Abnormal Thyroid Function Test Results in Systemic Lupus Erythematosus

Süleyman Büyükberber MD[1] , Orhan Şencan MD[1], Nuhmehmet Büyükberber MD[2] , Erbil Başeşme MD[3] , Murat Turgay MD[4]

Thyroid function tests and anti-microsomal antibody (anti-M) levels of 33 patients (30 female, 3 male) with systemic lupus erythematosus (SLE) and 16 healthy subjects (15 female, 1 male) were studied as control group. Anti-M was positive in 3 of 33 patients with SLE and in 1 of 16 control subjects, and there were no statistically significant differences between two groups. There were hypothyroidism in 4 of SLE patients and all of the control subjects were euthyroid. Hypothyroidism rate in SLE patient was significantly higher when compared to the control group. Total and free T3 levels and total and free T4 levels of SLE patients group were significantly lower and TSH levels were significantly higher when compared to the control group. In conclusion, hypothyroidism and "euthyroid sick syndrome" (ESS) incidence were high in patients with SLE, when compared to the control group. Although there was no statistically significant difference for anti-M positivity in 3 of 4 patients with hypothyroidism suggests that autoimmune thyroid disease is a frequent finding in SLE patients. [Journal of Turgut Özal Medical Center 1996;3(2):80-84]

Key Words: *Systemic lupus erythematosus, thyroid function tests*

Sistemik lupus eritematozusda anormal tiroid fonksiyon testi sonuçları

Sistemik lupus eritematozuslu (SLE) 33 hasta (30 kadın, 3 erkek) ve kontrol grubu olarak 16 sağlıklı bireyin (15 kadın, 1 erkek) tiroid fonksiyon testleri ve anti-mikrozomal antikor (anti-M) düzeyleri çalışıldı. SLE'li 33 hastanın 3'ünde ve 16 kontrol bireyinin 1'inde anti-M pozitifti ve iki grup arasında istatistiksel yönden fark yoktu. SLE'li hastaların 4'ünde hipotiroidi bulunurken, kontrol grubundakilerin tümü de ötiroiddi. SLE''li hastalardaki hipotiroidi oranı kontrol grubuna göre anlamlı şekilde daha yüksekti. SLE'li hastalardaki total ve serbest T3 ve total ve serbest T4 düzeyleri kontrol grubu ile karşılaştırıldığında anlamlı olarak daha düşük, TSH düzeyi ise daha yüksekti. Sonuç olarak, SLE'li hastalarda kontrol grubu ile karşılaştırıldığında, hipotiridi ve "ötiroid sick sendromu" (ESS) insidansı daha yüksekti. Hipotiroidili 4 hastanın 3'ünde bulunan anti-M pozitifliği istatistiksel olarak anlamlı olmasa da, SLE'li hastalarda otoimmün tiroid hastalığının sık görüldüğünü düşündürmektedir. [Turgut Özal Tıp Merkezi Dergisi 1996;3(2):80-84]

Anahtar Kelimeler: *Sistemik lupus eritematozus, tiroid fonksiyon testleri*

Thyroid disease has been recognized with many connective tissue disorders, including Sjögren's syndrome, rheumatoid arthritis, progressive systemic sclerosis, and other autoimmune conditions (1-13). In patients with systemic lupus erythematosus (SLE), the reported incidence of thyroid abnormalities varies between 7.5% and 24% (14,15). The majority of these patients have

[1] İnönü University School of Medicine, Department of Internal Medicine, Malatya
[2] Erciyes University School of Medicine, Department of Internal Medicine, Kayseri
[3] Ankara University School of Medicine, Department of Internal Medicine, Ankara
[4] Ankara University School of Medicine, Department of Immunology, Ankara

hypothyroidism associated with circulating antithyroid antibodies. However, there are several reports on the association between hyperthyroidism and SLE.

PATIENTS AND METHODS

Patients: All patients eligible for the study had been hospitalized between 1990 and 1994 and had been diagnosed as having SLE according to American Rheumatism Association criteria (16).

