

Dermatologic Therapy / Early View / e15261

ORIGINAL ARTICLE |  Full Access

An evaluation of the factors affecting the clinical and laboratory findings, prognosis, and treatment response in children with chronic urticaria

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First published: 14 December 2021

<https://doi-org.bibliosan.clas.cineca.it/10.1111/dth.15261>

This study was presented as a poster presentation at the XXVIII National Allergy and Clinical Immunology Congress (13–17 October 2021).

Abstract

Chronic urticaria (CU) is a rare disease in childhood, and studies in children are limited. In this study, the aim was to investigate the clinical and laboratory findings and demographic characteristics of children with CU and to determine the factors affecting prognosis. The study included 141 patients aged 0–18 years who were diagnosed with CU in the pediatric allergy outpatient clinic between January 1, 2013, and December 31, 2018. Risk factors related to prognosis were investigated by comparing the duration of CU and treatment response with clinical and etiological features. IBM SPSS version 24 was used for statistical analyses. In the study group, the female/male ratio was 69/55, and the median age at first visit was 9.5 years (min:1, max:17). Among patients, 63 (44.5%) had an accompanying atopic disease, and 23 (16.3%) had chronic disease. Of the patients, 124 (88%) had chronic spontaneous urticaria, and 17 patients (12%) had chronic inducible urticaria (CIU). Of those with CIU, 72.2% had symptomatic dermographism, 16.7% had cholinergic urticaria, and 11.1% had cold urticaria. After the evaluations, the most common pathological findings in our patients were intestinal parasitosis ($n = 14$), anemia ($n = 10$), and urinary tract infection ($n = 8$). The median total duration of urticaria was 47 weeks (min:8, max:284). The duration of urticaria was longer in patients with atopy ($p < 0.05$), and the group that went into remission with standard-dose antihistamine was the group with highest eosinophil count ($p = 0.022$). In most children with CU, the underlying cause/disease cannot be determined. In our study, treatable triggers were found in some of the patients. Therefore, it is appropriate for each patient to be evaluated with selected laboratory tests after detailed history and physical

examination.

1 INTRODUCTION

Urticaria is a condition characterized by the development of wheals (hives), angioedema, or both.¹ In total, 15%–25% of people experience urticaria at least once in their lifetime. Urticaria lasting longer than 6 weeks is defined as chronic urticaria (CU). CU is called chronic spontaneous urticaria (CSU) if the lesions occur spontaneously and chronic inducible urticaria (CIU) if they emerge due to a stimulus. CIU is triggered by specific environmental stimuli and is divided into subgroups based on the triggering conditions, such as symptomatic dermographism, cold urticaria, delayed pressure urticaria, heat urticaria, solar urticaria, vibratory angioedema, cholinergic urticaria, aquagenic urticaria, and contact urticaria. Although CSU can be associated with chronic infections, autoimmune diseases, allergic diseases, and malignancies, no cause can be identified in most patients.^{1–4} Studies reported that the rate of detecting the triggering factor for CU ranges from 21% to 83%.^{5, 6} International guidelines recommend performing provocation tests for CIU³ and investigating infections, autoimmune diseases, and allergic diseases for CSU.^{1, 2} The guidelines recommend basic investigations for patients with CU. Further laboratory examinations should be selected based on history, physical examination, and/or family history of the suspected disease. Detailed laboratory examination should be performed in patients with longstanding and/or uncontrolled disease. In addition, further examinations can also be performed in patients who have abnormal test results (e.g., patients can be evaluated for atopic diseases or parasitic infections in the presence of eosinophilia).³

Although antihistamines constitute the basis of treatment for CU, patient responses to treatment can be very variable. The first step in treatment is standard-dose antihistamines, and the subsequent steps are two- or fourfold doses of antihistamines in patients who do not respond to this treatment. The addition of montelukast, omalizumab, cyclosporine, and so forth, is recommended in patients who do not respond to the previous treatment regimen.^{7, 8}

There are a limited number of studies investigating the etiology, treatment approaches, and factors affecting prognosis in pediatric CU. The approach to pediatric CU is generally based on the guidelines for adult CU. This study aimed to evaluate the demographic characteristics, clinical findings, laboratory results, comorbidities, and treatment responses in pediatric patients followed up with CU diagnosis and to determine the risk factors associated with prognosis.

