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Araştırma Makalesi / Research Article

The Risk Factors for Autoimmune Thyroid Disorder in Children with Chronic Spontaneous Urticaria

Kronik Spontan Ürtikerli Çocuklarda Otoimmün Tiroid Hastalığı için Risk Faktörleri

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Abstract

Although the etiology of chronic spontaneous urticaria (CSU) in children is mostly idiopathic, there are studies supporting the autoimmune pathogenesis of disease in a subset of patients. CSU and autoimmune thyroid disease coexistence has been explored mostly in adults; however data in children is scarce. The aim of this study was to verify frequency of anti thyroid peroxidase (anti-TPO) antibody positivity and risk factors for autoimmune thyroid disorder in the children with CSU. In this retrospective descriptive study, a total of 126 children with CSU in two different centers were evaluated. The demographic and clinical features, coexisting connective tissue diseases, autoimmune and/or allergic diseases and complete blood count, total IgE, antinuclear antibody (ANA), anti-TPO antibody, free thyroxine (fT4), thyroid-stimulating hormone (TSH), skin prick test and autologous serum skin test (ASST) results that routinely performed for CSU in both centers were collected from medical records. Thyroid ultrasonography findings were also recorded in the patients with positive anti-TPO. Anti-TPO was positivite in 5 (4.0%) patients. Heterogenous paranchyme on thyroid US was detected in 3 of those. ANA was positive 10.1% of the patients. In anti-TPO positive patients, ANA positivity was significantly higher (60% vs 7.4%, respectively; p=0.003). Vitiligo was detected in 4 (3.2%) of patients and although it is not significant statistically, these patients had higher frequency of anti-TPO positivity compare to those without vitiligo (20% vs 2.5%, respectively; p=0.151). ANA positivity may be a risk factor for autoimmune thyroid disorder in patients with chronic spontaneous urticaria. Relationship between vitiligo and autoimmun thyroid disorder should also be investigated in patients with CSU in larger cohorts.

Keywords: Chronic urticaria; anti thyroid peroxidase antibody; thyroid autoimmunity; systemic lupus erythematosus; vitiligo

Özet

Kronik spontan ürtikerin (KSÜ) etiyolojisi çoğunlukla idiyopatik olmakla birlikte, hastaların bir kısmında patogenezde otoimmünitenin rol oynadığını destekleyen çalışmalar vardır. KSÜ ve tiroid otoimmünitesi birlikteliği çoğunlukla erişkinlerde araştırılmıştır; ancak, çocuklarda veriler sınırlıdır. Bu çalışmada, KSÜ tanısı almış çocuklarda anti tiroid peroksidaz (anti-TPO) antikor pozitifliği sıklığının saptanması ve otoimmun tiroid hastalığı için risk faktörlerinin belirlenmesi amaçlanmıştır. Bu retrospektif tanımlayıcı çalışmada, iki farklı merkezde KSÜ tanısı ile izlenen 126 hasta değerlendirilmiştir. Hastaların demografik ve klinik özellikleri, eşlik eden bağ doku hastalığı, otoimmün hastalık ve/veya allerjik hastalıkları ile her iki merkezde KSÜ hastalarında rutin olarak yapılan tam kan sayımı, total IgE, antinükleer antikor (ANA), anti-TPO antikor, serbest tiroksin (sT4) ve tirotiropin (TSH) düzeylerini içeren laboratuvar sonuçları; deri prick testi ve otolog serum deri testi (OSDT) sonuçları dosya verilerinden elde edildi. Anti-TPO pozitifliği saptanan hastaların tiroid ultrasanografisi bulguları da kaydedildi. Çalışmamızda 5 (%4.0) hastada anti-TPO pozitifliği saptandı. Bu hastaların 3'ünde tiroid US'de parankim heterojenitesi mevcuttu. ANA pozitifliği hastaların %10.2'sinde saptanmıştı. Anti-TPO pozitifliği olan hastalarda ANA pozitifliği anlamlı olarak yüksek idi (sırasıyla %60 ve %7.4, p=0.003). Dört hastada vitiligo tanısı mevcuttu ve bu hastalarda anti-TPO pozitifliği, vitiligo tanısı olmayan KSÜ tanılı hastalara göre istatistiksel olarak anlamlı olmamakla birlikte daha fazla saptandı (sırasıyla %20 ve %2.5, p=0.151). Kronik spontan ürtikerli çocuklarda ANA pozitifliği otoimmün tiroid hastalığı için risk faktörü olabilir. KSÜ'lü çocuklarda vitiligo ve otoimmun tiroid hastalığı ilişkisi daha geniş kohortlarda araştırılmalıdır.