We studied 33 patients (30 female, 3 male, mean age 32±14.2) with SLE. None of the patients had a history or clinical diagnosis of thyroid disease. Thyroid function tests and anti-M levels of 16 healthy subjects (15 female, 1 male, mean age 28±6.4) were also studied as control group.

Thyroid function test results, the anti-M levels, thyroid disease types and the drugs used, which may interfere these results are given in Table 1. The results of the control group are shown in Table 2.

Methods: Laboratory and immunologic tests were performed according to standart methods. Serum total and free thyroid hormone (T3 and T4), serum thyroid stimulating hormone (TSH), and anti-M are measured by radioimmunoassay (RIA).

Chi-square and Mann Whitney U tests were used for statistical analysis.

RESULTS

We studied thyroid function tests and anti-M positivity in the patients with SLE and compared with the results of the control group.

Anti-M was positive in 3 of 33 patients with SLE as compared with 1 in 16 control subjects, and there was no statistical difference between two

Table 1: Serum thyroid hormone and anti-M levels, types of the diagnosed thyroid diseases of the patients with SLE, and the drugs used by the patients*

No	TT3	TT4	fT3	fT4	TSH	Anti-M	Diagnosis	Drug
1	0.7	8.4	2.5	9.0	6.3	1125	Hypothyroidism	GK+NSAID
2	0.7	8.6	3.6	11.3	5.8	1451	Hypothyroidism	-
3	0.18	3.4	1.6	4.3	15.3	2040	Hypothyroidism	-
4	0.18	3.4	1.8	9.4	6.1	(-)	Hypothyroidism	-
5	0.7	6.5	1.8	14.2	0.95	(-)	ESS	GK+Cyc
6	0.56	6.0	3.5	9.6	0.6	(-)	ESS	GK
7	0.9	6.6	2.9	13.6	2.6	(-)	ESS	GK+Cyc
8	0.43	3.2	2.3	19.6	0.32	(-)	ESS	GK
9	0.59	12.3	2.4	23.1	0.7	(-)	ESS	GK
10	0.62	16.8	1.1	16.4	1.7	(-)	ESS	GK
11	1.5	10.4	5.8	18.6	0.51	(-)	ESS	GK+Cyc
12	0.24	12.3	2.5	23.9	0.6	(-)	ESS	GK
13	0.59	6.1	2.4	10.2	3.7	(-)	ESS	GK
14	0.49	4.6	4.6	12.4	0.7	(-)	ESS	GK
15	0.18	3.4	1.8	9.2	0.47	(-)	ESS	GK
16	0.63	6.7	3.0	9.6	1.7	(-)	ESS	GK
17	0.7	7.9	5.7	13.0	0.9	(-)	ESS	GK
18	0.68	5.5	3.8	10.8	1.2	(-)	ESS	GK
19	0.7	7.4	3.3	18.0	0.52	(-)	ESS	GK
20	0.7	4.6	1.3	7.6	1.2	(-)	ESS	GK
21	0.68	5.6	3.8	10.8	1.4	(-)	ESS	GK
22	0.7	5.5	3.3	12.5	2.5	(-)	ESS	GK
23	0.6	5.4	1.3	9.7	1.1	(-)	ESS	GK
24	0.53	5.1	4.8	12.4	0.47	(-)	ESS	GK
25	1.0	6.8	3.1	10.9	1.7	(-)	-	GK
26	1.3	7.9	5.4	17.0	0.97	(-)	-	GK
27	1.1	5.7	3.4	17.9	0.97	(-)	-	GK
28	1.1	6.2	4.5	10.2	1.7	(-)	-	GK
29	0.43	7.3	2.8	15.6	2.1	(-)	-	GK+Cyc
30	1.1	5.7	5.2	16.4	0.96	(-)	-	GK
32	0.89	16	5.1	13.9	1.5	(-)	-	GK
33	1.5	8.0	7.0	15.0	2.1	(-)	-	GK

