

Lupus Anticoagulant Positivity in Autoimmune Thyroid Diseases

Otoimmün Tiroid Hastalıklarında Lupus Antikoagulan Pozitifliği

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Abstract

Objective: Autoimmune thyroid diseases are often concomitant with the other autoimmune diseases. In this study, our aim was to assess the presence of lupus anticoagulant, which is an antibody involved in the etiology of thrombosis, in patients with autoimmune thyroid diseases.

Materials and Methods: A total of 118 thyroid patients and 54 healthy controls were involved in the study. The coagulation system parameters, thyroid function tests, ANA, anti-dsDNA, anti-TG, anti-TPO, and LA were analyzed.

Results: Lupus anticoagulant was found in 41.5% of the patients, in 5.63% of the control group, 45.9% of the patients with positive anti-thyroid autoantibody, 36.8% of the patients with negative anti-thyroid autoantibody. No statistically significant correlation was found between presence of LA and thyroid disease type or presence of autoantibodies.

Conclusions: The presence of LA was higher in patients than controls ($P=0.001$). *Turk Jem 2008; 12: 88-90*

Keywords: Autoimmune thyroid disease, lupus anticoagulant, anti-thyroid antibody, anti-nuclear antibody

Özet

Amaç: Otoimmün tiroid hastalıkları diğer tüm otoimmün süreçler gibi diğer otoimmün hastalıklarla birlikte görülebilmektedir. Bu çalışmada trombozun etyolojisinden sorumlu bir antikor olan lupus antikoagulanının otoimmün tiroid hastalığı olan kişilerdeki sıklığının araştırılması amaçlanmıştır.

Gereç ve Yöntemler: Çalışmaya toplam 118 hasta ve sağlıklı kontrol grubu olarak 54 hasta alınmıştır. Koagülasyon sistemi parametreleri, tiroid fonksiyon testleri, ANA, anti-dsDNA, anti-TG, anti-TPO ve LA testleri yapılmıştır.

Bulgular: Lupus antikoagulanı (LA) hastaların %41.5'de, kontrol grubunun ise %5.63'de pozitif bulunmuştur. Hastaların %45.9'da tiroid otoantikorları pozitif, buna karşılık %36.8'de tiroid otoantikorları negatif bulunmuştur. LA pozitifliği ile tiroid hastalıkları tipi ve otoantikor pozitifliği arasında istatistiksel olarak anlamlı bir farklılık saptanamamıştır.

Sonuç: Sonuç olarak, LA pozitifliği sıklığı tiroid hastalığı olanlarda, olmayanlarla karşılaştırıldığında daha fazla bulunmuştur ($P=0.001$). *Turk Jem 2008; 12: 88-90*

Anahtar kelimeler: Otoimmün tiroid hastalığı, lupus antikoagulanı, anti-tiroid antikor, antinükleer antikor

Introduction

Autoimmune thyroid diseases result from autoimmune response to thyroid antigens; these diseases are among the most common endocrine diseases. Autoimmune thyroid disease may appear as symptomatic or subclinical hyper- or hypothyroidism. Lupus anticoagulant (LA) is an autoantibody that causes elevation in phospholipid-dependent coagulation tests (1-3). The activity of LA may cause thrombosis in the deeper veins of the lower

extremities, arteries, and cerebral vessels. In pregnant women, LA may lead to spontaneous abortion. These antibodies are may be found in association with lupus erythematosus, antiphospholipid antibody syndrome, and infectious diseases, use of some drugs, and recurrent spontaneous abortions; LA may also be found in normal healthy people (4-8). Autoimmune diseases often appear concomitantly, and progression of one disease may be accompanied by progression in another. The aim of this study was to examine the presence of LA among patients with autoimmune thyroid disease.