Anahtar Kelimeler: Kronik ürtiker; anti tiroid peroksidaz antikoru; tiroid otoimmünitesi; sistemik lupus eritematozus; vitiligo

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1. Introduction

Chronic urticaria (CU), urticaria occurring twice or more a week and persisting for at least six weeks, is classified into chronic spontaneous urticaria (CSU) and inducible urticaria by specific eliciting factors (1). In previous studies, it has been shown that 30-50% of children with CSU had antibodies to the a-subunit of high-affinity IgE receptor (FcεRIa) and/or anti-IgE antibodies. Therefore, CSU is considered an autoimmune disorder at least in a subset of patients (2,3).

Hashimoto's thyroiditis (HT) is chronic lymphocytic thyroiditis associated with positive serum antibodies against mainly to thyroid peroxidase (anti-TPO) and thyroglobulin (anti-Tg). Anti-TPO positivity is very high (almost 90%) in patients with HT (4). Although the diagnosis of HT mostly based on antibody positivity, very rarely lymphocytic infiltration in the thyroid gland confirmed with cytological examination without antibody positivity is also diagnostic. Also, a patient is possible to have HT if heterogeneous and/or hypoechoic parenchyma is detected in thyroid ultrasonography (US).Prevalence of HT is relatively high (13%) in general population, however lower in children (5). In healthy children, anti-TPO positivity have been reported 3.4-4.8% (6-9). There is only one study for HT frequency in Turkish healthy school children and it was found to be 3.6% (10).

Coexistence of different autoimmune diseases is common, therefore the frequency of autoimmune thyroid disease in patients with CU has been explored in a number of studies (11-17). However these studies are mostly in adults and data in children is scarce (14-17).The understanding process between CSU and autoimmunity might help the prediction therapeutic options and prognosis of these patients. The aim of this study was to verify frequency of anti-TPO antibody positivity and risk factors for autoimmune thyroid disorder in the children with CSU.

2. Material and Methods

In this retrospective descriptive study, 126 children with CSU who were admitted in years between 2012 and 2017 in the Pediatric Allergy Clinics at Kocaeli University (52 patients) and Dr. Lutfi Kirdar Kartal Training and Research Hospital (74 patients) were evaluated.

Patients with isolated physical urticaria, infectious disease and food hypersensitivity were excluded. Written informed consent was obtained from the parents, and the study was approved by the local ethics committee in Kocaeli University (2019/153). The study was prepared in accordance with the Helsinki Declaration Criteria.

Demographic features, the age at symptom onset, personal history of atopic diseases (such as atopic dermatitis, asthma, allergic rhinitis), presence of angioedema, signs of connective tissue disease, personal history of urticaria, atopic disease and autoimmune conditions were collected from medical records. The physical examination findings and complete blood count, total IgE, antinuclear antibody (ANA), anti-TPO antibody, free thyroxine (fT4), thyroid-stimulating hormone (TSH), autologous serum skin test (ASST) and skin prick test results that routinely performed for CSU in both centers were also collected from medical records. Findings of thyroid US, performed only in the patients with positive anti-TPO, were also recorded.

Autologous serum skin test

Briefly, 0.05 ml of autologous serum and %0.9 sterile salin as a negative control were injected intradermally into the volar aspect. A skin prict test with histamine (10 mcg/ml) was used as a positive control. The mean of the two longest perpendicular wheal diameters were recorded after 30 minutes. ASST is considered positive when the wheal diameter of >1.5 mm compared with that elicited by saline (18).

Statistical analysis

All statistical analyses were performed using IBM SPSS for Windows version 20.0 (SPSS, Chicago, IL, USA). Kolmogorov-Smirnov tests were used to test the normality of data

distribution. Continuous variables were expressed as mean±standard deviation or median and categorical variables were expressed as counts (percentages). Comparisons of continuous variables between the groups were performed using the Mann Whitney U Test. Comparisons of cathegorical variables between the groups were performed using the Fisher's exact test in contingency tables. A two-sided p value <0.05 was considered statistically significant.