2 MATERIALS AND METHODS

This retrospective study was performed between December 1, 2019 and January 1, 2020 in a pediatric allergy outpatient clinic. Approval for the study was obtained from the local ethics committee (Approval Number: GO 19/337 and 2019/09-49), and the study was conducted in

accordance with the Declaration of Helsinki. The study included patients aged between 0 and 18 years who visited the pediatric allergy outpatient clinic between January 1, 2013, and December 31, 2018, and were followed up with CU diagnosis.

2.1 Study group

Patient files and hospital records were evaluated for 1084 patients who were examined in the pediatric allergy outpatient clinic between January 1, 2013, and December 31, 2018, and who were diagnosed with urticaria using the diagnostic code L50 according to the ICD-10 system. Patients with urticaria for longer than 6 weeks and aged 0–18 years were included in the study. The patients who received the diagnostic code L50 inconsistent with medical history and physical examination findings, those with acute urticaria or recurrent acute urticaria, those with missing information in the case report form, or those whose follow-up results could not be reached were excluded from the study. Information about demographic characteristics, clinical findings, duration of symptoms, accompanying atopic and chronic diseases, familial atopy, presence of CU and other chronic diseases, laboratory tests, skin prick and provocation tests, treatments, treatment responses, and duration of urticaria were obtained from patient files and included in the case report form. Patients without urticaria for at least 3 months were considered to be “under control”. Patients whose urticaria was under control using treatment were defined as “controlled with treatment”, patients whose urticaria was under control without treatment were defined as “in remission”, and patients whose urticaria persisted despite treatment were defined as “treatment-resistant”. The time from the onset of urticaria until remission was defined as “duration of urticaria”. Our treatment protocol followed the guidelines at that time and health policy in our country. The treatment steps were as follows: standard-dose antihistamine, two- or fourfold dose antihistamine, adding H₂ and/or H₁ sedative antihistamines, adding montelukast, and adding omalizumab (if the patient was older than 12 years).

2.2 Laboratory tests

The following data were recorded from patient files and the hospital data registry system: complete blood count (CBC) parameters, erythrocyte sedimentation rate, C-reactive protein, liver enzymes, total IgE level, serum complement (C3 and C4) levels, thyroid function tests (fT₄, thyroid-stimulating hormone [TSH]), thyroid autoantibodies (thyroglobulin antibody [anti-TG], thyroid peroxidase antibody [anti-TPO]), antinuclear antibody (ANA), double-stranded DNA antibody (anti-dsDNA), complete urine analysis, urine culture, *Helicobacter pylori* in stool test, ova and parasite (O&P) exam in stool, skin prick test (for foods and/or inhalant allergens, prick-to-prick tests), and specific IgE (screening test for inhalant allergens, screening test for food allergens). The mean platelet volume (MPV), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) were calculated, and all data were recorded on the case report form.

Results of laboratory parameters were evaluated and defined as low, normal, or high

according to the patient's age. Neutropenia was defined as neutrophil count $<1500/\text{mm}^3$, lymphopenia was defined as lymphocyte count $<1500/\text{mm}^3$, and eosinophilia was defined as eosinophils $>4\%$. Serum IgE level was evaluated according to age, and those above two standard deviations were defined as elevated IgE.⁹

2.3 Skin-prick test

The following allergens were used as common inhalant allergens in skin-prick tests: house dust mites (*Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*), grass pollen (hogweed, English grass, Timothy grass, Kentucky blue bluegrass, sweet vernal grass), fungi (*Alternaria*, *Aspergillus*), animal epithelium (cat, dog), cockroach (*Blatella germanica*), tree pollen (olive pollen, maple tree, horse chestnut, plane tree, acacia, linden), and weed pollens (*Artemisia*, *Parietaria*, *Plantago*). A prick-to-prick test was performed with the probable foods in patients with suspected food allergies. Histamine was used as a positive control, and 0.9% NaCl was used as a negative control. The results were evaluated 15 min after the test. A wheal size greater than 3×3 mm compared to the negative control was considered positive. Children with at least one positive skin test were considered sensitized.¹⁰

