Medical Journal of Bakırköy

Med J Bakirkoy 2024;20:104-108
DOI: 10.4274/BMJ.galenos.2023.2022.12-6

Research

Do Cytokines Play a Role in Chronic Spontaneous Urticaria in Childhood? IL-17 One of Them?

Çocukluk Çağındaki Kronik Spontan Ürtikerde Sitokinlerin Rolü Var mı? IL-17 Bunlardan Biri mi?

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ABSTRACT

Objective: Chronic spontaneous urticaria (CSU) is a common skin disorder that is considered to be an autoimmune disorder in a subset of patients. Because it is not always possible to find a trigger in CSU cases, it may be thought that various cytokines may play a role in the inflammatory processes associated with CSU. One of these markers is interleukin-17 (IL-17).

Methods: In this case-control study, serum IL-17 levels were measured in 50 patients with CSU and 35 healthy control subjects. Urticaria activity score (UAS-7) was used to assess disease activity.

Results: Serum levels of IL-17 in patients with CSU were not significantly different from those in healthy controls [mean and median: 3.98±3.88 (3.1) vs. 4.85±2.96 (3.9) pg/mL, p=0.063]. Serum levels of IL-17 in mild CSU patients did not differ significantly from those in moderate-severe CSU patients [mean and median: 4.24±4.33 (3.3) vs. 3.1±1.13 (3) pg/mL, p=0.30]. No significant differences in IL-17 levels were observed between autologous serum tests (ASST) (+) and ASST (-) patients with similar UAS, and serum IL-17 levels of patients did not significantly differ according to sex and antinuclear antibody positivity.

Conclusion: This is the first study to examine serum IL-17 levels in children with CSU. Further studies with a larger number of patients are needed to elucidate the role of IL-17 in the pathogenesis of childhood CSU.

Keywords: Chronic urticaria, children, interleukin -17

ÖZ

Amaç: Kronik spontan ürtiker (KSÜ), otoimmün bir bozukluk olarak da kabul edilen yaygın bir deri hastalığıdır. KSÜ olgularında her zaman tetikleyici bulmak mümkün olmadığından, KSÜ'ye bağlı enflamatuvar süreçlerde çeşitli sitokinlerin rol oynayabileceği düşünülmektedir. Bu belirteçlerden biri de interlökin-17'dir (IL-17).

Gereç ve Yöntem: Bu olgu kontrol çalışmasında, KSÜ'lü 50 hasta ve 35 sağlıklı kontrol hastasında serum IL-17 konsantrasyonu ölçüldü. Hastalık aktivitesini değerlendirmek için ürtiker aktivite skoru (UAS-7) kullanıldı.

Bulgular: KSÜ'lü hastalardaki serum IL-17 seviyeleri, sağlıklı kontrollerden önemli ölçüde farklı değildi [ortalama ve medyan: 3,98±3,88 (3,1) vs. 4,85±2,96 (3,9) pg/mL, p=0,063]. Hafif KSÜ hastalarında serum IL-17 seviyeleri, orta-şiddetli KSÜ hastalarından önemli ölçüde farklı değildi [ortalama ve medyan: 4,24±4,33 (3,3) vs. 3,1±1,13 (3) pg/mL, p=0,30]. Benzer UAS olan otolog serum testi (OST) (+) ve OST (-) hastalar arasında IL-17 düzeyleri arasında farklılıklar gözlenmedi ek olarak cinsiyet ve anti-nükleer antikor pozitifliğine göre de anlamlı farklılık izlenmedi.

Sonuç: Bu çalışma, kronik spontan ürtikerli çocuklarda serum IL-17 düzeylerini inceleyen ilk çalışmadır, IL-17'nin çocukluk çağı KSÜ patogenezindeki rolünü aydınlatmak için daha fazla sayıda hasta ile ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Kronik ürtiker, çocuklar, interlökin-17

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Cite as: Özçeker D, Yücel E, Dikker O. Do Cytokines Play a Role in Chronic Spontaneous Urticaria in Childhood? IL-17 One of Them?. Med J Bakirkoy 2024;20:104-108

Received: 05.01.2023
Accepted: 17.10.2023

INTRODUCTION

Recurrent itchy wheals and/or angioedema lasting more than six weeks are the hallmarks of chronic spontaneous urticaria (CSU), which is caused by many known or unknown etiologies (1). Overall, the prevalence of chronic urticaria (CU) in children seems to be below 1%, and there is no significant difference among genders (2-6). Scarce data are available on the epidemiology and etiology of CU in children. The pathogenesis of CSU remains unknown possible causes include foods, drugs, infections, pseudoallergies to food and drugs, insect stings and bites, and auto reactivity related to functional autoantibodies directed against the immunoglobulin E receptor (7).

