti-TPO, only another 4 with ATG, and none with both autoantibodies at first investigation who did not develop AT thereafter. Noteworthy is also that RF and anti-Ro/SSA antibodies were more frequent in patients with thyroid disease when first investigated than in the remainder. Even more important is our finding that those patients prone to develop thyroid dysfunction later could be identified in advance on the basis of their initial RF and anti-Ro/SSA antibody response. Hence, screening for thyroid dysfunction needs to be repeated, at least in patients with pSS, and particularly in those with thyroid-related autoantibodies, or with RF and/or anti-Ro/SSA antibodies at first evaluation.

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