Materials and Methods

This study was performed in University of Kocaeli, Faculty of Medicine, Clinical Department of Endocrinology and Metabolism between 01.09.2004 and 28.02.2005. One hundred eighteen of 165 patients with a recent diagnosis of thyroid disease entered the study. Of those 118 patients, 78 (66.1%) were female and 40 (33.9%) were male. The patients were classified into four groups: clinical hyperthyroidism, subclinical hyperthyroidism, clinical hypothyroidism, and subclinical hypothyroidism. Exclusion criteria were diabetes mellitus, liver disease, malignancy, pregnancy, drug treatment for thyroiditis, and blood creatinine level of >1.4 mg/dL.

After routine biochemical tests and inspections, peripheral blood samples were taken in order to analyze free T_3 , free T_4 , thyroid-stimulating hormone (TSH), antithyroglobulin (anti-Tg) antibody, antithyroperoxidase (anti-TPO) antibody, antinuclear antibody (ANA), anti-double stranded DNA (anti-dsDNA), prothrombin time (PT), and activated partial thromboplastin time (aPTT). Fifty-six healthy volunteers (31 female, 23 male; mean age 47.4 ± 16.7 years; age range 18-83 years) served as a control group. Members of the control group had normal histories, physical examinations, biochemical and whole blood examinations (including normal PT and aPTT), and no history of drug treatment for thyroiditis.

Blood samples were taken in the seated position, after 12-14 hours of fasting. Routine biochemical tests were performed by using Beckman Automatic Analyser at the University of Kocaeli, Faculty of Medicine, Laboratory of Biochemistry. The whole blood count was performed with the Cell-Dyn 3700 (Abbott Diagnostics).

All samples were evaluated by the STA Analyser (Diagnostica Stago) for aPTT (with STA-CK Prest Kit) and PT (with STA Neoplastin CI Plus Kit). ANA, anti-dsDNA, anti-Tg, and anti-TPO autoantibodies were detected with immunofluorescent assay (IFA); sT_3 , sT_4 , and TSH were detected with chemiluminescent immunoassay. All aPTT tests were carried out with Staclo Lupus Anticoagulant Kit (Diagnostica Stago).

Plasma samples were obtained from the 118 study patients and 54 controls. Those samples were centrifuged for 20 minutes, and plasma samples were obtained and kept at -80°C . Meanwhile, a plasma pool was formed from the plasma of 10 people whose PT and aPTT values were known to be normal. The pooled aPTT value was accepted as the reference value of the laboratory. Coagulation-based lupus anticoagulant tests were then carried out on plasma samples of each patient and control, and the results compared with the reference aPTT value. If the aPTT value of the sample was ≥ 8 seconds greater than the reference aPTT value, the sample was considered positive for LA. All the patients with a positive LA test had a second LA test 6 weeks later. The patients were considered LA positive if the second test result was also positive.

Statistical analysis

The data were analyzed with SPSS v.12.0 (Statistical Package for Social Sciences). For continuous variables t-test was used. Categorical variables were analyzed by using χ^2 test. The committee for research ethics approved the study (AEK 113/11). Informed consents were obtained from all study participants.

Results

In patients with known thyroid disease, 49 of 118 (41.5%) were LA positive; in contrast, 3 of 54 (5.6%) healthy controls were LA

positive (5.6%) (Table 1). The presence of LA was significantly different between groups ($p < 0.001$). There was no significant effect of gender on the presence of LA (Table 2). There was no significant difference in the percentage of ANA, anti-TPO, and anti-Tg autoantibodies between LA positive patients and LA negative patients. No correlation between the anti-TPO or anti-Tg autoantibodies alone and LA positivity was observed (Table 2). Since the presence of anti-TPO or anti-Tg autoantibodies alone may be associated with autoimmune thyroiditis, this situation was compared to the presence of LA. The presence of LA was observed in 45.9% (28 patients) in the positive autoantibody group and 36.8% (21 patients) in the negative autoantibody group. There was no statistically significant difference between these two groups (Table 3).