Because it is not always possible to detect a trigger in CSU cases, it may be thought that various cytokines could play a role in CSU-related inflammatory processes. One of these markers is interleukin-17 (IL-17). IL-17 is produced by T helper (Th) type 17 cells that bind to an IL-17 receptor expressed on endothelial, epithelial, and fibroblastic stromal cells. IL-17 is associated with many autoimmune disorders including multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis, and asthma (8-10). In this regard, IL-17 may have a role in the pathogenesis of CSU, and its levels can be a biomarker for detecting disease severity or therapeutic response in CSU. However, no study has been conducted only in children.

This study aimed to understand the role of IL-17 levels in the pathogenesis of CSU in terms of diagnosis, prognosis, and severity of the disease.

METHODS

Study Design and Participants

In this case-controlled study, fifty patients who were admitted to Okmeydanı Training and Research Hospital Pediatric Allergy Outpatient Clinic with a diagnosis of CSU and 35 age- and sex-matched healthy children were examined. A detailed history was taken from all patients, and physical was examined. Patients with urticaria vasculitis and concomitant allergic diseases and clinical evidence of physical urticaria, such as dermographism, cold urticaria, and cholinergic urticaria, were excluded. Antihistamine medications were discontinued 7 days before the study. Patients' age, sex, family history of atopy, duration of symptoms, serum total IgE levels, eosinophil percentage in complete blood count, antinuclear antibody, and results were recorded from patient files.

All patients' anti-histaminic treatments were discontinued for 10 days before IL-17 serum samples were collected.

Data Collection

Serum IL-17 Analysis

2 mL of blood were taken from the volunteers for IL-17 serum testing. The serum was held at room temperature for 20 min, centrifuged at 4000 rpm for 10 min, and stored at a temperature of -80 °C. We left the serums to dissolve at room temperature on the day of the analysis. Ready-to-use immune enzymatic test (ELISA) kits were used to detect IL-17A levels in the serum samples of participants. Serum IL-17 levels were analyzed using a kit branded Robonic ELISA plate reader®, ELISA, India. The results of analytical measurements were between 1.6 and 100 pg/mL for IL-17A. The minimal detection limit was 0.5 pg/mL.

The detected intra- and inter-assay variation coefficients were 7.1 % and 9.1 %, respectively.

Assessing Urticaria Severity

The disease activity and urticaria severity were assessed with the urticaria activity score 7 (UAS-7), which was calculated indirectly according to the recommendations of the EAACI/GA2LEN/EDF/WAO Guidelines (11). Patients were asked to record their assessment scores for 7 days using the UAS-7 and were grouped as mild, moderate, and severe.

Autologous Serum Tests

First, 10 mL of venous blood was taken from the patients into sterile plain tubes and left to coagulate for 30 min at room temperature. Blood was then centrifuged for 15 min at 500 g, and serum was eluted. ASST was conducted using 0.5 mL of the patient's own serum, and the physiological serum was injected intradermally into the flexor aspect of the forearm.

The greater than 1.5 mm or the diameter of the saline papule was accepted as a positive result after waiting for 30 min.

All ASSTs were performed by the same researcher.

Statistical Analysis

To evaluate the results of the study, IBM SPSS Statistics 22 was used for statistical analysis programs (SPSS IBM, Türkiye).

When assessing the operating data, the conformity of the parameters to the normal distribution was evaluated using the Shapiro-Wilks test. Continuous variables that were not normally distributed were presented as intermediates with interquartile intervals and were statistically analyzed using the Mann-Whitney U test. The chi-square test was used to determine categorical variables, presented in counts or percentages. Statistical significance was evaluated at $p<0.05$.

Ethics

This study was approved by the Okmeydanı Training and Research Hospital Clinical Research Ethics Committee (decision no: 1001, date: 09.10.2018). All subjects provided written informed consent before participation.