3. Results

We evaluated 126 patients (66 girls) with CSUaged between 0.8-17.9 years (mean age 9.4±4.6, median 9.0 years). 70.6% of the patients were under the age of 12.0 years. The mean duration of the disease in all patients was 10.1±17.0 months, ranged between 1.4 months to 11 years. Four (3.2%) patients also had vitiligo. Anti-TPO antibody was positive in 5 patients (4.0%). Three of those had heterogenous parenchyma in thyroid US (Table 1). One of these patients was diagnosed as HT before the onset of the CSU and was on levothyroxine treatment at the time of referral. Another patient was diagnosed at follow-up one year after admission.

Table 1. Features of the patients with positive anti-TPO

	Patient#1	Patient#2	Patient#3	Patient#4	Patient#5
Age (years)	16.7	9.7	11.7	4.7	9.1
Gender	Male	Male	Female	Female	Female
Duration of CSU (months)	4	4	3	2	6
Angioedema	-	+	+	-	+
Vitiligo	-	-	-	+	-
Atopy	-	-	+	-	-
ANA	-	+ (1/100)	+ (1/100)	+ (1/100)	-
ASST	+	-	+	-	+
Anti TG	Negative	Positive	Negative	Positive	Negative
fT4 (pmol/L)	12.4	14.1	11.7	11.3	10.9
TSH (IU/L)	1.75	1.81	1.58	1.20	3.50
Thyroid US	Normal	heterogeneous parenchyma	heterogeneous parenchyma	heterogeneous parenchyma	Normal

Anti-TPO: anti-thyroid peroxidase, ANA: antinuclear antibody, ASST: autologous serum skin test, anti-TG: anti-thyroglobulin, fT4: free thyroxine, TSH: thyroid stimulant hormone

Anti-TPO positivity also were calculated in different age groups. Anti-TPO positive in patients with CSU aged between 5-18 years and 12-18 years were 3.8% and 2.7%, respectively.

ASST was performed in 86 patients and detected positive in 39.5% of them. ANA was performed in 99 patients and detected positive in 10 (10.1%) of them. None of the patients were diagnosed as having a rheumatologic disease.

The patients with positive anti-TPO were compared with patients who were negative and both groups were similar in terms of age, gender, the duration of disease, presence of angioedema and history of atopy. The positivity of the ASST did not appear to be related with positive anti-TPO antibody. In anti-TPO positive patients ANA positivity was significantly higher (p=0.003) Comparison of all these features of patients with or withour anti-TPO were given in Table 2.

Table 2. Comparison of features of patients with or without anti-TPO

	Anti-TPO positive	Anti-TPO negative	p
Age (years), mean±SD	10.4±4.4	9.4±4.6	0.591
Girls , n (%)	3 (60.0)	63 (52.1)	0.545
Duration of disease, (months) mean±SD	3.8±1.5	10.3±17.3	0.753
Angioedema, n (%)	3 (60.0)	37 (30.6)	0.325
Atopy, n (%)	1 (20.0)	20 (16.5)	0.605
Vitiligo , n (%)	1 (20.0)	3 (2.5)	0.151
Ig E (kU/l) , mean±SD	157.6±150.0	118.7±141.5	0.371
Free thyroxine (pmol/L), mean±SD	12.1±1.2	11.9±1.9	0.616
TSH (IU/ml) , mean±SD	1.9±0.8	2.2±1.1	0.725
ANA positive, n (%)	3 (60.0)	7 (7.4)	0.003
ASST positive, n (%)	3 (60.0)	31 (38.3)	0.380

Anti-TPO: anti-thyroid peroxidase, TSH: thyroid stimulant hormone, ANA: antinuclear antibody, ASST: autologous serum skin test

4. Discussion

In our study, the prevalence of positive anti-TPO was 4.0% as similar to healthy children (6-10). The prevalence of positive anti-TG, the other antibody for autoimmune thyroid disease, could not be given in our study due to lack of results in some patients. By this reason, we selected the studies that was given anti-TPO prevalence rather than HT in children under 18 year of age with CU for a better comparison with our results (14-17). Anti-TPO prevalence in previous studies were summarized in Table 3.In our study, prevalence of anti-TPO in children with CSU was not as high as those found in adult studies (12, 13). However, this low prevalence is similar to other pediatric studies (14-17). Even in some studies, such as Sackesen et al (14) and Chansakulporn et al (17), none of the pediatric patients with CU had anti-TPO positivity. In our study median age of the patients 9 years and 70% of the patients are under 12 years of age. Manifestation of the autoimmune diseases increase mostly with age. Also, depending on the natural course of the thyroid autoimmunity, it may be manifested several years after the appearance of CSU.

