CONCISE REPORT

Autoimmune thyroid disease is associated with a diagnosis of secondary Sjögren's syndrome in familial systemic lupus

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Background: Autoimmune thyroid disease is common in systemic lupus erythematosus (SLE). About 20% of patients with SLE have secondary Sjögren's syndrome.

Methods: Families with more than one patient with SLE were identified. All patients met the revised classification criteria, although SLE-unaffected relatives were confirmed not to satisfy these criteria. Diagnosis of autoimmune thyroid disease and Sjögren's syndrome was made on the basis of a review of medical records, interview and questionnaire administered to patients with SLE, and by a questionnaire administered to SLE-unaffected subjects.

Results: Of a total of 1138 patients with SLE, 169 had a diagnosis of Sjögren's syndrome. Of these 50 (29.6%) patients also had autoimmune thyroid disease. Of the 939 patients with SLE with no diagnosis of Sjögren's syndrome, 119 (12.7%) had autoimmune thyroid disease ($\chi^2=20.1$, $p=0.000009$). There was no association of a diagnosis of hypertension with secondary Sjögren's syndrome (42% vss 47%). Among 2291 SLE-unaffected relatives, 44 had diagnosed primary Sjögren's syndrome and 16 (36.3%) of these also had autoimmune thyroid disease. 265 of 2247 (11.8%) subjects had autoimmune thyroid disease but no Sjögren's syndrome ($\chi^2=24.2$, $p<0.001$).

Conclusions: Autoimmune thyroid disease is found in excess among patients with SLE with a diagnosis of secondary Sjögren's syndrome, as well as among their SLE-unaffected relatives with a diagnosis of primary Sjögren's syndrome.

Human autoimmune disease can be conveniently divided into organ-specific diseases such as type 1 diabetes, thyroid disease, pernicious anaemia and multiple sclerosis, or systemic diseases such as rheumatoid arthritis, scleroderma and systemic lupus erythematosus (SLE). Although organ-specific autoimmune diseases occur in the same individuals more than expected by chance,¹ systemic autoimmune diseases do not usually occur together. The exception is Sjögren's syndrome, which can occur alone as primary disease but which is present in about 20% of persons with another systemic autoimmune disease.² The presence of Sjögren's syndrome with another systemic autoimmune disease is known as secondary Sjögren's syndrome, and is indistinguishable from primary Sjögren's with systemic autoimmunity in the form of anti-Ro (or SSA) and anti-La (or SSB) along with immune attack on the salivary and lacrimal glands leading to severe dry eyes and mouth.

SLE is a chronic, autoimmune, multisystem inflammatory disease that characteristically affects young women. Autoimmune thyroid disease, both hypothyroidism and hyperthyroidism, occurs commonly among patients with SLE.³ However, when compared with a well-matched control population, there is no evidence of an excess of autoimmune thyroid disease among patients with SLE.^{4–5} By contrast, some data indicate that patients

with primary Sjögren's syndrome have more autoimmune thyroid disease than controls,^{6–7} whereas other large studies do not find this association.⁸ One small study of 62 patients with SLE found autoimmune thyroid disease concentrated in those patients with secondary Sjögren's syndrome.^{9–10} We undertook this study to determine the relationship between a diagnosis of secondary Sjögren's syndrome and autoimmune thyroid disease in a large cohort of patients with SLE.

Patients and methods

We identified families with two or more patients with SLE in an effort to locate SLE susceptibility genes. Each putative patient with SLE had all available medical records reviewed, completed an extensive questionnaire relating to SLE manifestations as well as other illnesses, and was interviewed by a physician, physician's assistant or specially trained nurse.¹¹ All subjects classified as SLE met the 1982 revised criteria as amended.^{12–13} Non-SLE-affected relatives completed only the questionnaire. Each patient with SLE was matched for age, sex, ethnicity and location with a normal control. An individual was classified as having Sjögren's syndrome or autoimmune thyroid disease if he or she reported a diagnosis of the disease, or if a diagnosis of the disease was found in medical records. Hypothyroidism, Hashimoto's thyroiditis, Graves' hyperthyroidism and subacute thyroiditis comprised the diagnoses considered as autoimmune thyroid disease. Antibodies binding thyroid peroxidase (TPO) were determined by an ELISA, according to the manufacturer's instructions (AutostatII TPO, Hycor, Garden Grove, California, USA). The Institutional Review Board of both Oklahoma Medical Research Foundation, Oklahoma, USA, and the University of Oklahoma Health Sciences Center, Oklahoma, USA, approved the study.

