

Clinical and etiologic evaluation of the children with chronic urticaria

Dilek Azkur, M.D.,¹ Ersoy Civelek, M.D.,² Müge Toyran, M.D.,² Emine Dibek Mısırlıoğlu, M.D.,² Mustafa Erkoçoğlu, M.D.,³ Ayşenur Kaya, M.D.,² Emine Vezir, M.D.,² Tayfur Giniş, M.D.,² Ayşegül Akan, M.D.,² and Can Naci Kocabaş, M.D.⁴

ABSTRACT

Background: Chronic urticaria (CU) is a skin disorder defined as daily or almost daily exhibition of pruritic and transient wheals that last for >6 weeks. CU is divided into two subtypes: chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU).

Objectives: To evaluate the clinical features, possible causes, associated findings, and laboratory results of different subtypes of CU in children according to a new classification.

Methods: In this study, we evaluated the clinical features, laboratory investigations, and provocation tests of children with different subtypes of CU according to a new classification.

Results: Two hundred and twenty-two children (59.9% girls) were enrolled in the study. Of the study patients, 59.9% and 40.1% were diagnosed as having CSU and CIndU, respectively. Antithyroid antibody levels were positive in 7.1% of the patients with CSU, 32.8% of the children had positive 14C-urea breath test results, and 6.5% of the patients had positive stool examination results for parasites. Autologous serum skin test results were positive in 53.5% of the patients with CSU. Of the patients with CIndU, 77.5% had symptomatic dermographism, 16.8% had cold urticaria, 2.2% had cholinergic urticaria, 2.2% had solar urticaria, and 1.1% had aquagenic urticaria.

Conclusion: Children with CSU represent the majority of patients with CU, and more than a half of these patients might have autoimmune urticaria. Symptomatic dermographism was the most common type of CIndU.

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Chronic urticaria (CU) is a skin disorder defined as daily or almost daily exhibition of pruritic and transient wheals that last for >6 weeks.¹ Both children and adults can acquire CU, but it seems to be less common in children. Overall, CU affects 0.1–0.3% of children.² Approximately 50% of patients with CU have both urticaria and angioedema, 40% have only urticaria, and 10% have angioedema as their main manifestations.³ CU is divided into two subtypes: chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU).¹ Specific environmental stimulus triggers inducible urticaria, or it is precipitated by an increase in core body temperature. CIndU involves symptomatic dermographism, cold urticaria, delayed

pressure urticaria, heat urticaria, solar urticaria, vibratory angioedema, cholinergic urticaria, aquagenic urticaria, and contact urticaria.¹ Different subtypes of urticaria can occur in the same patient. Urticarial vasculitis and some syndromes associated with urticaria (e.g., Muckle-Wells syndrome, Schnitzler syndrome) should be considered in the differential diagnosis if the wheals persist for >24 hours and leave residual pigmentation changes, and if there also are systemic symptoms such as recurrent fever, fatigue, and arthritis.^{4,5}

CU can result from many different causes, such as infections, foods, and autoimmunity.^{6,7} CU is thought to be mediated by functional autoantibodies against immunoglobulin E (IgE) itself or against the α -chain of the high-affinity receptor for IgE (Fc ϵ R1 α) in 45–55% of the patients.⁸ The basophil mediator release assay is the criterion standard to demonstrate these functional autoantibodies.⁹ The autologous serum skin test (ASST) and the autologous plasma skin test are nonspecific simple screening tests for identifying patients with autoantibody-associated urticaria.^{10,11} Previous studies indicated that up to 38–45% of children with CU have positive ASST results.^{12,13} Most studies about the epidemiology, pathogenesis, and treatment of CU pertain to adults. In the medical literature, a few studies investigated the etiology and clinical features of children with CU.^{13–17} European Academy of Allergy and Clin-

From the ¹Pediatric Allergy and Immunology, Faculty of Medicine, Kirikkale University, Kirikkale, Turkey, ²Pediatric Allergy and Immunology, Ankara Children's Hematology Oncology Education and Research Hospital, Ankara, Turkey, ³Pediatric Allergy and Immunology, Faculty of Medicine, Abant İzzet Baysal University, Bolu, Turkey, and ⁴Pediatric Allergy and Immunology, Faculty of Medicine, Muğla Sıtkı Kocman University, Muğla, Turkey