2.4 Specific IgE levels in blood

Specific IgE levels in blood were measured for the patients who could not have skin tests but were suspected of being sensitized to an inhalant or food allergen. These tests were performed with the enzyme-linked immunosorbent assay (ELISA) method by using an inhalant screening test for *Dermatophagoides pteronyssinus*, *Cladosporium herbarum*, rye, birch, mugwort, timothy grass pollen, and cat and dog epithelial sIgEs. In patients with suspected food allergies, screening tests were performed for wheat, codfish, soybean, milk, peanut, egg white sIgE, and foods containing almond, hazelnut, peanut, or coconut depending on the suspected foods. Test results above 0.35 kIU/L were considered positive.¹⁰

2.5 Provocation tests

An exercise provocation test was performed for patients with suspected cholinergic urticaria. For symptomatic dermographism, the back or volar face of the forearm was evaluated 5 min after scratching with a hard object. The ice-cube test was performed for patients who were thought to have cold urticaria; ice cubes in a thin plastic bag were placed on the skin for 10 min, and the test was considered positive if an urticaria plaque formed.³

2.6 Statistical analysis

Statistical analyses were performed using the SPSS program version 24 (IBM). The conformity of the data to normal distribution was evaluated with the Shapiro–Wilk and Kolmogorov–Smirnov tests. Categorical variables were expressed as numbers (n) and percent (%), numerical variables that showed normal distribution were expressed as mean $\pm$ SD, and those that did not show normal distribution were expressed as median,

interquartile range (IQR), and (minimum–maximum). Independent sample *t*-test was used to compare continuous variables in two groups with normal distribution; Mann–Whitney *U* or Kruskal–Wallis tests were used to compare variables that did not have normal distribution. Risk factors affecting prognosis in CU, CSU, and CIU were evaluated first with univariate logistic regression and then with multivariate logistic regression analysis. The *p*-values <0.05 were considered significant.

3 RESULTS

The study included a total of 141 patients with CU who met the inclusion criteria. The female/male ratio was 69/55, and the median age at first admission was 9.5 years (min: 1 max: 17). Of the patients, 124 (88%) had CSU, and 17 (12%) had CIU. At the time of admission, 63 (44.5%) of the patients had an accompanying atopic disease, and 23 (16.3%) had an accompanying chronic disease. The demographic characteristics, clinical findings, chronic diseases, and family histories of the patients at the time of admission are shown in Table 1.

TABLE 1. Characteristics of children with chronic urticaria, *n* = 141

Patient characteristics	
Female gender, <i>n</i> (%)	78 (55.3)
Age at symptom onset, years (median) (IQR) (min–max)	9.5 (7) (1–17)
Follow-up duration, week (median) (IQR) (min–max)	47 (118) (8–528)
Chronic spontaneous urticaria, <i>n</i> (%)	124 (88)
Chronic inducible urticaria, <i>n</i> (%)	17 (12)
Symptomatic dermographism, <i>n</i> (%)	14 (9.9)
Angioedema, <i>n</i> (%)	23 (16.3)
Allergic diseases, <i>n</i> (%)	
Asthma	15 (10.6)
Allergic rhinitis	25 (17.7)
Atopic dermatitis	4 (2.8)
Food allergies	8 (5.6)
Drug allergies	11 (7.8)
Chronic diseases, <i>n</i> (%)	
Nephrological diseases	

All patients had available CBC results; the most common abnormalities were eosinophilia (12.8%), lymphopenia 17 (12%), leukocytosis 11 (7.8%), and anemia 10 (7.1%). After CBC, the most frequently requested tests were transaminases, kidney function tests, thyroid function tests, acute phase reactants, urinalysis, and total IgE. The skin prick test with foods was performed in 19 patients, of which 31.6% were positive and the skin prick test with inhalant allergens was performed in 69 patients, of which 27.5% were positive. The most frequently detected inhalant allergen positivity was for tree pollens. All patients with CU had a dermographism provocation test, 9.9% of which were positive. The exercise test was positive in two of three tested patients with cholinergic urticaria, and the ice cube test was positive in one of the two tested patients with cold urticaria. All abnormalities detected in the patients are shown in Table 2.