Results

In all, 1138 patients with SLE were evaluated for the diagnosis of secondary Sjögren's syndrome and autoimmune thyroid disease. A total of 169 (prevalence 14.9%) of these had Sjögren's syndrome, whereas 199 (prevalence 7.8%) had autoimmune thyroid disease (table 1). Among patients diagnosed with Sjögren's syndrome, 50 of 169 (29.6%) patients also had autoimmune thyroid disease, whereas only 149 of the 969 (15.4%) patients with SLE without Sjögren's syndrome had thyroid disease ($\chi^2=20.1$, $p=0.000009$; odds ratio 2.3; 95% confidence interval 1.59 to 3.36). Thus, autoimmune thyroid disease was found significantly more frequently in patients with SLE with a concomitant diagnosis of secondary Sjögren's syndrome (table 1). As a control, we examined the association of hypertension with secondary Sjögren's syndrome and found that 42% of the patients with SLE diagnosed with Sjögren's syndrome also had a diagnosis of high blood pressure documented, whereas 47% of those without Sjögren's syndrome had

Abbreviations: SLE, systemic lupus erythematosus; TPO, thyroid peroxidase

Table 1 Relationship between Sjögren's syndrome and thyroid disease among patients with lupus (n = 1138)

	Autoimmune thyroid disease		
	Present	Absent	Total
Sjögren's syndrome			
Present	50	119	169
Absent	149	820	969
Total	199	939	1138

$\chi^2 = 20.1$, $p < 0.001$; odds ratio 2.3 (95% CI 1.59 to 3.36).

hypertension. Thus, there was no association of a diagnosis of Sjögren's syndrome with hypertension ($p = \text{NS}$ by χ^2 testing).

We also examined the SLE-unaffected relatives of the patients with SLE in these families. Most of these family members were primary relatives (ie, parents or siblings), but some were secondary (ie, aunts, uncles and cousins). In all, 44 non-SLE-affected relatives reported a diagnosis of Sjögren's syndrome (prevalence 1.9%), of whom 16 (36.4%) had been diagnosed with autoimmune thyroid disease. Meanwhile, 265 of 2247 (prevalence 11.8%) SLE-unaffected relatives without Sjögren's syndrome had thyroid disease. Thus, thyroid disease was even more over-represented among the relatives of patients with SLE with primary Sjögren's syndrome (table 2).

A total of 581 unrelated controls were evaluated for Sjögren's syndrome and autoimmune thyroid disease by questionnaire only. In all 49 (7.9%) subjects gave a history of thyroid disease and 5 (0.9%) gave a history of Sjögren's syndrome. No unrelated control had a diagnosis of both conditions.

We have relied above on patient self-identification as having Sjögren's syndrome or on the finding of a diagnosis of Sjögren's syndrome in the medical record. However, definitive documentation that these patients met the combined US-European criteria for classification of Sjögren's syndrome¹⁴ was possible only for <10% of patients. In fact, most of the diagnoses and records were made before the development of these latest criteria. To determine whether our findings are applicable to these present diagnostic standards, we examined a subset of individuals. There were 45 patients with SLE who met the following criteria: complained of dry eyes, complained of dry mouth, woke during the night to drink liquids because of dry mouth, had anti-Ro in their sera by double immunodiffusion, and either stated that they had Sjögren's syndrome or had a diagnosis of Sjögren's syndrome in their medical records. Of these 45 patients, 10 (22.2%) had autoimmune thyroid disease. This rate of thyroid disease was not different from that found in the entire group diagnosed with Sjögren's syndrome and considered above (50/169 vs 10/45, $\chi^2 = 0.95$, $p = \text{NS}$).

