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Natural History and Influencing Factors of Chronic Urticaria in Children

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ABSTRACT

Purpose: Chronic urticaria (CU) can reduce the quality of life of children and their parents, but there are only a few studies on the course of CU in children. This study aimed to investigate the natural course of CU in children and identify the factors that influence its prognosis.
Methods: We evaluated 77 children diagnosed with CU, who were monitored for at least 48 months. Subjects were classified as either chronic spontaneous urticaria (CSU) or other CU, and the clinical features were compared. Remission was defined as having no symptoms without treatment for more than 1 year. The remission rate was analyzed, and the factors influencing the prognosis were investigated.
Results: The average age of the study population was 5.96 ± 4.06 years, and 64 (83.1%) patients had CSU. The remission rates at 6 months, 1 year, 2 years, 3 years, and 4 years after symptom onset were 22.1%, 40.3%, 52.0%, 63.7%, and 70.2%, respectively, for children with CU. For children with CSU, these values were 23.4%, 43.7%, 56.2%, 68.7%, and 75.0%, respectively. The total serum immunoglobulin E (IgE) levels were positively correlated with disease duration ($r = 0.262$, $P = 0.021$); no other factors were associated with the duration of the disease.
Conclusions: A high proportion of children with CU were classified as CSU. No indicators, except for total IgE were found to predict the timing of spontaneous remission. The CU remission rate identified in this study is expected to be used as one of the reference data for the progress of CU in patients.

Keywords: Chronic urticaria; chronic spontaneous urticaria; chronic inducible urticaria; child

INTRODUCTION

Urticaria, a disease causing wheals and/or angioedema,[1] is known to be caused by the release of mediators, such as histamine, prostaglandin, and leukotriene, triggered by the mast cell and basophil degranulation of an immunological or non-immunological reaction.[2,3] Chronic urticaria (CU) is defined as urticaria lasting for 6 weeks or more.[1] The prevalence of CU, which is currently increasing, was found to be 0.02%–5.0% globally and approximately 0.16%–2.3% in Korea.[4] It is known that children have lower prevalence of CU than adults.[5] CU is generally classified as chronic spontaneous urticaria (CSU) or inducible urticaria based on the triggering factors. CSU is of an unknown etiology,[6] whereas inducible urticaria, including

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physical urticaria (e.g., dermographism, solar urticaria, and delayed pressure urticaria) and nonphysical urticaria (e.g., aquagenic urticaria, cholinergic urticaria, and contact urticaria), has a specific trigger.[6] In addition to these 2 subtypes, there are other types of CU due to infection, food, autoimmune diseases, etc., depending on the etiologic classification.[7,8] The most common CU is CSU, accounting for 21%–83% of chronic urticaria.[9]

The symptoms of CU worsen and improve repeatedly, and 42% of cases persist for more than 1 year.[10] The duration of the disease is approximately 1– 5 years, but can be longer for more serious cases.[11] However, the factors influencing the prognosis of the disease remain unclear. Although CU is not a fatal disease, it may considerably impair patients' quality of life in several ways; it is also relatively difficult to predict its prognosis. Children with CU reportedly had more absences and decreased school performances compared with those with other allergic diseases.[12] Analysis of its psychological impact revealed that the quality of life of patients with urticaria scored below the 20th percentile of general population.[12] Patients with CU also suffer from sleep disturbances, cosmetic problems, adverse effects from medications, and emotional stress.[13-15] Previous reports have associated CSU with infection, autoimmunity, and low vitamin D levels[16]; however, further studies on the factors related to CU are warranted. Studies on the natural course and associated factors of pediatric CU are limited as well.[17]

Therefore, this study aimed to investigate the clinical features and natural course of CU in children.

MATERIALS AND METHODS

Subjects

We enrolled 77 patients below the age of 18 years who visited Kyungpook National University Children's Hospital from March 2014 to July 2017 and were diagnosed with CU based on symptoms lasting for over 6 weeks. We excluded subjects with hospitalization history, emergency room or hospital visits due to infection, fever, and history of taking drugs such as nonsteroidal anti-inflammatory drugs 1 month prior to consultation. Those with underlying disorders (*i.e.*, heart, endocrine, or nervous system disorders) and receiving related medications were also excluded. Patients were followed up for a minimum of 4 years. Disease evaluation and progression were assessed over the phone if a personal visit was not possible. This study was approved by the Institutional Review Board (IRB) of Kyungpook National University Chilgok Hospital (IRB No. 2020-08-021).