RESULTS

Demographic Data and Patient Characteristics

A total of 85 children (50 patients, 35 controls) were evaluated in this study. The median age was 10 (quartiles: 7.5-14) years, and 50.6% (n=43) were male. The median duration of symptoms was 3.5 (minimum-maximum: 2-40) months. There was no difference in age or sex between the patient and control groups.

The majority of our patients had mild to moderate disease severity, and other clinical findings are presented in Table 1.

Cytokine Data

Serum levels of IL-17 in patients with CSU were not significantly different from healthy controls [median (quartiles): 3.1 (2.6-4.6) vs. 3.9 (3.0-6.3) pg/mL, p=0.063; Figure 1] (Table 2).

Levels of IL-17 in mild CSU patients did not differ significantly versus moderate-severe CSU patients [median (quartiles): 3.3 (2.6-4.9) vs. 3.0 (2.5-3.7) pg/mL, p=0.30].

Table 1. Demographic and clinical characteristics of patients with CSU

	n	%
Sex female/male	24/26	48/52
Angioedema (n=50)$_{n,\%}$	13	26
Family history of atopy (n=50)$_{n,\%}$	6	12
Additional-allergic diseases		
No	41	82
Yes*	9	18
UAS (n=50)$_{n,\%}$		
Mild	39	78
Moderate	10	20
Severe	1	2
ASST (n=30)$_{n,\%}$ positivity	13	43
ANA (n=50)$_{n,\%}$ positivity	11	22
Skin prick test positivity (n=38)$_{n,\%}$	12	31.6
	Median	**Min-max**
Total IgE levels (Ku/L)	63.1	2.8-811
Eosinophil levels (%)	2	0.1-11.2

CSU: Chronic spontaneous urticaria, ASST: Autologous serum test, ANA: Antinuclear antibody, IgE: Immunoglobulin E, UAS: Urticaria activity score, min-max: Minimum-maximum
*Asthma (n=6), allergic rhinitis (n=2), atopic dermatitis (n=1)

No significant differences in IL-17 levels were observed between ASST (+) and ASST (-) patients with similar UAS, and serum IL-17 levels of patients did not significantly differ according to sex and antinuclear antibody positivity (Table 2).

DISCUSSION

CSU pathogenesis has not been fully understood. In this study, although CSU patients had lower serum IL-17 levels than healthy subjects, the difference was not statistically significant. There are many studies about IL-17 and CU, but the results are very controversial, and there are no studies conducted in children (12-18).

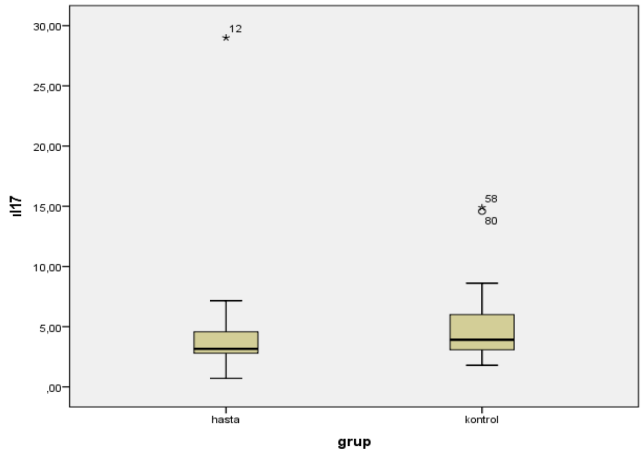

Figure 1. Comparison of plasma levels of IL-17 between CSU patients and control groups
IL-17: Interleukin 17, CSU: Chronic spontaneous urticaria

Table 2. Evaluation of IL-17 levels in patients with CSU according to groups, gender, ASST, ANA positivity, and severity of the disease by UAS

		IL-17 level Median (min-max)	p-value
Group	Patient group	3.1 (2.6-4.6)	0.63
	Control group	3.9 (3.0-6.3)	
Sex	Female	4.1 (2.9-5.6)	0.015*
	Male	3.3 (2.4-3.9)	
ASST	Negative	3.0 (2.0-4.1)	0.572
	Positive	3.1 (2.0-5.1)	
ANA	Negative	3.1 (2.8-4.5)	0.879
	Positive	3.0 (1.9-4.9)	
UAS	Mild	3.3 (2.6-4.9)	0.303
	Moderate	3.0 (2.5-3.7)	