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Address correspondence to Can N. Kocabaş M.D., Pediatric Allergy and Immunology, Faculty of Medicine, Muğla Sıtkı Kocman University, Muğla, Turkey

E-mail address: cankocabas@yahoo.com

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ical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization (EAACI/GA2LEN/EDF/WAO) recently published a guideline for classification of urticaria.¹ In this study, we aimed to assess the clinical features, possible causes, associated findings, and laboratory results of the different subtypes of CU in children according to the new classification.¹

METHODS

Patients

This prospective study was conducted at the outpatient department of Pediatric Allergy and Immunology, Ankara Children's Hematology Oncology Training and Research Hospital, between February 2010 and August 2014. The patients who were <18 years of age and followed up with a diagnosis of urticaria and/or angioedema for at least a duration of 6 weeks and with CIndU were included in the study. However, patients with acute spontaneous urticaria were excluded from study. The ethics committee of Ankara Children's Hematology Oncology Training and Research Hospital approved the study protocol. The following data were recorded: age at admission, sex, duration of symptoms, triggering factors, type of CU, accompanying diseases, personal and family history of atopic diseases, physical examination, laboratory investigations, skin-prick tests (SPT), and provocation tests.

Laboratory Investigations

Laboratory investigations included complete blood cell counts, liver transaminase values, erythrocyte sedimentation rate, C-reactive protein level, urine analysis and culture, serum levels of complement C3 and C4, total and allergen specific IgE (sIgE) levels, free thyroxine level, thyroid stimulating hormone level, antithyroglobulin level, antithyroid peroxidase autoantibody level, antinuclear antibody (ANA) level, anti-double-stranded DNA antibody level, rheumatoid factor, hepatitis B virus surface antigen, antibody titers for hepatitis B and hepatitis C virus, stool examination for parasites, and 14C-urea breath test for the diagnosis of *Helicobacter pylori* results. Cryoglobulins and cold hemagglutinin values were measured for patients with cold urticaria.

Skin Test Procedures

All patients without dermographism underwent SPTs with commercial allergen extracts: pollens (grass, tree, and weed pollen), house-dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), fungal allergens (*Aspergillus*, *Cladosporium*, and *Alternaria*), animal dander (cat and dog), and cockroach (Stallergenes, SA, Antony, France). For children <2 years old, pollens were not applied and cow's milk (ALK-Aiello,

Madrid, Spain), egg white, wheat, peanut, soybean, and fish (Stallergenes) were included. For patients who had symptoms from foods, suspected foods were tested with commercial extracts and/or fresh foods by the prick-prick technique. Histamine (10 mg/mL) was used as a positive control and diluent as a negative control for the test. SPT results were considered positive if a wheal size was ≥ 3 mm compared with the negative control. An ASST was performed as previously described.¹¹ Briefly, 0.05 mL of fresh autologous serum and 0.9% sterile saline solution as the negative control were injected intradermally into the volar aspect of the forearm, and histamine (10 mg/mL) was applied as the positive control. Thirty minutes after the injections, a mean wheal diameter of ≥ 1.5 mm when compared with the control was considered a positive test reaction.

Allergen sIgE Testing

The sIgE levels of the suspected allergens were studied by using the ImmunoCAP methodology (Phadia, Uppsala, Sweden). IgE levels of >0.35 kU/L were considered positive.

Provocation Tests

The provocation tests were performed according to the EAACI guidelines.^{1,18} For the diagnosis of symptomatic dermographism, moderate stroking of the skin (volar forearm) with a wooden spatula was performed. For the cold urticaria, a melting ice cube in a thin plastic bag was applied on the volar forearm for 5 minutes. If the test result was negative at 5 minutes, then the test was repeated for 10 and for 20 minutes. In patients who showed a negative test reaction with the ice cube, an arm was immersed in cold water at 5–10°C for 10 minutes and was assessed 10 minutes after the end of provocation testing. Solar urticaria was diagnosed by provocation test with a visible light source (slide projector) positioned 10 cm from the patient's volar forearm and was confirmed by exposure to natural sunlight. For assessment of cholinergic urticaria, a treadmill exercise test was performed until the patient began to sweat and up to 15 minutes beyond. A challenge with a wet compress at body temperature for 20 minutes was performed to confirm the diagnosis of aquagenic urticaria. To confirm food allergy, open food challenges with suspected foods were performed on patients who had no convincing history of anaphylaxis.

