Thyroid Abnormalities in Systemic Lupus Erythematosus: a Study in 100 Brazilian Patients

Alterações Tireoideanas no Lúpus Eritematoso Sistêmico: um Estudo em 100 Pacientes Brasileiros

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ABSTRACT

Introduction: *the association of thyroid abnormalities with systemic lupus erythematosus (SLE) is not well established.* ***Objective:*** *to study the prevalence of thyroid dysfunction in hundred lupus patients and evaluate a possible association between thyroid dysfunction and SLE disease activity.* ***Methods:*** *a total of one hundred patients with SLE underwent assessment for clinical and laboratorial thyroid abnormalities. Clinical activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI).* ***Results:*** *seventeen patients (17%) had abnormal thyroid function by laboratory testing, which included ten patients (10%) with subclinical hypothyroidism, two patients (2%) with subclinical hyperthyroidism, four patients (4%) with primary hypothyroidism and one patient with serum thyroxine below the normal range. Regarding antithyroid antibodies, six patients were positive, as follows: four (4%) for antiperoxidase, one (1%) for antithyroglobulin and one (1%) for both antibodies. SLE disease activity was not significantly different between groups, regardless of the presence of thyroid dysfunction.* ***Conclusion:*** *these results show that thyroid abnormalities are frequently found in SLE patients. However, it does not appear to be an association between thyroid abnormalities and SLE clinical disease activity.*

Keywords: *systemic lupus erythematosus, autoimmunity, autoimmune thyroiditis, hypothyroidism, hyperthyroidism.*

RESUMO

Introdução: a associação entre alterações tireoideanas e o lúpus eritematoso sistêmico (LES) não está bem esclarecida. **Objetivo:** estudar a prevalência de disfunção tireoideana em 100 pacientes lúpicos brasileiros e avaliar uma possível relação com a atividade da doença. **Métodos:** cem pacientes com LES foram avaliados em busca de alterações clínicas e laboratoriais relacionadas à função tireoideana. Para atividade do LES foi utilizada a escala *Systemic Lupus Erythematosus Disease Activity Index* (SLEDAI). **Resultados:** 17 pacientes (17%) apresentaram alterações da função tireoideana que incluíram dez casos (10%) de hipotireoidismo subclínico, dois casos (2%) de hipertireoidismo subclínico, quatro pacientes (4%) com hipotireoidismo primário e um paciente com tiroxina sérica abaixo do normal. Em seis pacientes, os anticorpos contra tireóide foram positivos: quatro (4%) para antiperoxidase, um (1%) para antitireoglobulina e um (1%) para ambos. A atividade do LES não foi significantemente diferente entre os grupos com e sem alterações tireoideanas. **Conclusão:** esses resultados mostram que alterações tireoideanas são freqüentemente encontradas em pacientes lúpicos. Entretanto, não parece haver associação entre alterações tireoideanas e atividade clínica do LES.

Palavras-chave: lúpus eritematoso sistêmico, auto-imunidade, tireoidite auto-imune, hipotireoidismo, hipertireoidismo.

INTRODUCTION

Autoimmune diseases are related to genetic, hormonal and environmental factors. They can be systemic or organ specific and even coexist in the same individual. The association between systemic lupus erythematosus (SLE) and thyroid abnormalities was first described in 1961 by White et al[1] and Hijmans et al[2], who showed that the presence of thyroid disturbance appeared to be more frequent in SLE patients than in the general population. However, divergences still exist in relation to prevalence[3-7, 8]. Furthermore, antiperoxidase and antithyroglobulin antibodies have been frequently found in SLE patients when compared to control groups[9, 10], as well as in the general population[3, 8]. There are still questions about the frequency of this association, its association SLE disease activity and the role of antithyroid antibodies. Besides, it is not known whether corticosteroid therapy and immunosuppressant used in the treatment of SLE

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can influence the incidence and evolution of thyroid disturbance. The objective of this study is to describe the prevalence of clinical and laboratory abnormalities associated to the thyroid in a population of one-hundred Brazilian patients with a diagnosis of SLE, and a possible association between these factors and the activity of the disease.