Discussion

Anti-TPO antibodies have been observed in approximately 90% of autoimmune thyroiditis patients in several studies. Those antibodies are found positive in 99% to 100% of patients with Hashimoto thyroiditis and 67% to 80% of patients with Graves' disease. Antithyroglobulin (anti-Tg) antibodies are less sensitive than anti-TPO antibodies and are positive in 76% to 100% of patients with Hashimoto thyroiditis and 33% of patients with Graves' disease. For this reason, autoimmune cannot be excluded solely on the basis of these antibodies (particularly Graves' disease). In some patients with autoimmune thyroiditis, thyroid-stimulating hormone (TSH) receptor antibodies are useful in diagnosis. Thyroid ultrasonography, TSH receptor antibody test and thyroid fine-needle aspiration biopsies

Table 1. Presence of lupus anticoagulant in patient and control groups

Lupus Anticoagulant	Patient	Control	P
Positive	49 (41.5%)	3 (5.6%)	0.001*
Negative	69 (58.5%)	51 (94.4%)	0.001*
Total	118 (100%)	54 (100%)	

*Significant difference in presence of lupus anticoagulant

Table 2. Lupus anticoagulant by gender and autoantibody status. There is no statistically significant difference between the positivity of anti-thyroid antibodies and LA positivity

	LA (+)	LA (-)	P
Gender			0.987
female	33 (63.5%)	76 (63.3%)	
male	19 (36.5%)	44 (36.7%)	
Anti-TPO	16 (32.7%)	28 (40.6%)	0.382
Anti-Tg	20 (40.8%)	25 (36.2%)	0.615
Anti-TPO and/or Anti-Tg	28 (45.9%)	21 (36.8%)	0.320
ANA	8 (16.3%)	14 (20.3%)	0.588

Anti-TPO: anti-thyroid peroxidase, anti-Tg: anti-thyroglobulin, ANA: antinuclear antibody

Table 3. The relationship of antithyroid antibodies (ATA) to presence of lupus anticoagulant (LA)

	LA (+)	LA (-)	p	Number
ATA positive	28 (45.9%)	33 (54.1%)	0.322	61
ATA negative	21 (36.8%)	36 (63.2%)	0.322	57

should be performed by parenchyme heterogeneity, to identify if the thyroid disease is autoimmune for patients positive for both anti-Tg and anti-TPO antibody (9-12). In our patients, autoimmune thyroiditis could not be excluded, since those investigations were not performed for the 57 patients positive for both anti-Tg and anti-TPO antibody. It is important to remember that 10% to 20% of the normal asymptomatic population is positive for thyroid autoantibodies (9,10).

Other than case reports, we could only find one study concerning LA positivity in autoimmune thyroid diseases (13), although there have been many studies of anticardiolipin antibody in these patients.

Although the presence of LA was seen less frequently in association with hypothyroid function than hyperthyroid function, it was not accepted as statistically significant since the patient number was low (LA was positive in 1 of 6 patients). However the LA positivity was observed as 45.6% for all hyperthyroid patients (clinical and subclinical) and 33.3% for all hypothyroid patients. Tani et al reported a study comparing 532 patients with autoimmune thyroiditis (327 Graves' disease and 205 Hashimoto thyroiditis) and 396 with non-autoimmune thyroiditis. They compared 33 autoimmune thyroiditis patients (6.2%) with prolonged aPTT and otherwise normal levels of other coagulation factors with 8 patients (2%) with non-autoimmune thyroiditis. LA was investigated in the blood samples of those patients with platelet neutralization process (PNP); positivity was observed for 17 of 33 patients in the autoimmune thyroiditis group (51%), and 2 of 8 patients in the non-autoimmune thyroiditis group (25%) (13). In our patients, 45.9% (28 patients) in the positive autoantibody group were also positive for LA, and 36.8% (21 patients) in the negative autoantibody group were LA positive (Table 2). Only 3 of 54 healthy controls (5.6%) were LA positive. According to these findings, the results of our study are similar to their study. The most sensitive test for LA is the kaolin coagulation time, which shows the phospholipid level in the plasma (7,8). This method was used in our study. The sensitivity of this method has been reported as 97% to 100% (4,5,13,14). The differences in findings between our study and that of Tani likely reflect the difference in testing methods. Also, Tani et al investigated the LA positivity for only those patients with extended aPTT values (15).