Statistics

All statistical analyses were performed with the SPSS 18.0 program (SPSS Inc., Chicago, IL). We expressed categorical variables as percentages. The values are presented as means and standard deviations (SD) for

data that demonstrated a normal distribution and as medians and interquartile ranges for data that did not demonstrate a normal distribution. The χ^2 test was performed to compare the nonparametric data, the Mann-Whitney test was used for non-normally distributed data, and the independent *t*-test was used for normally distributed continuous data to compare patients with positive and negative results for ASST. A *p* value of <0.05 was considered statistically significant.

RESULTS

During the study period, 222 children with a diagnosis of CU were recruited. The mean age $\pm$ SD was 10.1 ± 4.5 years and 133 patients (59.9%) were female. Eighty-nine children (40.1%) had CU with angioedema. Among the study patients, 133 (59.9%) had CSU and 89 (40.1%) had CIndU

Characteristics of the Patients with CSU

The characteristics of the patients with CSU are shown in Table 1. Seventy-two patients with CSU were girls (54.1%); the mean age was 10.1 ± 4.5 years. Thirty-one children (23.3%) had allergic diseases, 3 patients had autoimmune disease, and 26 patients (19.5%) had one or more important diseases that accompanied CSU (Table 2). The results of laboratory examination to determine the etiology are shown in Table 1. In summary, urine culture showed *Escherichia coli* growth in one patient. Although the patient continued having CSU, there was not any bacterial growth in the urine culture after antibiotic treatment. In 6 of 93 patients, a parasitic infection was detected by stool examination (*Endameba histolytic*, *Endameba coli*, *Guardia labia*, *Iodamoeba butschlii*, *Blastocystis* spp., and *Enterobius vermicularis*). All the patients used appropriate antiparasitic medications. One patient who had infestation of *E. vermicularis* showed remission of urticaria after treatment.

Antithyroid antibody levels were positive in 9 of 126 patients (7.1%). Two of these patients were diagnosed with Hashimoto thyroiditis. ANA and anti-double-stranded DNA positivity was detected in five and two patients, respectively. Rheumatoid factor positivity was determined in one patient. None of them were diagnosed with any rheumatic diseases, but all of them are now under follow-up for the risk of rheumatic diseases. The 14C-urea breath tests were carried out in 61 patients with CSU to determine *H. pylori* level and found positive results in 20 patients. Three patients with *H. pylori* refused treatment. Fifteen of 17 patients continued to have urticaria, one had complete remission, and one had partial improvement after treatment. Dermographism occurred in 25 of 133 patients (18.7%) during SPT. Allergic sensitivity was detected in 13 patients (9.7%) (Table 1). SPTs were performed and/or

Table 1 Clinical features and laboratory findings of patients with chronic spontaneous urticaria

Patients characteristics	
Age, mean $\pm$ SD, y	10.1 $\pm$ 4.5
Girls, no. (%)	72 (54.1)
Duration of symptoms, median (IQR), mo	5.5 (2.5–13.5)
Presence of angioedema, no. (%)	71 (53.4)
Dermographism, no. (%)	25 (18.7)
Family history of allergic conditions, no. (%)	47 (35.3)
Family history of chronic urticaria, no. (%)	12 (9.0)
Laboratory findings	
Leukocytosis, no. (%)	8/132 (6.0)
Eosinophils, median (IQR), no./mm ³	100 (100–200)
Eosinophils $> 4\%$, no. (%)	17/132 (12.9)
Increased total IgE level, no. (%)	38/128 (29, 6)
Elevated transaminase level, no. (%)	3/120 (2.5)
Elevated ESR level (>20 mm/hr), no. (%)	23/113 (20.4)
Increased CRP value (>0.8 mg/dL), no. (%)	11/122 (9.0)
Abnormal urine test result, no. (%)	6/128 (4.7)
Positive urine culture result, no. (%)	1/95 (1.1)
Stool examination result positive for parasites, no. (%)	6/93 (6.5)
HBsAg positivity, no. (%)	0/130 (0.0)
Anti-HCV positivity, no. (%)	0/72 (0.0)
Abnormal thyroid function test result, no. (%)	3/130 (2.3)
Positive thyroid antibodies, no. (%)	9/126 (7.1)
ANA positivity	5/126 (4.0)
Anti-dsDNA positivity	2/125 (1.6)
Rheumatoid factor positivity	1/103 (1.0)
Positive 14C-urea breath test	20/61 (32.8)
Allergic sensitization in skin-prick test, no. (%)#	
Pollen	9/133 (6.7)
House-dust mite	5/133 (3.7)
Animal dander	1/133 (0.7)
Cockroach	1/133 (0.7)
Food	1/133 (0.7)
Positive autologous serum skin test	53/99 (53.5)