* TT3: Total T3, TT4: Total T4, fT3: Free T3, fT4: Free T4, TSH: Thyroid Stimulating Hormone, Anti-M: Anti Microsomal Antibody, ESS: Euthyroid Sick Syndrome, GK: Glucocorticoid drugs, Cyc: Cyclophosphamid

groups (p>0.005). There was clinical hypothyroidism in one of the patients and anti-M level of this patient was 2040. TSH levels of 2 patients, with anti-M levels of 1451 and 1125, were 6.3 and 5.8 μu/ml respectively, and these findings were consistent with subclinical hypothyroidism. In another words Anti-M was positive in 3 of 4 hypothyroidic patients in varying levels.

While all of the subjects from control group were euthyroid, anti-M was positive in 1 subject. The hypothyroidism rate in SLE patients was significantly higher when compared to control group.

There was grade II thyroid gland enlargement in 2 of the 4 patients with high anti-M levels, grade I thyroid enlargement in 4 of the euthyroid patients, and there was a hypoactive thyroid nodule in 1 of the euthyroid patients. In control group, there was a grade II thyroid enlargement only in the anti-M positive subject.

Total T3 levels of 23 patients with SLE were below or at the lower limit of the normal (normal levels: 0.7-2.6 ng/ml) (Table 1). In control group, total T3 level of one subject was 0.7 ng/ml. Total T3 levels of the SLE patients group were significantly lower when compared to control group (p<0.05).

Total T4 levels of 4 patients were below and 1 patient's was above the normal range (normal: 4.5-13.0 μg/dl). Total T4 levels of all the subjects in control group were in normal range. This total T4 deficiency in the SLE patients group was also statistically significant (p<0.05). (Table 1).

Free T3 levels of 12 patients with SLE (36.3%) were at the lower limit of normal or below the normal range (normal: 2.5-8.5 pmol/l). Free T3 levels were significantly depressed in 3 of the 4 clinical hypothyroidic patients (p<0.05). Free T3 levels were within the normal limits in all subjects of the control group (Table 2).

Free T4 levels were low only 5 of the 33 patients (normal: 9.4-25.0 pmol/l) and 4 of the 5 patients with low free T4 had clinical hypothyroidism. Free T4 levels of all the control group were within normal limits and this deficiency in patients group was statistically significant (p<0.05).

TSH levels were above normal in 4 patients and these patients were diagnosed as having hypothyroidism. In control group, TSH levels of all subjects were within normal limits (normal: 0.25-4.3 μu/ml) (p<0.05).

DISCUSSION

While some studies have indicated that, as with other autoimmune diseases, autoimmune thyroid disease incidence is higher in SLE, some other studies have not. (14,15,17-19)

In this prospective study, there were clinical hypothyroidism in 1 patient, subclinical hypothyroidism in 3 patients, and 4 of 33 patients

Table 2: Serum thyroid hormone and anti-M levels of control group*

No	TT3	TT4	fT3	fT4	TSH	Anti-M	Diagnosis	Drugs
1	1.6	8.9	7.1	20.8	0.7	451	H. Thyroiditis	(-)
2	1.7	12.0	7.4	15.6	1.0	(-)	Normal	(-)
3	1.1	7.9	6.5	14.8	0.6	(-)	Normal	(-)
4	1.5	10.2	5.6	14.6	0.9	(-)	Normal	(-)
5	1.3	8.2	6.5	18.7	0.9	(-)	Normal	(-)
6	1.4	8.1	6.0	19.0	1.9	(-)	Normal	(-)
7	0.9	10.6	5.0	21.0	1.9	(-)	Normal	(-)
8	1.2	8.0	6.0	18.3	0.8	(-)	Normal	(-)
9	1.5	7.6	6.2	17.8	0.8	(-)	Normal	(-)
10	1.2	8.9	4.9	18.3	1.5	(-)	Normal	(-)
11	1.6	12.0	7.2	23.2	0.8	(-)	Normal	(-)
12	1.7	12.0	7.2	23.2	0.8	(-)	Normal	(-)
13	0.9	6.1	4.9	20.7	2.4	(-)	Normal	(-)
14	0.9	8.8	5.4	20.9	0.7	(-)	Normal	(-)
15	1.6	12.2	7.0	21.2	0.8	(-)	Normal	(-)
16	1.4	8.1	6.0	19.0	1.9	(-)	Normal	(-)