PATIENTS AND METHODS

According to the American College of Rheumatology[11], all of the one hundred patients selected for the study fulfilled the criteria for classification as SLE. In addition, they had no previous diagnosis of thyroid dysfunction and were not pregnant. All patients were attende to the Rheumatology Unity of Hospital das Clínicas of Universidade Federal de Minas Gerais (UFMG), *as outpatients were evaluated from January to December, 1999. Their average age was 34.2 years (range from 15 to 73) and the average duration of the disease was 6.1 years (range from 0.1 to 22 years). Ninety three patients (93%) were female, 69 (69%) were mixed race, nineteen were Caucasians (19%) and twelve (12%) were negroids. All patients gave written informed consent for their participation in the study. All patients were evaluated by the same investigator (AMK), who is responsible for both clinical evaluation for thyroid disfunction as well as SLE disease activity, and for providing the collection of serum samples for laboratory testing. The activity of SLE was evaluated using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)[12]. The dosages of thyroid stimulating hormone (ultra-sensitive TSH), free thyroxine (fT4), triiodothyronine (T3), and the study of antiperoxidase and antithyroglobulin antibodies were undertaken using chemiluminescence assays purchased from Diagnostic Products Corporation, Los Angeles, CA (DPC).*

The Student's "t" test, working at the 95% confidence level, was used for the statistical analysis of significance.

RESULTS

Among hundred patients, seventy six (76%) had clinical signs or symptoms that could suggest thyroid dysfunction. The most common symptoms included: emotional instability in thirty (39.5%), anxiety in twenty eight (36.8%), weight loss and increased appetite in twelve (15.8%), fatigue and disability in twenty seven (35.5%), sleep disturbances in twenty one (27.6%), and menstrual disturbances in eighteen (23.7%) patients. Four patients had an enlarged thyroid, estimated to be approximately twice than their normal size (based on clinical examination), and in only one case laboratory changes were compatible with subclinical hypothyroidism. Regarding SLE, the clinical characteristics included, thirty five (35%) presenting with nephritis, seven (7%) had central nervous system involvement and eleven patients (11%) had cutaneous vasculitis. All patients were on pharmacological treatment that included: prednisolone in ninety three patients (93%), antimalarials in fourty-six (46%), pulse cyclophosphamide in twentyseven (27%), azathioprine in fourteen (14%), and thalidomide in two (2%). The average dose of prednisolone was 21.2 mg/d. Other medications in use included: phenytoin, methyldopa, nifedipine, enalapril, hydrochlorothiazide, furosemide, sodium warfarin and acetylsalicylic acid.

The thyroid function alterations tests were present in seventeen patients (17%), all of them were female. Isolated high level of TSH was the most frequently found abnormality, that was present in ten patients (10%). Four patients (4%) had a laboratory diagnosis of primary hypothyroidism. In two patients (2%), the level of TSH was low with fT4 and T3 normal; in one of the patients (1%) the fT4 was below normal. Four patients with primary hypothyroidism comprised 5.3% of the total of seventy six patients with clinical signs and symptoms. The patients were distributed into 5 groups according to the laboratory test results: group 1 - TSH/fT4 normal; group 2 - TSH elevated/ fT4 normal (subclinical hypothyroidism); group 3 - TSH elevated/fT4 reduced (primary hypothyroidism); group 4 - TSH reduced/fT4 normal (subclinical hyperthyroidism) and group 5 - fT4 reduced/TSH normal (Table 1). Table 2 illustrates the clinical and laboratory characteristics of patients with altered thyroid function (Table 2).

Antithyroid antibodies were positive in six patients (6%), four of them (4%) were positive only for antiperoxidase

TABLE 1
DISTRIBUTION OF THYROID FUNCTION TESTS FOR 100 PATIENTS WITH SLE

Groups	fT4	TSH	N° of patients n=100 (%)
1	Normal	Normal	83 (83%)
2	Normal	Increased	10 (10%)
3	Reduced	Increased	4 (4%)
4	Normal	Reduced	2 (2%)
5	Reduced	Normal	1 (1%)

fT4, free thyroxin; TSH, thyroid stimulating hormone.