We have classified the subjects as having autoimmune thyroid disease according to their medical history given in a questionnaire in the case of the SLE-unaffected relatives and the normal controls, or according to questionnaire, medical records review and interview in case of patients with SLE. To determine whether these individuals had biochemical evidence of autoimmune

thyroid disease, we measured antibodies binding TPO, which is a common autoantigen in all forms of autoimmune thyroid disease.¹⁵ We found a significant difference in anti-TPO titres between patients with SLE who had been classified as autoimmune thyroid disease and patients with SLE classified as not having autoimmune thyroid disease (fig 1). There was no association of anti-TPO with either anti-Ro, which was found in 68% of the patients diagnosed with Sjögren's syndrome, or anti-La, found in 20% of the patients with Sjögren's syndrome.

DISCUSSION

We have found that diagnoses of Sjögren's syndrome and autoimmune thyroid disease are strongly associated in families with SLE. This association was found among patients with SLE with secondary Sjögren's syndrome who had a relative risk for thyroid disease of 2.3. The association was also found among SLE-unaffected relatives of patients with SLE, where the relative risk of autoimmune thyroid disease among the 44 patients diagnosed with primary Sjögren's syndrome was 4. We found no association between the two illnesses in the unrelated control population, although the number of subjects with Sjögren's syndrome was small. It seems likely that these patients with SLE and their SLE-unaffected relatives are especially at risk for the combination of Sjögren's syndrome and autoimmune thyroid disease, probably related in part to their predisposition to SLE.

A number of studies have found no association between primary Sjögren's syndrome and autoimmune thyroid disease^{8, 3}. The largest of these studied 160 patients with Sjögren's syndrome and 75 healthy controls in a cross-sectional design. A total of 36% of the patients with Sjögren's syndrome and 27% of the controls had autoimmune thyroid disease, and this difference was not significant.⁸ Another large study found a significant difference in that 41 (30%) of 137 patients with Sjögren's syndrome had autoimmune thyroid disease whereas only 5 (4%) of 120 controls had the same.⁷ These studies differed in several ways—for example, the second study included only women and the controls were not healthy normals but patients with either sciatica or osteoarthritis. In the first study, the healthy controls were free of symptoms possibly attributable to Sjögren's syndrome,⁸ whereas in the second study, the controls were known to not have antinuclear antibodies, rheumatoid factor, anti-Ro or anti-La.⁷ None of these differences definitely explains the discordant conclusions. However, perhaps the most important difference is the rate of thyroid disease in the controls. In the study of D'Arbonneau *et al*⁷ that finds a difference between subjects with Sjögren's syndrome and controls, a mere 4% of the controls had autoimmune thyroid disease. These controls were women who were age matched to the patients, whose average age was 53.6 years. Thus, this is a strikingly low prevalence of autoimmune thyroid disease in a cohort of older adult women.¹⁶ We wonder whether this report found a low prevalence of thyroid disease in the controls instead of a high prevalence of Sjögren's syndrome.

Many persons may give a history of autoimmune thyroid disease without documented past disease. Thus, the strategy we used to classify subjects as having autoimmune thyroid disease might result in false positives. Subjects identifying themselves as having autoimmune thyroid disease had anti-TPO in their sera at levels higher than those who did not thus identify themselves. There were, of course, several individuals in the autoimmune thyroid disease groups who were negative for the antibodies, but this is the expected outcome as these antibodies may disappear from the serum after many years of disease.¹⁷ Meanwhile, others in the group without clinical thyroid disease were antibody positive, which was again an expected finding.