Method

The medical records of CU patients were reviewed retrospectively. The following items were recorded: patient's sex and medical history, age at what urticaria was first developed, age at first visit, duration of the disease, presence of allergic diseases other than urticaria (*i.e.*, asthma, atopic dermatitis, food allergy, and allergic rhinitis), and family history of allergic disease. ImmunoCAP tests for 6 types of food (ThermoFisher Scientific Inc., Uppsala, Sweden), multiple antigen simultaneous test (MAST, AdvanSure Alloscan, LG Life Sciences, Daejeon, Korea) for food antigen, antigen test for hepatitis B (HBs Ag/Ab), and parasite fecal test were performed. Total serum immunoglobulin E (IgE), serum immunoglobulin G/A/M, total eosinophil count in peripheral blood, serum eosinophil cationic protein (ECP), complements (CH50, C3, and C4), vitamin D level, and antinuclear antibody (ANA) were

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also evaluated for all subjects. If necessary, a skin prick test (SPT) was conducted. Allergens suspected of being associated with urticaria were checked with immunoCAP, MAST, and SPT; the provocation test was not conducted. However, the association between the allergy test results and CU was confirmed by thoroughly checking the presence or absence of urticaria while introducing or removing the suspected antigen through the patient's medical history.

Classification of Subjects

Classification by cause

Cases with an unknown cause were classified into the CSU group. Cases with identified causes, including physical urticaria, infection, food/inhalant allergy, and autoimmune disease, were classified into the other CU group.

Classification by frequency of symptoms

Chronic urticaria was classified according to the frequency of urticaria at first visit; domestic and international reference data were applied.[16,18-20] Cases with urticarial symptoms occurring daily or more than twice a week and persisting for more than 6 weeks were defined as chronic continuous urticaria (CCU). Cases with a symptom interval of more than 1 week but not more than 6 weeks and lasting for more than 6 weeks were classified as chronic recurrent urticaria (CRU).[16,19]

Classification by urticaria duration before remission

Remission was defined having no symptoms of urticaria for more than 1 year without any treatment (*i.e.*, remission at 6 months means showing no symptoms of urticaria for more than 1 year after 6 months of symptom period). The cases were classified according to the duration of the symptom period before remission: symptom period I, 6 weeks–6 months; II, 6–12 months; III, 12–24 months; IV, 24–36 months; and V, 36–48 months. The remission rate was calculated in each of these symptom periods.

Statistical analysis

Statistical analysis was performed using PASW Statistics ver. 18.0 (SPSS Inc., Chicago, IL, USA). The associations between the variables were evaluated using Spearman correlation analysis, and the characteristics of the classified groups were compared using independent *t*-test and χ^2 test. Subsequently, one-way analysis of variance and Kruskal-Wallis test were used to compare the characteristics of three or more groups. Finally, *post hoc* analysis was conducted. The factors related to remission were determined via Cox regression. The level of statistical significance (*P* value) in this study was set at less than 0.05.

RESULTS

Demographics and clinical characteristics of the subjects

A total of 107 children diagnosed with CU from March 2014 to July 2016 were enrolled, and further assessment was performed over the phone if it was difficult to check their latest condition with the medical records. Among 107 patients, 77 were included in the analysis after excluding 29 patients whose contact information was unavailable and one who declined to provide information. Their mean age was 5.96 ± 4.06 years (mean ± standard deviation), with more boys than girls in a ratio of 1.57:1 (47:30). The mean duration of urticaria was 29.56 ± 28.45 months. The mean frequency of urticaria at first visit was 2.77 ± 2.05 days a week, occurring once every 2 days to twice a week. The most common accompanying allergic disease was food allergy (22.4%), followed by allergic rhinitis (17.6%) (**Table 1**). The most

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Table 1. Demographics and clinical characteristics of the subjects (n = 77)