SD = Standard deviation; IQR = interquartile range; IgE = immunoglobulin E; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; HBsAg = hepatitis B virus surface antigen; anti-HCV, antibody to hepatitis C virus; ANA = antinuclear antibody; anti-dsDNA, anti-double-stranded DNA antibody.

#Some patients had more than one sensitization.

Table 2 Comorbidities of the patients with chronic spontaneous urticaria*

	No. (%)
Allergic diseases	
Asthma	16 (12.0)
Allergic rhinitis	16 (12.0)
Atopic dermatitis	6 (4.5)
Food allergies	1 (0.7)
Autoimmune diseases	
Autoimmune thyroiditis	2 (1.5)
Oligoarticular juvenile rheumatoid arthritis	1 (0.7)
Other diseases	
Gastritis	3 (2.2)
Gastroesophageal reflux	3 (2.2)
Precocious puberty	3 (2.2)
Familial Mediterranean fever	2 (1.5)
Epilepsy	2 (1.5)
Hypothyroidism	2 (1.5)
Recurrent urinary tract infections	2 (1.5)
Acute lymphoblastic leukemia	1 (0.7)
Polycystic ovary syndrome	1 (0.7)
Acute rheumatic fever	1 (0.7)
Growth hormone deficiency	1 (0.7)
Mental retardation	1 (0.7)
Isovaleric acidemia	1 (0.7)
Hypoparathyroidism	1 (0.7)
Tuberculin skin test positivity	1 (0.7)
Nephrolithiasis	1 (0.7)
Social anxiety disorder	1 (0.7)

*Some patients had more than one disease.

level of sIgE was measured for nine patients suspected to have CSU and food allergy. Open food challenges were performed, and none of the patients were diagnosed with food allergy. One patient had a positive SPT result and a high sIgE level (1.71 kU/L) against honey but was not challenged because she had a convincing history of anaphylactic reaction.

The ASST was performed in 99 patients. The reasons why 34 patients did not undergo ASST were as follows: 18 patients had dermographism, 8 patients were not able to discontinue use of antihistamines because of disease activity, 3 patients were <1 year old, and 5 patients refused the procedure. The mean (standard deviation) age was 10.5 ± 4.6 years, and 55 patients (55.5%) were girls. Fifty-three of 99 patients (53.5%) had positive ASST results. The median size of positive ASST wheals elicited by the serum and controls were 7.2 mm (interquartile range, 6–9 mm) and 3.0 mm (interquartile range, 0–4 mm), respectively. Features of patients with positive and negative ASST are shown in Table 3. The patients with ASST positive and ASST negative results showed

no statistically significant differences for age, sex, duration of symptoms, presence of asthma and autoimmune diseases, laboratory findings, family history of CU, and sensitivity for SPT.

The patients with CSU ages ≥ 10 years were compared with younger patients in terms of clinical and laboratory features. There were no significant statistical differences in terms of sex, ASST positivity, allergic diseases, and important diseases that accompany CSU among the age groups. However, patients >10 years old have had longer symptom durations, a high percentage of angioedema, positive thyroid antibody values, and positive ¹⁴C-urea breath test (data not shown).

Characteristics of the Patients with CIndU

Features of patients with CIndU are shown in Table 4. Cold weather triggered cold urticaria in 12 patients (80%), touching cold objects triggered it in 11 patients (73.3%), and consumption of cold drinks triggered it in 3 patients (20%). Generalized and localized urticaria was seen in 11 patients (73.3%) and 4 patients (26.7%), respectively. Only one patient had systemic symptoms with cold urticaria. A 15-year-old boy who had urticaria on the limbs and arms when exposed to cold weather had anaphylaxis 10 minutes after swimming in a pool.

