Is Chronic Urticaria an Autoimmune Disease?: Letter to the Editor

Kronik Ürtiker Otoimmün Bir Hastalık mıdır?

Başak KANDİ, MD,[a]
Sevilay OĞUZ, MD,[b]
Demet ÇİÇEK, MD,[a]
Nermin KILIÇ, MD,[c]
Nurhan HALİSDEMİR,[d]
Yunus SARAL, MD[e]

Departmens of [a]Dermatology
[c]Biochemistry, School of Medicine, Fırat University,
Department of [d]Theory of Probability and Processes of Probability, Faculty of Sicience and arts, Fırat University, Elazığ,
[b]Clnic of Dermatology, Gaziantep Şehit Kamil State Hospital, Gaziantep,
[e]Department of Dermatology, School of Medicine, Rize University, Rize

Geliş Tarihi/*Received:* 16.04.2009
Kabul Tarihi/*Accepted:* 10.09.2009

Yazışma Adresi/*Correspondence:*
Demet ÇİÇEK, MD
Department of Dermatology, School of Medicine, Fırat University, Elazığ, TÜRKİYE/TURKEY
dr.demetcicek@hotmail.com

Key Words:
Urticaria; autoimmune diseases

Anahtar Kelimeler:
Ürtiker; otoimmün hastalık

Chronic urticaria (CU) is a common clinical condition in which urticaria attacks occur almost daily and persist more than six weeks. No underlying etiology can be detected in many CU patients, and these cases are called chronic idiopathic urticaria (CIU).[1]

The most recent information on the pathogenesis of CU suggests that many cases have an underlying autoimmune disease. Ten to forty percent of CU patients have immunoglobulin (Ig) G-structure antibodies against IgE or the alpha chain of high-affinity IgE receptors in their serum.[1-3] Additionally, the facts that high levels of autoantibodies such as anti-TG and anti-TPO in CIU patients, and their response to immunosuppressive treatments such as cyclosporine A attracted attention to autoimmunity's importance in CU's etiology.[4-7]

Chronic immunologic inflammation in an organ might be a potential risk for developing autoimmunity in another organ or tissue because of genetic predisposition.[1] On the basis of this relationship, we evaluated anti-TG, anti-TPO and anti-GPC antibodies; vitamin B12 levels; and thyroid functions in CIU patients and we investigated the relationship between CIU and autoimmunity.

A total of 100 (71 females and 29 males) CIU patients and 20 (16 females and 4 males) healthy control subjects were enrolled into the study. Demographic characteristics of the study group are summarized in Table 1.

The data obtained were evaluated using the SPSS v11.0 statistical software package. All values were expressed as mean ± standard deviation. A Chi-square analysis test was performed to evaluate the distribution of sexes between groups and Mann Whitney U test was used to compare the data of the patient and the control groups. The level of statistical significance was set at $p< 0.05$.

Anti-TPO antibodies were found positive in 15 of 100 patients, anti-TG antibodies in 23 of 100 patients and both anti-TPO and anti-TG antibodies

TABLE 1: Demographic properties of patients.

	Patient	Control	p
The number of patients (n)	100	20	
Age (Years)	35.65 ± 11.40	31.45 ± 10.00	>0.05
Sex (F/M)	29/71	4/16	>0.05

were found positive in 11 of 100 patients. Anti-GPC antibodies were positive in 10 of 100 patients. Only three patients had anti-TPO, anti-TG and anti-GPC antibodies. None of the patients in the control group had positive anti-TPO antibodies, anti-TG antibodies or anti-GPC antibodies.

A comparison of the values in the patient and control groups revealed that mean serum levels of free T4, anti-TG, anti-TPO and anti-GPC antibody in the CIU patients were statistically significantly higher than those in the control group (p= 0.012, 0.04, 0.02 and 0.05 respectively). No significant difference was seen in mean serum free T3 levels (p> 0.05). Mean serum TSH levels were statistically significantly lower in CIU patients when compared to the control group (p= 0.010). Mean serum vitamin B12 levels were also statistically significantly lower in CIU patients (p= 0.000) (Table 2).

Leznoff et al. first reported the relationship between CU and thyroid autoimmunity in 1983.[5] Their study included 140 CU patients and 427 healthy controls. The authors found that serum thyroid microsomal antibody (anti-TMA) titers were higher in CU patients (12.1%) than those in healthy controls (5.6%). Six years later, in 1989, in another study with 624 CU patients, Leznoff et al showed the presence of anti-TMA and anti-TG antibodies in 90 patients (14%).[6] They observed that 44 patients with high antibody levels also showed clinical signs of thyroid disease; treatment was started with 0.15-20 mg/day L-thyroxine in 46 patients (because of hypothyroidism or severe CU signs) and remission occured after 4-8 weeks. In addition, 13 CU patients had vitiligo, adrenalitis, parathyroiditis and pernicious anemia, and a relationship was noted between CU and other autoimmune diseases.[6] At the end of this study, authors stated that a subgroup of CIU might be an autoimmune disease of the skin and mucous membranes that is associated with thyroid autoimmunity, in the same way that diseases in the polyendocrine autoimmune disease spectrum were associated with thyroid autoimmunity. In the present study, we established that the thyroid autoantibodies were higher than these previous studies in the literature in CIU patients.