Characteristics	Result
Age at onset (yr)	5.96 ± 4.06
Sex (male:female)	47:30 (1.57:1)
Duration of symptoms at the first visit (day)	266.13 ± 412.69
Clinical symptoms	
Wheal only	66 (87.1)
Wheal with angioedema	11 (12.9)
Angioedema only	0 (0.0)
CCU:CRU	54:23 (2.34:1)
Duration of disease (mon)	29.56 ± 28.45
Comorbid conditions	
Food allergy	19 (22.4)
Allergic rhinitis	15 (17.6)
Atopic dermatitis	8 (9.4)
Asthma	5 (5.9)
Cause	
Unknown (chronic spontaneous urticaria)	64 (83.1)
Food allergy	5 (6.0)
Aeroallergen allergy	3 (3.6)
Cold urticaria	2 (2.4)
Solar urticaria	1 (1.2)
Infection (Mycoplasma infection)	1 (1.2)
Autoimmune disease	1 (1.2)

The values are presented as mean ± standard deviation or number (%).
CCU, chronic continuous urticaria; CRU chronic recurrent urticaria.

common cause of CU was idiopathic (n = 64; 83.1%), followed by food allergy (6.0%; milk allergy: 3, wheat allergy: 2), aeroallergen allergy (3.6%; 1 dog dander allergy: 1, pollen allergy: 2), cold urticaria (2.4%), solar urticaria, infection (mycoplasma infection), and autoimmune disease (1.2%; Henoch-Schönlein purpura) (**Table 1**).

Laboratory test for subjects

Out of the 77 patients with CU, 24 (31.2%) were atopic with positive IgE to more than one allergen, and the mean total serum IgE was 164.49 ± 309.75 IU/mL. An increase in total IgE by over 200 IU/mL was observed in 19 patients (22.4%). Eosinophilia (> 500/μL) was seen in of 9.1% of patients (n = 7).[21,22] Three subjects were positive for ANA. No patient showed abnormal findings in liver function tests, antigen test for hepatitis B, parasite fecal test, and complements (CH50, C3, and C4) test (**Table 2**).

Table 2. Laboratory analysis of the subjects (n = 77)

Variable	Results
Atopic rate (Presence of allergen-specific IgE)	24 (31.2)
Total eosinophil count (/mm^3)	250.42 ± 204.07
Eosinophilia (> 500)	7 (9.1)
Total serum IgE (IU/mL)	164.49 ± 309.75
Elevated IgE (> 200)	19 (22.4)
ECP (μg/L)	21.93 ± 22.40
25-OH Vitamin D (ng/mL)	22.03 ± 9.58
Antinuclear antibody positive	3 (3.9)
Abnormal liver function test	0 (0)
HBs Ag positive	0 (0)
Positive stool exam for parasite infection	0 (0)
Decreased complement (C3, C4, CH50)	0 (0)

The values are presented as mean ± standard deviation or number (%).
IgE, immunoglobulin E; ECP, eosinophil cationic protein.

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Comparison of the CSU and other CU groups

The CSU group had significantly higher ECP than those in the other CU group (23.63 ± 23.83 vs. 13.59 ± 10.37; $P = 0.019$), but no significant differences in other laboratory tests were observed between 2 groups. There were no significant differences in the duration of symptoms at first visit, remission rate, total disease duration between the 2 groups of patients in remission (data not shown).

Comparison of patients with CCU and CRU among the CU group

No significant differences in age, sex, and laboratory tests were found between the CCU and CRU groups. The duration of symptoms at the first visit ($P < 0.001$) was significantly longer for the CRU group. There were no differences in remission rates and duration of the disease for all patients, as well as in total disease duration among patients with observable remission in each group (**Table 3**).

Comparison of patients with CCU and CRU among the CSU group

No significant differences in age, sex, laboratory tests, remission rates, and duration of the disease between the patients with CCU and CRU of the CSU group. No significant difference was found in the total duration of the disease among patients with observable remission as well (**Table 4**).