*TT3: Total T3, TT4: Total T4, fT3: Free T3, fT4: Free T4, TSH: Thyroid Stimulating Hormone, Anti-M: Antimicrosomal Antibody, H. Thyroiditis: Hashimato Thyroiditis

with SLE (12.2%). This hypothyroidism rate was statistically significant when compared to the control group ($p<0.05$). These findings are in correlation with other studies in the literature. Weetman and Walport reported a 24% subclinical hypothyroidism rate (15). Gordon and Isenberg reported a 10% subclinical hypothyroidism rate, and Miller et. al. reported a 10% subclinical and clinical hypothyroidism rate (14, 20).

Although there is no statistical difference between SLE and control groups for anti-M positivity, the finding of hypothyroidism in 3 patients with high anti-M levels suggests that autoimmune diseases may be a frequent finding in SLE patients.

The low levels of total T3 and free T3 in patients group may be the most important finding in this study. This condition is called as "euthyroid sick syndrome" (ESS) and characterized by by low levels of T3 and T4, which is not in correlation with TSH increase and without any clinical primary thyroid disease but a systemic disease. The incidence of ESS was reported between 40-70% in various conditions (21). The most frequent abnormal thyroid function test finding in ESS is low levels of T3. Although total T3 levels of 23 of 33 patients were at the lower limit or below the normal in this study. TSH levels were high only in 4 patients and these patients had clinical hypothyroidism. There were ESS in remaining 19 cases (57% of patients with SLE). Also free T3 levels were below normal limits in 12 patients. Four of them were with clinical hypothyroidism and TSH levels were normal in remaining 8 patients. There was no significant decrease in total and free T4 levels.

The drugs used in SLE, such as glucocorticoids, nonsteroidal antiinflammatory drugs, diuretics, phenytoin and chloroquin; may cause low total and free T3 and also low TSH levels (22). Thirty of 33

patients (90.9%) were using glucocorticoids. Glucocorticoids acutely inhibits TSH secretion, especially in stress doses, and decreases serum TBG concentrations. They also inhibit convertion of T4 to T3, and while causing low or very low TSH and T3 levels, total and free T4 slightly decrease. Even in primary hypothyroidism patients, TSH levels may remain in normal range. As a result of these changes, the actual hypothyroidism rate may be higher than we found.

SLE and autoimmune thyroid disease are at the two endpoints of a shared immunogenetic mechanism. It has been shown that there are shared HLA types in autoimmune thyroid disease and SLE. While HLA-A1, -B8 and -DR4 are frequently found in patients with SLE. HLA-DR3 and -B8 are found in autoimmune atrophic thyroiditis (14,21,23,24).

As a result, hypothyroidism incidence was found high or in patients with SLE, when compared to control group. Although there was no statistical difference for anti-M positivity between SLE patients and the control group, the high incidence of hypothyroidism suggests that autoimmune thyroid diseases are a frequent finding in SLE patients.