TABLE 2. Abnormal laboratory and clinical findings of children with chronic urticaria

Parameters	n/n* (%)
Anemia	10/141 (7.1)
Leukocytosis	11/141 (7.8)
Neutropenia (<1500/mm ³)	2/141 (1.4)
Lymphopenia (<1500/mm ³)	17/141 (12.0)
Eosinophilia (>4%)	18/141 (12.8)
Thrombocytopenia (<150,000/mm ³)	1/141 (0.7)
Elevated transaminase level	4/135 (2.9)
Abnormal renal function test	4/133 (3.0)
Abnormal TSH result	3/119 (2.5)
Positive thyroid antibodies	7/99 (7.1)
Elevated ESR level (>20 mm/h)	10/107 (9.3)
Increased CRP value	6/80 (7.5)
Abnormal urine test results	10/136 (7.3)
Positive urine culture results	8/84 (9.5)
Parasites in stool	4/71 (5.6)

Note: n/n represents the number of positive test results and the number of tested patients.

As a result of patient history, physical examination, laboratory tests, and follow-up, 14 patients were diagnosed with intestinal parasites, 10 patients with anemia, eight patients with urinary tract infection, two patients with microscopic hematuria, two patients with *H. pylori* infection, two patients with selective IgA deficiency, and one patient each with Henoch Schönlein vasculitis, isolated elevated transaminase, gastroesophageal reflux disease (GERD), autoimmune thyroiditis, celiac disease, and idiopathic thrombocytopenic purpura (ITP). Based on the patient history and provocation tests, two patients (1.4%) were diagnosed with CSU and symptomatic dermographism, 12 patients (8.5%) with symptomatic dermographism, three patients (2.1%) with cholinergic urticaria, and two patients (1.4%) with cold urticaria. None of the patients with positive results from the food-specific IgE and skin prick food tests had symptoms compatible with food allergy, and all of them were considered sensitization. All patients with sensitization to inhalant allergens had an additional atopic disease such as allergic rhinitis or asthma. Abnormal laboratory test results in other patients were not associated with a particular disease or improved during the follow-up period. Diseases diagnosed as a result of patient history, physical examination, and laboratory tests and their relationship with CU are shown in Table 3.

TABLE 3. Diseases diagnosed as a result of history, physical examination, or laboratory tests, and relationship with chronic urticaria

Diagnosis	Possible association with CU (Yes/No/?)	Chronic urticaria remission with treatment ^a n (%)
Anemia, n = 10	No	0 (0)
Urinary tract infection, n = 8	Yes	5 (3.5)
Parasitosis, n = 14 ^b	Yes	12 (85.7)
Microscopic hematuria, n = 2	?	?
<i>Helicobacter pylori</i> infection, n = 2	Yes	2 (100)
Selective IgA deficiency, n = 2	?	?
Henoch-Schönlein vasculitis, n = 1 ^c	?	0 (0)
Isolated liver enzyme elevation, n = 1	?	?

Diagnosis	Possible association with CU (Yes/No/?)	Chronic urticaria remission with treatment ^a n (%)
Gastroesophageal reflux disease, n = 1 ^c	No	0 (0)

^a Ratio of patients with treatable disease among those diagnosed with chronic urticaria.

^b Parasite treatment was given to 10 patients due to the history/suspicion, although it was not found in the examinations, and urticaria regressed in nine of these patients.

^c Diagnosis was based on history and physical examination at the first visit to the clinic.

Urticaria was under control in 136 (96.5%) patients with CU. Standard-dose antihistamine was required in 53 of the patients (37.6%), high-dose antihistamine in 17 patients (24.1%), H1 and H2 antihistamines in 23 (16.3%), and H1 and H2 and sedative H1 antihistamines in 6 (4.3%). Urticaria improved with the addition of montelukast to antihistamine treatment in 29 patients (20.6%), and with the addition of omalizumab in eight patients. Five (3.5%) patients whose urticaria persisted despite the use of H1 antihistamine, H2 antihistamine, sedative H1 antihistamine and montelukast (and omalizumab if the patient older than 12 years) were considered resistant to treatment. Treatment responses of the patients are shown in Table 4.

TABLE 4. Treatment step in which urticaria was controlled

Treatment step	Remission n = 122 n (%)	Under control with treatment n = 14 n (%)	Treatment-resistant n = 5 n (%)
Standard dose antihistamine	53 (37.6)	–	–
High dose antihistamine ^a	16 (11.4)	1 (0.7)	–
H1 and H2 antihistamines	22 (15.6)	–	1 (0.7)
H1, H2 and sedative H1 antihistamines	6 (4.3)	–	–
Montelukast ^b	18 (12.8)	12 (8.5)	4 (2.8)
Omalizumab ^b	7 (4.9)	1 (0.7)	–

^a Twofold dose in 10 (6.9%) patients. ^b Used in addition to other treatments.