We have relied on a self-reported diagnosis of Sjögren's syndrome, or this condition given as a diagnosis in the medical

Table 2 Relationship between Sjögren's syndrome and thyroid disease among lupus-unaffected relatives (n = 2291)

	Autoimmune thyroid disease		
	Present	Absent	Total
Sjögren's syndrome			
Present	16	28	44
Absent	265	1982	2247
Total	281	2010	2291

$\chi^2 > 20$, $p < 0.001$; odds ratio 4 (95% CI 2.1 to 7.5).

Figure 1 The titre of anti-thyroid peroxidase (anti-TPO) is given for patients with systemic lupus erythematosus (SLE) classified as having autoimmune thyroid disease (centre, SLE and thyroid disease) on the basis of interview, questionnaire and medical record review, for patients with SLE with no reported autoimmune thyroid disease (right, SLE; no thyroid disease) as well as controls with a history of autoimmune thyroid disease but no SLE (left, thyroid disease; no SLE). The titre of the "SLE and thyroid disease" group was no different from that of the individuals classified as thyroid disease but no SLE (by Student's *t* test, $t = -0.41$, $p = \text{NS}$). The titres of patients with SLE and thyroid disease were, however, statistically different from those found in the sera of the patients with SLE; no thyroid disease ($t = 3.3$, $p = 0.0007$). Likewise, the titres of sera of the patients with thyroid disease were statistically different from those of the patients with SLE with no thyroid disease ($t = 2.05$, $p = 0.025$). A titre < 50 (marked by dark line) is considered normal.

record. In fact, the great majority of those so diagnosed or reporting this diagnosis could not be shown to meet the combined US–European Sjögren's syndrome classification criteria.¹⁴ In practical terms, this means that neither objective testing of tear or saliva production nor salivary gland biopsy was commonly found in the medical record. Patients meeting three criteria (dry eyes, dry mouth and anti-Ro) of four needed for classification had the same rate of thyroid disease as other patients in whom Sjögren's syndrome was diagnosed. Thus, the lack of definitive diagnosis based on the commonly agreed research classification criteria is a weakness of our study. On the other hand, combinations of clinical symptoms such as dry mouth, dry eyes and sore mouth correctly classify $>90\%$ of patients with Sjögren's syndrome and normal controls.¹⁸ Thus, it is highly likely that most of our cohort had the disease.

At least 10 cohorts of patients with SLE have been examined for autoimmune thyroid disease,³ with prevalence ranging from 2.4% to 11.4%. Most of these studies did not include sex- and age-matched controls. We found that the point prevalence of thyroid disease was 7.8% in these patients with SLE, which is higher than in most studies. Our patients were all from families with at least two patients with SLE. Such patients may be at higher risk of other autoimmune diseases than isolated patients with SLE. Furthermore, different ascertainment of thyroid disease from study to study is common.

Autoimmune thyroid disease is common in the general population, especially among women. In fact it is so common that the American College of Physicians recommends a case-finding approach. By this strategy, all women >50 years of age who have not had a thyroid-stimulating hormone measured within 5 years should undergo this test when seeing their healthcare provider, regardless of the reason for the visit.¹⁹ This recommendation was made partly because of the insidious nature of hypothyroidism. This diagnosis may be particularly difficult in patients with SLE in whom the symptoms of hypothyroidism might be attributed to SLE or its treatment. Thus, given the level of thyroid autoimmunity we have found in patients with SLE with secondary Sjögren's syndrome, it seems prudent to screen these patients periodically with a serum thyroid-stimulating hormone. In addition, patients with primary Sjögren's syndrome who have a relative with SLE should also be screened.

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Competing interests: RHS holds multiple patents related to autoimmune disease, none licensed and none under consideration for licensing. He receives research funding from the USA National Institutes of Health, the US Department of Veterans Affairs and the Oklahoma Center for the Advancement of Science and Technology. JBH is a Mary Kirkland Scholar. He holds multiple patents related to autoimmune disease. He is on the Board of Directors and holds options for IVAX Diagnostics. He is an Officer, on the Board of Directors and holds equity in JK Autoimmunity. He is funded by USA National Institutes of Health, the Alliance for Lupus Research, Mary Kirkland Fellowship and US Department of Veterans Affairs.

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