Ice cube challenge was performed on 15 patients with cold urticaria and a positive response was found in 12 patients (80%). The patients with a negative ice-cube challenge result showed a positive reaction when the cold water test was performed. Three patients with cold urticaria showed allergic sensitivity by SPT (two patients to pollen and one patient to honey). Two patients had solar urticaria. One of these patients showed clinical signs all year round and did not see a significant benefit from the medications, the other developed a tolerance to sunlight in the spring and had no significant symptoms in the summer and autumn. Results of provocation tests with sunlight and the projector light were positive for both patients.

In two patients with cholinergic urticaria, showering with hot water and exercising triggered symptoms. Results of provocation tests with exercise were positive for both patients, and pinpoint lesions were developed on the trunk after exercise. A 15-year-old girl whose urticaria was triggered by water regardless of its temperature was diagnosed with aquagenic urticaria. After the provocation test, the patient showed hives on the contact areas with a wet compress, but the result of the ice cube challenge was negative. Among the patients with symptomatic dermographism, one patient was diagnosed with lentil allergy and another was diagnosed with cow's milk allergy confirmed by open food challenge. The laboratory findings of the patients with

Table 3 Demographic features and laboratory findings of patients with CSU with positive and negative ASST results

	Positive ASST Results (n = 53)	Negative ASST Results (n = 46)
Age, mean $\pm$ SD, y	10.7 $\pm$ 3.8	10.2 $\pm$ 4.6
Girls, no (%)	32 (60.4)	23 (50.0)
Duration of symptoms, median (IQR), mo	6.0 (3.0–15.0)	6.7 (2.8–25.5)
Presence of angioedema, no. (%)	28 (52.8)	24 (52.2)
Asthma, no. (%)	7 (13.2)	5 (10.9)
Autoimmune disease, no. (%)	4 (7.5)	1 (2.2)
Family history of chronic urticaria, no. (%)	6 (11.3)	4 (8.7)
Family history of autoimmune disease, no. (%)	5 (9.4)	2 (4.3)
Eosinophils > 4%, no. (%)	5/51 (9.6)	6/46 (13.0)
Increased total IgE level, no. (%)	13/49 (26.5)	7/46 (15.2)
Elevated ESR value (>20 mm/hr), no. (%)	10/46 (21.7)	11/42 (26.2)
Increased CRP level (>0.8 mg/dL), no. (%)	4/48 (8.3)	6/44 (13.6)
Positive ¹⁴ C-urea breath test, no. (%)	6/24 (25.0)	9/24 (37.5)
Positive thyroid antibody level, no. (%)	5/51 (9.8)	3/43 (7.0)
ANA positivity, no. (%)	3/51 (5.9)	1/44 (2.3)
Anti-dsDNA positivity, no. (%)	0/49 (0.0)	1/44 (2.3)
Allergic sensitization in skin-prick test, no. (%)	7/53 (13.2)	6/46 (13.0)

CSU = Chronic spontaneous urticaria; ASST = autologous serum skin test; SD = standard deviation; IQR = interquartile range; IgE = immunoglobulin E; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; ANA = antinuclear antibody; anti-dsDNA, anti-double-stranded DNA antibody.

CIndU are shown in Table 4. Three of 33 patients with symptomatic dermatographism showed parasites by stool examination (two patients with *Giardia lamblia* and one patient with *Entamoeba histolytica*). All the patients used appropriate antiparasitic medications.

DISCUSSION

In the present study, we evaluated clinical features and laboratory tests of 222 children who had CU. Although CU is a well-defined disease in adult patients, there are limited data available about children. It was reported that patients with CU had 66–93% CSU, 4–33% had physical urticaria, and 1–7% had cholinergic urticaria.¹⁹ Sackesen *et al.*²⁰ reported that 52.9% of children with CU had physical urticaria. In the present study, we defined children with CU as having CSU in 59.9% of the cases and as having CIndU in 40.1% of the cases. Many factors are investigated to find the etiology of CU. Whether or not laboratory tests should be carried out to detect etiology of CU is controversial. The observation that patients treated for *H. pylori* experienced healing of urticaria has led researchers to a relationship between *H. pylori* and CU.²¹ It was reported that the rate of *H. pylori* IgG positivity was found 9.7–17.6% of the time in children with CU studies from Turkey.^{14,20} In our study, 32.8% children with CSU had positive ¹⁴C-urea breath tests. We did not see any

significant reduction in the symptoms of patients after the treatment.