Urticaria was in remission in 122 patients (86.5%); the median duration of urticaria in these patients was 16 weeks (min: 8–max: 328). In 14 patients (10%), urticaria was under control with treatment; the median duration of urticaria in these patients was 43.5 weeks (min:11–max: 252). In 5 patients (3.5%), urticaria could not be controlled despite treatment; the median duration of urticaria in these patients was 174.0 weeks (min: 80–max: 284). The durations of urticaria for patients were classified based on their treatment responses and shown in Table 5.

TABLE 5. Duration of urticaria according to treatment response of patients

Duration of urticaria	Remission <i>n</i> = 122	Under control with treatment <i>n</i> = 14	Treatment resistant <i>n</i> = 5
Duration of urticaria, month (median) (IQR) (min–max)	16 (27) (8–238)	43.5 (54.0) (11–252)	174.0 (150.0) (80–284)
2–6 months <i>n</i> (%)	35 (28.7)	1 (7.1)	–
7–12 months <i>n</i> (%)	31 (25.4)	2 (14.3)	–
13–18 months <i>n</i> (%)	17 (13.9)	2 (14.3)	–
19–24 months <i>n</i> (%)	8 (6.6)	–	–
25–36 months <i>n</i> (%)	9 (7.4)	2 (14.3)	–
37–48 months <i>n</i> (%)	8 (6.6)	1 (7.1)	2 (40)
49–60 months <i>n</i> (%)	4 (3.3)	2 (14.3)	1 (20)
>60 months <i>n</i> (%)	10 (8.1)	4 (28.6)	2 (40)

The treatment step, which brought urticaria under control, was investigated with respect to patient age, gender, autoantibody positivity, eosinophil count, MPV, NLR, and PLR, family history of atopy, the presence of atopic, chronic, or autoimmune disease, and CU. The eosinophil count was the highest in the group that went into remission with standard-dose antihistamine, and the difference was statistically significant ($p = 0.022$). However, there was no difference between the groups with urticaria brought under control by different treatment steps with respect to other parameters ($p > 0.05$). The relationships between the durations of urticaria and patient age, gender, autoantibody positivity, eosinophil count, MPV, NLR, and PLR, family history of atopy, the presence of atopic, chronic, or autoimmune disease, and CU were also investigated. The time to remission was longer in patients with CU accompanied by atopic diseases ($p = 0.014$), but there was no relationship between the duration of urticaria and other parameters ($p > 0.05$). In addition, no correlation was found between the duration of CU and age, percentage of eosinophils, MPV, NLR, and PLR.

4 DISCUSSION

In this study, we evaluated patients with CU and found that CU is commonly accompanied by chronic or atopic diseases, but there was no causal relationship between CU and these diseases in the majority of patients. It was determined that CU rarely improved with treatment of the accompanying disease. In addition, the group with higher eosinophil count responded to treatment more easily, and the duration of urticaria was longer in the group with a history of atopy; however, a reliable marker associated with prognosis could not be determined.

In our study, the median age of our patients was 9.5 years, and the mean age was 9.2 years. Similarly, previous studies found CU to be more common in school children.^{5,6} In adults, CU is observed 2–4 times more often among women compared to men.¹ In our study, CU was observed slightly more frequently in girls than boys, and incidence varied between 44% and 54% in other studies conducted with children.⁴ This finding suggests that the incidence of CU in childhood is similar in both genders.