In thyroid patients, it is difficult to attribute the presence of LA to autoimmunity, since significant LA positivity was obtained when the thyroid patients with negative autoantibody were compared to the control group. This situation may reflect autoimmune thyroid disease with negative tests for autoanti-

bodies. The effects of thyroid hormone abnormalities on the synthesis of immunoglobulin may also be responsible for the LA positivity in thyroid patients. Interestingly, the frequency of LA was greater in patients with hyperthyroidism than hypothyroidism, although the difference was not statistically significant. It is not known if the presence of LA causes an increased risk for thrombosis in patients with thyroiditis. Further research is needed to understand the clinical implications of these findings.

References

1. Goodnight SH, Griffin JH. Hereditary thrombophilia. Williams Hematology 6. edition (Ed: Beutler E, Lichtman MA, Coller BS, Kipps TJ, Selgshon U). New York, McGraw-Hill Medical Publishing Division, 2001, 1697-714.
2. Khamashta MA, Cuadrado MJ, Mujic F, Taub NA, Hunt BJ, Hughes GRV. The management of thrombosis in the antiphospholipid-antibody syndrome. N Engl J Med 1995; 332: 993-7.
3. Levine JS, Branch DW, Rauch J. The antiphospholipid syndrome. N Engl J Med 2002; 346: 752-63.
4. Rand JH. Lupus anticoagulants and related disorders. Williams Hematology 6. edition (Ed: Beutler E, Lichtman MA, Coller BS, Kipps TJ and Selgshon U). New York, McGraw-Hill Medical Publishing Division, 2001, 1715-33.
5. Alving BM. The antiphospholipid syndrome; clinical presentation, diagnosis, and patient management. Consultative Hemostasis and Thrombosis 1. edition (Ed: Kitchens CS, Alving BM, Kessler CM). Philadelphia, WB Saunders Company, 2002, 269-76.
6. Handin R. Disorders of the platelet and vessel wall. Harrison's Principles of Internal Medicine 15. edition (Ed: Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL). New York, McGraw-Hill Medical Publishing Division, 2001, 745-62.
7. Gali M. Which antiphospholipid antibodies should be measured in the antiphospholipid syndrome? Haemostasis 2000; 30 (Suppl 2): 57-62.
8. Merrill JT. Which antiphospholipid antibody tests are most useful? Rheum Dis Clin North Am 2001; 27: 525-49.
9. Larsen PR, Davies TF. Hypothyroidism and thyroiditis. Williams Textbook of Endocrinology 10. edition (Ed: Larsen PR, Kronenberg HM, Melmed S, Polonsky KS). Philadelphia, WB Saunders Company, 2003, 423-57.
10. Greenspan FS. The thyroid gland in lupus. Basic and Clinical Endocrinology 6. edition (Ed: Greenspan FS, Gardner DG). New York, McGraw-Hill Medical Publishing Division, 2001, 201-72.
11. Sniezek JC, Francis TB. Inflammatory thyroid disorders. Otolaryngol Clin North Am 2003; 36: 55-71.
12. Champion BR, Rayner DC. Thyroid autoantigens and regulation of thyroiditis. Thyroid autoimmunity (Ed: Rayner DC, Champion BR). Berlin and Heidelberg, Springer-Verlag, 1995, 67-90.
13. Brandt JT, Triplett DA, Alving B, Scharrer I. Criteria for the diagnosis of lupus anticoagulant: an update. On behalf of the subcommittee on lupus anticoagulant/ antiphospholipid antibody of the scientific and standardization of the ISTH. Thromb Haemost 1995; 4: 1174-85.
14. Esmon CT. Regulatory mechanisms in hemostasis: natural anticoagulants. Hematology: Basic Principles and Practice 4. edition (Ed: Hoffman R, Benz AJ Jr, Shattil SJ, Furie B, Cohen HJ, Silberstein LE, McGlave P). Philadelphia, Churchill Livingstone, 2005, 1817-24.
15. Tani Y, Morita M, Noguchi S. Prevalence of prolonged aPTT and lupus anticoagulant in autoimmune thyroid disease. Rinsho Byori 1997; 45: 899-902. (Abstract) (In Japanese).