Table 3. Reported anti-TPO frequencies under 18 years of age

	n	Age range (years)	Study population	Anti-TPO positive%
NHANES III study (2002) [6]	17,353	>12.0	Healthy people 12 yr of age or older	4.8
Kaloumenou et al (2008) [7]	440	5.0-18.0	Healthy school children living in the iodine-replete area	4.6
Kabelitz et al (2003) [8]	660	1.0-19.0	Healty children and adolescents with a normalized iodine intake	3.4
Loviselli et al (2001) [9]	8,040	6.0-15.0	Healthy schoolchildren living in areas with mild to moderate iodine deficiency	3.0
Dogan et al (2011) [10]	1,000	11.0-18.0	School children	3.2
Leznoff et al (1989) [12]	90	8.0-72.0	Patients with CIU	14.0
Bakos et al (2003) [13]	48	14.0-75.0	Patients with CU	33.0
Sackesen et al (2004) [14]	17	2.0-19.0	Children with various forms of urticaria	0.0
Levy et al (2003) [15]	187	6.0-18.0	Children with CU	2.1
Sahiner et al (2011) [16]	82	0.7-17.2	Children with CSU	3.7
Chansakulporn et al (2014) [17]	92	4.0-15.5	Children with CSU	0.0
Present study	126	0.8-17.9	Children with CSU	4.0

We shown that anti-TPO positivity was higher in children with angioedema, twicely, however the numbers of patients were limited and this difference was not significant. Karagol et al(20) were reported that anti-TPO positivity was 12.5% in children with recurrent angioedema, and this ratio is also higher than children with CU.It should be investigated whether this association increases the risk of autoimmune thyroid disease.
We demonstrated that atopic patients did not show a significant difference compared with non-atopics for thyroid autoimmunity. To date, few papers in the literature address the relationship between atopy and thyroid autoimmunity in children with CSU and they reported that there was no difference between atopic and nonatopic patients (15,22).

In present study, ASST positivity was higher in anti-TPO positive patients but not statistically significant. O'Donnell et al (19) reported that the clustering of anti-TPO positivity among ASST positive patients is significant with a 4.4 relative risk in adults with CU. The previous studies suggested that the children with positive ASST should be searched for the presence of thyroid pathologies (16,18). Although ASST positivity suggests a strong autoimmune association in CSU, two of anti-TPO positive patients with autoimmune disease in our study had negative results of ASST.

We think that the false negative results of ASST in these patients due to degradation of histamine releasing factors while the serum is being prepared might be another reason. However, there are also similar results in other studies. In O'Donnell's study, there were cases with positive thyroid antibodies and negative ASST (4.3% of the ASST negative patients had positive anti-TPO) (19). Kilic et al (20) also reported 15% thyroid autoimmunity in CU children with negative ASST.

Our patients with vitiligo, another autoimmune pathology, had 7.5 times higher frequency of anti-TPO positivity compare to those without vitiligo, although not statistically significant. In a study by Kakourou et al reported that almost ¼ of the children with vitiligo had autoimmune thyroiditis (23). Relationship between vitiligo and autoimmun thyroid disorder should also be investigated in patients with CSU in larger cohorts.

Some studies reported the prevalence of ANA positivity in healthy individuals as 0.1-5% (24-26). In our study, prevalence of ANA positivity in children with CSU (10.1%) were higher than healthy individuals. None of the our patients with positive ANA were diagnosed as having a specific rheumatologic disease when evaluated by a pediatric rheumatologist. Generally, antibodies related to autoimmune disease may persist several years without a clinical symptom. Therefore, in these patients, periodic assessment for development of new symptoms is reasonable. However, although thyroid autoimmunity has been reported in patients with CSU, the prevalence of systemic lupus erythematosus (SLE) in CSU is not well known, especially in children. In adults, a few case reports have shown chronic autoimmune urticaria at the onset of SLE. These reports suggest that CSU can be the first manifestation of SLE (27).In our study, prevalence of positive anti-TPO was significantly higher in ANA positive patients.

In conclusion, ANA positivity may be a risk factor for autoimmune thyroid disorder in patients with chronic spontaneous urticaria. Relationship between vitiligo and autoimmun thyroid disorder should also be investigated in patients with CSU in larger cohorts.

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