CU is examined in two categories as CSU and CIU. In our study, most of the patients were found to have CSU. In a meta-analysis of 10 studies, 85.1% of patients with CU were shown to have CSU.¹¹ In a study by Azkur et al. in which 222 children with CU were examined, 59.9% of the patients had CSU.⁵ The fact that both studies in the literature that found CIU to be more common than CSU (60% and 68.8%) were conducted in Korea hints that particular genetic and/or environmental factors might contribute to CIU.^{12,13} In our study, most of our patients with CIU had symptomatic dermographism. Apart from symptomatic dermographism, a few of our patients had cholinergic urticaria and cold urticaria. Symptomatic dermographism is the most common subgroup of CIU, and its frequency varies between 45% and 77.5% in different studies.¹¹ In previous studies, other common types of CIU were cholinergic urticaria and cold urticaria, although the order changed other types of CIU were very rare in children, and all these results in the literature were consistent with our findings.^{6,12-14}

Considering the relationship between CU and atopy, approximately one-third of our patients had an atopic disease; about half of these were allergic rhinitis (17.7% of patients with CU), followed by asthma (10.6%). In a previous study by Şahiner et al.,⁵ the most common atopic diseases in CU patients were asthma (10.1%), allergic rhinitis (7.1%), and atopic dermatitis (2.0%). Jirapongsananuruk et al.¹⁵ reported that 12.8% of patients had asthma, 14.9% had allergic rhinitis, and 2.1% had atopic dermatitis. Different from these studies, the most common atopic disease in our study was allergic rhinitis. The higher incidence of allergic rhinitis in our study group is thought to be compatible with the fact that allergic rhinitis is a more common disease in the general population.

In our study, 15.6% of the patients with CU had another chronic disease at the time of admission. The most common disease group was nephrological diseases. Autoimmune

diseases were present in three patients: Henoch-Schonlein vasculitis, Hashimoto's thyroiditis, and ITP. Similar to our study, Azkur et al. found chronic diseases in 19.5% and autoimmune diseases in 1% of patients.⁶ In other studies, the frequency of comorbid diseases in patients with CU ranged from 4.3% to 23%.¹¹ There was no data on the causal association between the patients' comorbidities and CU.

In our study, the most common abnormalities detected in CBC were eosinophilia, lymphopenia, and leukocytosis. Eosinophilia was thought to be associated with atopic diseases and parasites. In four of our patients, parasite infestation was found during examinations. In addition, 10 more patients with a suspected history of parasites or eosinophilia were given antiparasitic treatment. In our study, urticaria findings improved in 12 of 14 patients who were treated for parasites. Jirapongsananuruk et al.¹⁵ stated that parasites were detected in the stools of 5.3% of children with CU, but treatment did not have a significant contribution to remission of CU in their study. Azkur et al. reported that parasites were detected in 6.5% of patients who had stool samples examined.⁶ Arik et al.¹⁶ detected parasites in 21 children (10%) with CU and reported that urticaria completely disappeared in 10 of these patients, decreased in six, and did not change in five of these patients after the treatment. They found that the rate of CSU associated with parasitic infection in their patients was 4.7%. According to the results of all these studies, it appears appropriate to investigate parasite infestation in patients with CU or to initiate empirical treatment in suspected cases, especially in endemic regions. The second most common hematological abnormality was lymphopenia. Wu et al. demonstrated the coexistence of lymphopenia and CU after thymectomy in one case.¹⁷ In our study, lymphopenia improved in all these patients during follow-up, and no causal relationship was found between CU and lymphopenia.

It was reported that the pathogenesis of CU also involves autoimmunity, and CU may be accompanied by autoimmune diseases. Most of the patients in our study were tested for autoimmunity. Although autoantibody positivity was much higher, only four patients were diagnosed with autoimmune disease. It was reported that autoimmune diseases such as autoimmune thyroid disease and systemic lupus erythematosus vary between 0% and 27.5% in adult patients with CU.¹⁸ In contrast to adults, the scarcity of studies about autoimmune diseases in children led to the association of children's CU only with autoimmune thyroiditis, anti-thyroid antibodies, and celiac disease. Case-control studies show that the prevalence of autoimmune thyroiditis is 10–30 times higher in children with CSU than the general population.¹⁷⁻²⁰ Levy et al. found that thyroid autoantibody levels were high in 4.3% of children with CU (19). Azkur et al.⁶ found thyroid auto-antibodies in 7.1% and ANA positivity in 4% of the patients with CU, while Şahiner et al.⁵ found ANA positivity in 13.6%. Autologous serum test (AST) and basophil histamine release test (BHRT) can be used to demonstrate autoimmune etiology in CU. Although the use of BHRT rather than AST is recommended in children, unfortunately BHRT is not a routine test in our country and can only be used in developed and selected centers or for research purposes. In studies

conducted, the rate of positivity among children with CU who underwent AST ranged from 46.7% to 53.5%.^{5, 6} AST was not performed for any of our patients in our hospital due to obstacles in the preparation of AST, difficulties in administering the test to children, and interpreting the results. However, it was thought that the high autoantibody positivity in our patients might be related to autoimmunity in the pathogenesis of CU.