TABLE 2
CLINICAL AND LABORATORY RESULTS OF LUPUS PATIENTS WITH THYROID DYSFUNCTION

Number of series	Age (years)	Sex	Duration of illness (years)	fT4 (ng/dL)	TSH (µUI/ml)	ATPO (<1/100)	ATA (<1/100)	Clinical signs and symptoms
Subclinical hypothyroidism								
6	28	F	6	0.99	9.5	Neg	Neg	Increased appetite, emotional swings, menstrual disturbance, weight gain
21	31	F	1	1.5	11.5	Neg	Neg	Palpitations, muscular weakness, depression, cold intolerance
25	73	F	12	0.95	11.7	Neg	Neg	Absent
27	47	F	18	1.2	6.3	Neg	Neg	Weight loss, drowsiness, anxiety
31	26	F	7	1.3	7.59	Neg	Neg	Absent
33	38	F	17	1.2	5.2	Neg	Neg	Anxiety, emotional swings, muscular weakness and depression
51	39	F	15	0.95	5.9	Neg	Neg	Anxiety, heavy periods, drowsiness
52	53	F	3	1.2	5.5	Neg	Neg	Anxiety, appetite loss
70	23	F	4	0.86	5.8	Neg	Neg	Weight loss, hoarseness, muscular weakness, dejection
75	60	F	12	1.2	5.51	Neg	Neg	Weight gain, appetite loss
Hypothyroidism								
16	36	F	5	0.65	7.33	Neg	Neg	Weight gain
17	33	F	16	0.57	8.15	Neg	Neg	Anxiety, emotional swings, weight gain, muscular weakness and dejection
20	31	F	3	0.71	5.2	Pos	Neg	Anxiety, emotional swings, cold intolerance, weight gain, menstrual disturbance
89	17	M	1	<0.31	39.5	Neg	Neg	Weight loss, muscular weakness, dejection, appetite loss
Subclinical hyperthyroidism								
19	48	F	1	1.7	0.012	Neg	Neg	Anxiety, weight loss and appetite loss, menstrual disturbances
55	37	F	10	1.2	0.2	Neg	Neg	
T4Llow								
48	35	F	11	0.5	1.24	Neg	Neg	Muscular weakness, dejection, hot flushes, weight gain, constipation

Abbreviations: fT4, free thyroxin; TSH, thyroid stimulating hormone; ATPO, antiperoxidase antibody; ATA, antithyroglobulin antibody; Neg, negative; Pos, positive.

antibody, one of them (1%) was positive for antithyroglobulin antibody and one of them (1%) was positive for both antibodies (Table 3). Laboratory alterations were also found compatible with primary hypothyroidism, in one patient, who was positive for antiperoxidase antibodies.

None of the six male patients showed abnormalities in the thyroid function tests or the presence of antithyroid antibodies.

The average of SLEDAI was 5.26 (SD 6.05) in patients with normal thyroid function, and 7.44 (SD 7.75) in patients with abnormalities. The difference between the values of SLEDAI was not statistically significant, regardless of the presence of thyroid abnormalities ($p>0.05$).

DISCUSSION

Autoimmune diseases can occur concomitantly in the same patient in various forms of association. In 1956,

Table 3
Distribution of anti thyroid autoantibodies in six patients with SLE and their respective thyroid function

Number of series	ATPO*	ATA**	Thyroid function
12	Positive	Negative	Normal
15	Positive	Positive	Normal
20	Positive	Negative	Hypothyroidism
29	Negative	Positive	Normal
46	Positive	Negative	Normal
62	Positive	Negative	Normal

** ATPO, antiperoxidase antibody.*
*** ATA, antithyroglobulin antibody.*

Roitt et al[13] described three patients with rheumatoid arthritis and Hashimoto's thyroiditis. In 1961, the first cases of SLE and Hashimoto's thyroiditis were reported[1, 2]. Since these initial studies, the association of systemic and organ specific autoimmune diseases has been investigated. Although the presence of autoimmune thyroid alterations occurs more frequently in SLE patients than in the general population, this subject is still a matter of controversy.