TABLE 2: Mean serum levels of free T3, free T4, TSH, anti-TPO, anti-TG and anti-GPC antibodies, and vitamin B12.

	Patient (n= 100)	Control (n= 20)	P
Free T3	2.97 ± 0.88	2.69 ± 0.41	0.187
Free T4	1.34 ± 0.24	1.21 ± 0.14	0.012
TSH	1.57 ± 1.36	1.95 ± 0.73	0.010
Anti-TPO	143.37±192.47	9.5±8.40	0.020
Anti-TG	181.88±229.78	29.38±30.90	0.040
Vitamin B12	264.86±91.13	432.85±127.72	0.000
Anti-GPC	3.28±5.66	0.90±1.46	0.050

Normal test values in our laboratory are as follows: free T3: 1.57-4.71 pg/mL; Free T4: 0.93-1.71 ng/dL; TSH: 0.27-4.2 µIU/mL; Anti-TPO <50 IU/mL; Anti-TG < 150 IU/mL; Vitamin B12: 174-878 pg/mL; Anti-GPC< 15 IU/mL.

The following studies focused mostly on the relation between the CU's duration and the presence of thyroid antibodies. Toubi et al, who prospectively followed CU patients for five-years period, reported that CU attacks continued in 52% of those with positive thyroid autoantibodies, but in only 16% of those with negative thyroid autoantibodies, with a statistically significant difference.[7] This study of the relationship between autoimmunity and CU's duration and severity, revealed that long-lasting CU results from the prolonged stimulation of T-cells followed by prolonged polyclonal activation,and the production of various cytokines that could induce secretion of autoantibodies.

Nonendocrine organ-specific autoimmune diseases associated with autoimmune thyroid disease include pernicious anemia, diabetes mellitus, primary sclerosing cholangitis, primary hyperparathyroidism and vitiligo.[1,4-7] Recently, autoimmune mechanisms have been emphasized in CIU's etiology. Mete et al,[4] evaluated vitamin B12 levels, anti-GPC antibodies and thyroid autoantibodies in CIU patients. They found that serum vitamin B12

level was below normal range in 33% of CIU patients. Thyroid autoantibodies were found to be positive in 54.5% and anti-GPC antibodies were found to be positive in 36.4%. They reported that these data were highly statistically significant. The study showed no difference between low and normal B12 levels with regard to IgG Helicobacter pylori antibody's incidence and hematological or neurological manifestations of B12 deficiency.[4] These results support the previous studies, which suggest an autoimmune basis to CIU. In comparison with this study, we found that anti-GPC antibodies were also increased in relatively low percentage (10%) of CIU patients.

In conclusion, we found that CIU patients had increased levels of anti-thyroid and anti-GPC antibodies. It should be borne in mind that CIU can be together with autoimmune diseases, and specific endocrine and immunologic tests should be conducted to clarify the disease's etiology, especially in patients who are resistant to treatment.

REFERENCES

1. Kaplan AP. Clinical practice. Chronic urticaria and angioedema. N Engl J Med 2002;346(3): 175-9.
2. Utaş S. [Autoimmune urticaria]. Turkiye Klinikleri J Dermatol-Special Topics 2008; 1(1):12-9.
3. Utaş S. [Etiology, pathogenesis and therapeutic approaches in chronic urticaria]. Turkiye Klinikleri J Int Med Sci 2005;1(6):22-7.
4. Mete N, Gulbahar O, Aydin A, Sin AZ, Kokuludag A, Sebik F. Low B12 levels in chronic idiopathic urticaria. J Investig Allergol Clin Immunol 2004;14(4):292-9.
5. Leznoff A, Josse RG, Denburge J, Dolovich J. Association of chronic urticaria and anjioedema with thyroid autoimmunity. Arch Dermatol 1983;119(8):636-40.
6. Leznoff A, sussman GL. Syndrome of idiopathic chronic urticaria and angioedema with thyroid autoimmunity: a study of 90 patients. J Allergy Clin Immunol 1989;84(1):66-71.
7. Toubi E, Kessel A, Avshovich N, Bamberger E, Sabo E, Nusem D, et al. Clinical and laboratory parameters in predicting chronic urticaria duration: a prospective study of 139 patients. Allergy 2004;59(8):869-73.