Parasitic infections are thought to play a role in some patients with CU. Jirapongsananuruk *et al.*¹³ reported that 5.3% children with CU had parasites in their stools and that treatment did not show any significant contribution for remissions of CU. In our study, one patient showed remission of urticaria after treatment, but another five patients continued to have CU symptoms. Autoimmune diseases such as autoimmune thyroid disease and systemic lupus erythematosus are common in adult patients with CU.^{8,22} However, this rate was relatively low in children. Levy *et al.*²³ found that 4.3% of children with CU had high thyroid autoantibody levels. In our study, 7.1% of patients had thyroid antibody positivity and patients >10 years old had high percentages of positive thyroid antibody levels. Thyroid hormone serum levels were normal in all the patients. Two of these patients were diagnosed with autoimmune thyroiditis and were treated with levothyroxine. Another two patients were diagnosed with autoimmune thyroiditis.

In our study, ANA positivity and anti-double stranded DNA positivity were detected in five and two patients, respectively. These patients were examined for connective tissue diseases, but there were no pathologic findings. Jirapongsananuruk *et al.*¹³ found that

Table 4 Clinical features and laboratory findings of patients with CIndU

	Symptomatic Dermatographism (n = 69)	Cold Urticaria (n = 15)	Other Types of CIndU (n = 5)	Total (n = 89)
Patients characteristics				
Age, mean $\pm$ SD, y	9.8 $\pm$ 4.6	11.2 $\pm$ 4.5	12.3 $\pm$ 3.8	10.3 $\pm$ 4.6
Girls, no. (%)	47 (68.1)	10 (66.6)	4 (80.0)	61 (68.5)
Duration of symptoms, median (IQR), mo	5.5 (2.0–24.0)	12.0 (1.0–24.0)	13.0 (8.5–130.0)	7.0 (2.2–24.0)
Presence of angioedema, no. (%)	15 (21.7)	4 (26.6)	0 (0.0)	19 (21.3)
Asthma, no. (%)	8 (11.6)	1 (6.7)	2 (40.0)	11 (12.4)
Allergic rhinitis, no. (%)	7 (10.1)	2 (13.3)	1 (20.0)	10 (11.2)
Atopic dermatitis, no. (%)	4 (5.8)	0 (0.0)	1 (20.0)	5 (5.6)
Food allergies, no. (%)	2 (2.8)	1 (6.7)	0 (0.0)	3 (3.3)
Important diseases accompanying CSU, no. (%)	7 (10.1)	3 (20.0)	0 (0.0)	10 (11.2)
Family history of allergic conditions, no. (%)	24 (34.8)	4 (26.7)	1 (20.0)	29 (32.6)
Family history of chronic urticaria, no. (%)	6 (8.7)	2 (13.3)	1 (20.0)	9 (10.1)
Laboratory findings, no. (%)				
Leukocytosis	1/66 (1.5)	0/9 (0.0)	0/5 (0.0)	1/80 (1.25)
Eosinophils > 4%	8/66 (12.1)	1/15 (6.6)	0/5 (0.0)	9/86 (10.4)
Increased total IgE level	23/64 (35.9)	6/15 (40.0)	1/2 (50.0)	30/81 (37.0)
Elevated ESR level, >20 mm/hr	6/47 (12.7)	5/9 (55.5)	0/2 (0.0)	11/58 (18.9)
Increased CRP level >0.8 mg/dL	2/50 (4.0)	1/13 (7.7)	0/4 (0.0)	3/67 (4.4)
Stool examination, positive for parasites	3/33 (9.1)	0/7 (0.0)	—	3/40 (7.5)
Positive thyroid antibodies	2/52 (3.8)	1/15 (6.6)	0/3 (0.0)	3/70 (4.2)
ANA positivity	1/48 (2.0)	1/14 (7.1)	0/4 (0.0)	2/66 (3.0)
Anti-dsDNA positivity	0/41 (0.0)	0/14 (0.0)	0/4 (0.0)	0/59 (0.0)
Cold agglutinin	—	0/6 (0.0)	—	0/6 (0.0)
Cryoglobulin	—	0/9 (0.0)	—	0/9 (0.0)
Allergic sensitization in skin-prick test	—	3/13 (23.0)	1/4 (25.0)	4/17 (23.5)

CIndU = chronic inducible urticaria; SD = standard deviation; IQR = interquartile range; CSU = chronic spontaneous urticaria; IgE = immunoglobulin E; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; ANA = antinuclear antibody; anti-dsDNA = anti-double-stranded DNA antibody.