A previous study, by Miller et al[6], evaluating 332 lupus patients showed thyroid dysfunction in 7.5% of them, with a presence of hypothyroidism in 6.6%. In a series of studies published by Tsai et al[8], the incidence of hypothyroidism was 8.8%. In the present study, we found a prevalence of 4%. On the other hand, in a retrospective study of Asian SLE patients shown by Goh et al[5], more thyrotoxicosis (2.8%) was found than hypothyroidism (0.9%) or thyroiditis (0.6%). Although the results of these studies show discrepancies in relation to the thyroid dysfunction types more commonly encountered, there is evidence of a higher probability of lupus patients developing autoimmune changes of this gland, as compared to the general population, where the incidence of hypothyroidism is estimated to be of 1%[14]. It is of interest to note that in the majority of the studies the analysis concerning the presence of thyroid dysfunction was made by cross-sectional observation rather than by prospective methods[5, 6, 8-10].

In agreement with other studies[6, 15, 16], subclinical hypothyroidism and primary hypothyroidism were the most common alterations among our patients (4% and 10%, respectively); however, in patient was the diagnosis of primary hyperthyroidism been made. Two patients did show alterations consistent with subclinical hyperthyroidism, characterized by the low levels of TSH in the absence of antithyroid autoantibodies and, in this situation, there is controversy about the clinical evolution of the disease[17]. Since the prevalence of hyperthyroidism in the general population is estimated at 1.9%, it is probable that the presence of SLE does not predispose patients to this endocrine disorder. Supporting this conclusion it is the fact that the association between SLE and Graves' disease has rarely been described[18,19].

In our study, six patients (6%) were positive for antibodies against the thyroid, however, in only one patient was the diagnosis of primary hypothyroidism made. An incidence of 43% of positivity for autoantibodies against the thyroid has been described in children with lupus [20], while in the studies of Kausman et al[21] and Magaro et al[22] a positivity of21% and 45.5% was described, respectively. It is not known if the drugs used in the treatment of SLE can inhibit the production of these antibodies.

The details of the main studies about thyroid function in patients with lupus are summarized in Table 4.

Table 4
Studies of thyroid function and the presence of auto-antibodies in patients with SLE (%)

Parameters	Goh 1986[5]	Miller 1987[6]	Tsai 1993[8]	Park 1995[15]	Pyne 2002[16]	Present study
Number of cases	319	332	45	63	300	100
Primary hypothyroidism	0.94	6.6	8.8	9.5	5.7	4
Subclinical hypothyroidism	0	39**	ND	1.6	ND	10
Hyperthyroidism	2.82	3	ND	3	1.7	0
FT4 low	ND	ND	ND	ND	ND	1
Subclinical hyperthyroidism	ND	ND	ND	ND	ND	2
Anti-thyroid antibodies	ND*	20**	46.7	27	14	6

** ND, no available data.*
*** Research undertaken with 175 patients.*

In seventy six percent of patients in our study, clinical manifestations that could suggest thyroid disease were present; and in 5.3%, a diagnosis of primary hypothyroidism was made. A great variety of symptoms and signs are possible manifestations that could be described as thyroid dysfunction or could be exclusively related to lupus. It is interesting to note that rheumatic manifestations are also frequently found in thyroid disease, even in euthyroid patients, suggesting the possible role of the underlining autoimmune imbalance[23, 24].

SLEDAI used in the present study did not show

statistically significant differences between the groups with or without abnormalities in thyroid function. Similar data were reported in the study by Park et al[15] which used the European Consensus Lupus Activity Measurement (ECLAM), where it was suggested that the course of the two diseases, although interlinked, may be independent.

The study of thyroid function in patients with SLE comes up against some factors of interference, such as, the state of lupus activity, the age of patients and the use of immunosuppressive drugs. Furthermore, the absence of a control group in this study does not permit the categorical assumption of a link between these two diseases.

However, it is worth emphasizing that individuals with SLE frequently have abnormal results in one or more thyroid function tests, as well as positivity for autoantibodies against the thyroid. In this sample, the frequency of these findings was 17% and 6%, respectively. Subclinical hypothyroidism was the most common diagnosis (10%) and there was no association between the presence of thyroid dysfunction and the level of SLE activity.

The results of this study suggest that SLE patients appear to be more prone to develope hypothyroidism, as compared to the general population. This should be taken into consideration when evaluating these patients.

Declaramos a inexistência de conflitos de interesse.

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