Mann-Whitney U test, *p<0.05. PS: One of the children with a severe UAS score was excluded from the analysis.
CSU: Chronic spontaneous urticaria, ASST: Autologous serum test, ANA: Antinuclear antibody, IL-17: Interleukin 17, UAS: Urticaria activity score, min-max: Minimum-maximum

Daschner et al. (12) reported lower IL-17 serum levels in only adults with CSU. They found lower serum IL-17 levels in patients with CSU with or without sensitization against Anisakis simplex. Th17 cell functions may be insufficient and IL-17 levels may be suppressed in patients with CSU (12). Degirmenci et al. (13) reported no significant difference in serum IL-17 levels between CSU patients and healthy controls. In contrast, Atwa et al. (14) reported increased IL-17 serum levels in CSU patients older than 12 years, which was related to disease severity. Dos Santos et al. (15) found that the IL-17 level of CU patients is higher than that of control patients. Chen et al. (16) found higher serum levels of IL-17 in adults, especially in ASST-positive patients. Similarly, Lin et al. (17) detected higher serum IL-17 concentrations in adult patients with CSU. We believe that these variable outcomes may have resulted from the different types of urticaria, as indicated by Daschner et al. (12).

Th17 cells and their cytokine, IL-17, result in the secretion of several inflammatory factors and autoantibody production; thus, they serve an important role in the initiation and maintenance of autoimmune and inflammatory processes in variable disorders (19). Serum IL-17 plays a role in other allergic diseases; therefore, diverse results can be obtained in various allergic diseases. If we had included those with concomitant allergic disease, we might have found lower serum levels of IL-17 in patients with CSU. A potential role of IL-17 has been described in the pathology of inflammatory skin disorders, such as atopic dermatitis, contact hypersensitivity, and psoriasis. This indicates that IL-17 is an important mediator of tissue inflammation; however, high intense expression of IL-17A was shown in the skin of patients with CSU, both in lesional or non-lesional skin biopsies, compared with healthy skin (20). In this study, there was no difference in serum IL-17 levels among ASST (-) and ASST (+) CSU patients. Previous studies demonstrated that serum levels of tumour necrosis factor-α, IL-10, IL-13, IL-17, and IL-23 were higher in ASST (+) than in ASST (-) CSU patients (14-16, 20).

Degirmenci et al. (13) reported no significant difference in serum IL-17 levels according to ASST results. In line with our results, the ASST (-) patient group had significantly lower IL-17 levels than the control group. Serum levels of IL-17 did not differ in ASST (-) and ASST (+) patients in the study by Grzanka et al. (18), similar to the results of our study.

CSU patients with mild, moderate, or severe symptoms and healthy subjects had no differences in serum IL-17 levels. Similarly, Grzanka et al. (18) did not find a relationship between serum IL-17 levels and disease severity determined using UAS-7. Atwa et al. (14) showed a significant correlation between disease activity as assessed by UAS-7 for 7 days before blood sampling and serum IL-17 concentration. They specified that elevated IL-17 resulted from the activation of mast cells involved in urticarial processes. The most numerous cells containing IL-17 in human skin are mast cells, lymphocytes, and neutrophils. Diverse stimuli result in these cells producing IL-17. It may be speculated that IL-17-producing Th17 cells and IL-17 levels vary according to urticaria severity. In our study, we did not notice any relationship between UAS-7 and serum IL-17 levels, which may be attributed to the low number of patients in the severe group.

CONCLUSION

In conclusion, IL-17 may not have an important role in childhood CSU pathogenesis because no significant difference was found in serum IL-17 levels between CSU patients and healthy children, and no correlation was found with disease severity. This is the first study to examine serum IL-17 levels in children with chronic spontaneous urticaria. Further studies with a larger number of patients are needed to elucidate the role of IL-17 in the pathogenesis of childhood CSU.

ETHICS

Ethics Committee Approval: This study was approved by the Okmeydanı Training and Research Hospital Clinical Research Ethics Committee (decision no: 1001, date: 09.10.2018).

Informed Consent: All subjects provided written informed consent before participation.

Authorship Contributions

Surgical and Medical Practices: D.Ö., E.Y., O.D., Concept: D.Ö., E.Y., Design: D.Ö., E.Y., Data Collection or Processing: D.Ö., E.Y., Analysis or Interpretation: D.Ö., E.Y., O.D., Literature Search: D.Ö., E.Y., Writing: D.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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