REFERENCES

1. Kyle V, Hazleman BL. The thyroid. Clin Rheum Dis. 1981; 7:711-22.
2. Karsh C, Pavlidis N, Weintraub BD, Moutsopoulos HM. Thyroid disaese in Sjögren's syndrome. Arthritis Rheum 1980; 23:1326-9.
3. Jonsson H, Nived O, Sturfelt G. Thyroid disorders in systemic lupus erythematosus are associated with secondary Sjögren's syndrome (letter). Ann Rheum Dis 1987; 46:349.
4. Jonsson H, Nived O, Sturfelt G.Symptomatic secondary Sjögren's syndrome in patients with systemic lupus erthematosus. Scand J Rheumatol (Suppl) 1986; 61:166-9.
5. Buchanan WW, Crooks J, Alexander WD, Koutras DA, Wayne EJ, Gray KG. Association of Hashimoto's thyoiditis and rheumatoid arthritis. Lancet 1961; 1:245-8.
6. Thomas DJB, Young A, Gorsuch AN, Bottazzo GF, Cudworth AG. Evidence for an assocition between rheumatoid arthritis and autoimmune endocrine disease. Ann Rheum Dis 1983; 42:297-300.
7. Wahlberg P, Nyman D, Carlsson SA. 25 year follow-uo the Aland thyroid study of 1956. Thyroid status and incidence of rheumatoid arthritis. Acta Endocrinol (Kopenh) (suppl) 1983; 251:47-52.
8. Gordon MD, Klein I, Dekker A, Rodnan GP, Medsger KA. Thyroid disease in progressive systemic sclerosis: Increased frequency of glandular fibrosis an hypothyroidism. Ann Intern Med 1981;95:431-5.
9. Withrington RH, Seifert MH. Hypothyroidism associated with mixed connective tissue disease and its response to steroid therapy. Ann Rheum Dis 1981; 40:315-6.

10. Vierhapper H, Grubeck-Loebenstein B, Ferenci P, Lochs H, Bratusch-Marrain P, Waldhausl W. Alterations in thyroxine metabolism in Crohn's diease. Hepatogastroenterology 1981; 28:31-3.
11. Gray RS, Borsey DQ, Seth J, Herd R, Brown NS, Clarke BF. Prevalance of subclinical thyroid failure in insulin-dependent diabetes. J Clin Endocrinol Metab 1980; 50:1034-7.
12. Carmel R, Spencer CA. Clinical and subclinical thyroid disorders associated with pernicious anemia. Arch Intern Med 1982; 142:1465-9.
13. LeRiche NGH, Bell DA. Hashimoto's thyroiditis and polyarteritis. Ann Rheum Dis 1982; 43:594-8.
14. Miller FW, Moor GF, Weintraub BD, Steinberg AD. Prevalance of thyroid disease and abnormal thyroid function test results in patients with systemic lupus erythematosus. Arthritis Rheum 1987; 30:1124-31.
15. Weetman AP, Walport NJ. The association of autoimmune thyroiditis with systemic lupus erythematosus. Br Med Rheum 1987; 26:359-61.
16. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield N, Schaller JG, Tatal N, Winchester RJ. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982; 25:1271-7.
17. Goh KL, Wang F. Thyroid disorders in systemic lupus erythematosus. Ann Rheum Dis 1986; 45:579-83.
18. Mulhern LM, Masi AT, Schulman LE. Hashimoto's disease: A search for associated disorders in 170 clinically detected cases. Lancet 1961; I:269-73.
19. Doniach D, Nilsson LR, Roitt IM. Autoimmune thyroiditis in children and adolescents. II. Immunological correlations and parents study. Acta Paediatr Scand 1965; 54:260-74.
20. Gordon T, Isenberg D. The endocrinologic associations of the autoimmune rheumatologic diseases. Semin Arthritis Rheum 1987; 17:58-70.
21. Kaplan MM; Reed LP. Symposium on thyroid disease. Med Clin North Am 1985; 69:871-6, 894-923, 1035-48.
22. Cavalieri RR. The effects of non-thyroid disease and drugs on thyroid function tests. Med Clin North Am 1991; 75:27-39.
23. Conemi JJ. The autoimmune diseases. JAMA 1987; 258:2920-30.
24. Walport MJ, Black CM, Richard BJ. The immunogenetics of SLE. Clin Rheum Dis 1982; 8:3-21.

Correspondence address:
Yrd.Doç.Dr. Süleyman BÜYÜKBERBER
İnönü Üniversitesi Tıp Fakültesi
İç Hastalıkları ABD
Turgut Özal Tıp Merkezi
MALATYA