ANA positivity occurred in 23% of patients, but none of them were diagnosed for connective tissue diseases as in our study. Sahiner *et al.*¹⁴ reported that ANA positivity was present in 13.8% of patients, and a patient with arthralgia was followed up for connective tissue diseases. The presence of chronic autoimmune urticaria is reported in 30–40% of patients with CU.²⁴ A diagnosis of chronic autoimmune urticaria can be carried out with *in vivo* and *in vitro* tests.²⁵ One limitation of the study was that we were not able to perform a basophil histamine release test for detection of autoantibodies due to the lack of laboratory facilities. the ASST is a simple test to show autoreactivity, but a positive ASST result alone is not specific for autoim-

mune CU.²⁶ Brunetti *et al.*¹² studied autoimmune urticaria by using the ASST and the basophil histamine release test in children. They reported sensitivity and specificity of the ASST for the identification of anti-FcεR1 antibodies of 78 and 85%, respectively. The prevalence of positivity of ASST was determined to be between 38.3 and 46.7% of children.^{12–14} In the present study, ASST positivity (53.5%) was slightly higher than other studies.

Previous studies did not determine any difference between an ASST response and age, sex, or personal and familial history of atopy.^{12,26–28} An EAACI/GA(2)LEN task force report showed no difference in quality of life scores, severity of disease, diagnosis, and

prognosis between patients with positive and negative ASST results.¹¹ In accordance with the literature, our study revealed no difference between patients with positive and negative ASST results in terms of age, sex, symptom duration, the presence of angioedema, acute-phase proteins, 14C-urea breath test, ANA positivity, thyroid autoantibody response, and sensitivity for SPT.

Physical urticaria is characterized with angioedema, urticaria, and pruritus on the skin. There are a few studies about physical urticaria in childhood. Khakoo *et al.*² found that the subtypes of CIndU in children were dermographic in 38%, cholinergic in 19%, mixed physical subtypes in 17%, delayed pressure in 9%, cold urticaria in 9%, heat urticaria in 2%, and unspecified in 4%. In our study, as in the study by Komarow *et al.*,²⁹ girls were predominant in the CIndU group (68.5%). Even though symptomatic dermographism is the most common subtype of physical urticaria, there are very limited studies about this issue. Taskapan and Harmanyeri³⁰ conducted a study about symptomatic dermographism with 40 patients (28 women and 12 men) whose ages varied between 7 and 65. In their study, five patients (12.5%) were atopic, and they had SPT reactivity to house-dust mites, two patients (5%) had hyperthyroidism, and one patient had type 2 diabetes. In our study, 47 patients (68.1%) were girls, 8 patients (11.6%) had asthma, 7 patients (10.1%) had allergic rhinitis, and 2 patients had autoimmune thyroiditis.

Cold urticaria is thought to be rare in children. In a series of 30 children with cold urticaria evaluated with the ice cube test, 17 (58.6%) had a positive response.³¹ Eleven patients (36.7%) experienced systemic symptoms and researchers found no secondary causes. In the current study, 80% of the patients showed positive results from the ice cube test. Only one patient experienced systemic symptoms and described the use of adrenaline autoinjector. None of the patients had family histories of cold urticaria or cryoglobulinemia. Cholinergic urticaria is a common type of CIndU and is especially seen in young adults and is associated with bronchial hyperresponsiveness.^{32,33} In the present study, two patients with cholinergic urticaria had asthma and urticaria triggered both by exercising and by taking a shower with hot water. Solar urticaria is a rare type of CIndU. To the best of our knowledge, the two children with solar urticaria were the first reported from our country. Pathogenesis of aquagenic urticaria is not very well known. It has been indicated that absorption of a toxic water-soluble compound might be exerting an effect of perifollicular mast cell degranulation with the release of histamine.³⁴ Three children from our country were reported to have aquagenic urticaria.³⁵

CONCLUSIONS

CSU (59.9%) and CIndU (40.1%) were found in a large group of children with CU in the present study.

ASST results were positive in 53.5% of patients with CSU. Our data supported other researchers' findings that gathering detailed histories and conducting physical examinations are the most important steps toward deciding the need for further laboratory investigations.

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