Food allergy is a rare cause of CU.¹⁸ Food allergies are more common in children than adults in the general population. While the frequency of food allergy reported by families in children aged 6–9 years is 5.7%, the frequency of food allergy confirmed by a double-blind placebo-controlled food challenge test was found to be 0.8%.²⁰ Studies showed that the frequency of food allergies in patients with CU was lower than expected; in a case series of children with CU, the prevalence of food allergies varied from 0% to 8.6%.^{21, 22} In our study, patients with suspected food allergies were evaluated with a skin prick test or sptIgE. All positive test results were considered as sensitization, and no relationship could be demonstrated between food allergies and CU in the patients. Informing the patients with CU and their families that food allergy is a rare cause of CU will both prevent unnecessary dietary practices due to suspected food allergies and reduce applications to hospital for allergy tests.

In our study, only one-third of our patients recovered with standard dose antihistamines, while others had to add certain drugs such as high doses of antihistamines, multiple antihistamines or omalizumab.

In a meta-analysis of CU in childhood, 63.8% of patients responded to fourfold increased doses of second-generation antihistamines. However, this study was performed with patients over 12 years of age, and there is not enough evidence about the safety of increased doses in children yet.^{23, 24} In our study, the rate of fourfold dose antihistamine was low; instead, the addition of montelukast and/or H2 antihistamine and H1 sedative antihistamine to twofold dose antihistamine was found to be more frequent. It was thought that this result might be related to concerns about the safety of fourfold dose antihistamine use in children.

An important issue in CU is the unpredictability of the duration of the disease. In our study, the median duration of CU was 47 weeks. Azkur et al. found the median duration of urticaria was 5.5 months, while Şahiner et al. found that it was 2.5 years and reported that patients were followed up for 18.1 years.^{5, 6} Studies performed to identify the natural course of CU in the pediatric population indicate that the remission rates were 16.5%–37%, 36%–54%, and 50%–67.5% after 1-, 3-, and 5 years from the onset of symptoms, respectively.^{2, 5, 25, 26}

In our study, CU lasted longer in patients with atopy. In a study investigating the relationship between clinical and laboratory findings and the duration of CU, Arık et al. found that the severity of the disease may be related to the duration of CSU.²⁷ No clear predictors of disease remission based on demographic data and abnormal test results were

established.²⁵

Another criterion related to prognosis in our study was the treatment step at which CU was brought under control. No relationship was found between the response to CU treatment and age, gender, presence of chronic disease, family history of atopy or autoimmunity, or eosinophilia in our patients.

The most important limitation of our study is being a retrospective study based on the review of patient files. As CU is a long-term disease, there were a limited number of patients included in the study because some of the patients dropped out of follow-up for various reasons. Patients whose condition improves generally do not continue the follow-up, and therefore, follow-up results could not be obtained for all patients and there was a large amount of data recorded in a non-standard manner. In addition, due to the retrospective design of the study, data about the patients' quality of life could not be obtained. However, the fact that the study presents real-life data from a tertiary allergy center covering a 6-year period makes our study valuable.

In conclusion, the fact that laboratory tests were found to be normal in most of the patients in our study or that they were unrelated to CU suggests that detailed investigations are not required for all patients. It will be more appropriate to limit the laboratory tests to suspected cases with clinical signs and/or to cases with prolonged or treatment-refractory disease. There is a need for further studies to define reliable markers of prognosis.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Conception or design of the work: Tuba Tuncel and Burçin Özen, *Data collection:* Ozlem Sancakli, Handan Duman Şenol, Emine Ece Ozdogru, and Tuba Tuncel, *Data analysis and interpretation:* Burçin Özen, Ozlem Sancakli, and Tuba Tuncel, *Critical revision of the article:* Ozlem Sancakli and Tuba Tuncel, *Final approval of the version to be published:* Ozlem Sancakli and Tuba Tuncel.

Open Research



DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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