Remission rates and influencing factors of remission for CU

The remission rates were assessed at 5 time points based on symptom duration before remission. The remission rates at 6 months (I), 1 year (II), 2 years (III), 3 years (IV), and 4 years (V) after symptom development were 22.1%, 40.3%, 52.0%, 63.7%, and 70.2%, respectively. In the CSU group, they were 23.4%, 43.7%, 56.2%, 68.7%, and 75.0%, respectively (**Fig. 1**). Moreover, higher total serum IgE was associated with longer duration of the disease ($r = 0.262$; $P = 0.021$) (**Fig. 2**). The remission rates were not correlated with age, sex, and laboratory test results, such as peripheral eosinophil count and serum ECP.

No prognostic factors related to remission were found in the other CU group. In the CSU group, higher total IgE was correlated with lower remission rates ($P = 0.019$) (**Table 5**). Among all CU patients, no differences were found in sex, age of onset, duration of symptom at the first visit, presence of angioedema, and other laboratory findings.

Table 3. Comparison between patients with CCU and CRU among the entire CU group

Variable	CCU	CRU	*P* value
Number of patients	54 (70.1)	23 (29.9)	
Male/female	32/22	15/8	0.628
Age (yr)	5.85 ± 4.15	6.20 ± 3.92	0.730
Laboratory profile			
Total eosinophil count(/mm^3)	258.93 ± 226.50	230.43 ± 140.28	0.505
Eosinophilia (> 500)	5 (9.3)	2 (8.7)	0.849
Total serum IgE (IU/mL)	134.13 ± 182.66	235.77 ± 493.44	0.189
Elevated IgE (> 200)	13 (24.1)	6 (26.1)	0.854
ECP (μg/L)	23.63 ± 25.30	17.95 ± 12.95	0.198
25-OH Vitamin D (ng/mL)	22.81 ± 10.13	20.16 ± 8.05	0.227
Duration of symptoms at the first visit (day)	157.56 ± 170.45	521.04 ± 649.23	< 0.001
Remission rate	39 (72.2)	18 (78.2)	0.577
Duration of disease (mon)	27.63 ± 25.10	34.10 ± 35.31	0.432
Duration of disease in patients with remission (mon)	14.42 ± 14.51	19.91 ± 16.52	0.236

The values are presented as mean ± standard deviation or number (%).
CCU, chronic continuous urticaria; CRU, chronic recurrent urticaria; CU, chronic urticaria; IgE, immunoglobulin E; ECP, eosinophil cationic protein.

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Table 4. Comparison between patients with CCU and CRU among the CSU group

Variable	CSU	CCU	CRU	*P* value
Number of patients	64 (100)	47 (73.4)	17 (26.6)	
Male/female	40/24	29/18	11/6	0.826
Age (yr)	6.11 ± 4.01	6.21 ± 4.12	5.85 ± 3.78	0.755
Laboratory profile				
Total eosinophil count (/uL)	258.44 ± 214.06	267.23 ± 233.40	234.12 ± 151.45	0.589
Eosinophilia (> 500)	6 (9.3)	4 (8.5)	2 (11.8)	0.693
Total serum IgE (IU/mL)	127.67 ± 172.53	130 ± 187.92	121.21 ± 124.94	0.859
Elevated IgE (> 200)	14 (21.9)	10 (21.28)	4 (23.5)	0.847
ECP (μg/L)	23.63 ± 23.83	25.09 ± 26.7	19.58 ± 12.76	0.418
25-OH Vitamin D (ng/mL)	22.36 ± 9.29	22.99 ± 9.72	20.61 ± 7.98	0.369
Duration of symptoms at the first visit (day)	200.36 ± 224.59	161.66 ± 168.77	307.35 ± 316.48	0.086
Remission rate	49 (76.6)	35 (74.5)	14 (82.4)	0.511
Duration of disease (mon)	25.73 ± 23.69	26.73 ± 24.86	22.98 ± 20.53	0.580
Duration of disease in patients with remission (mon)	14.72 ± 13.83	14.53 ± 14.68	15.19 ± 11.93	0.881

The values are presented as mean ± standard deviation or number (%).
CCU, chronic continuous urticaria; CRU, chronic recurrent urticaria; CSU, chronic spontaneous urticaria; IgE, immunoglobulin E; ECP, eosinophil cationic protein.

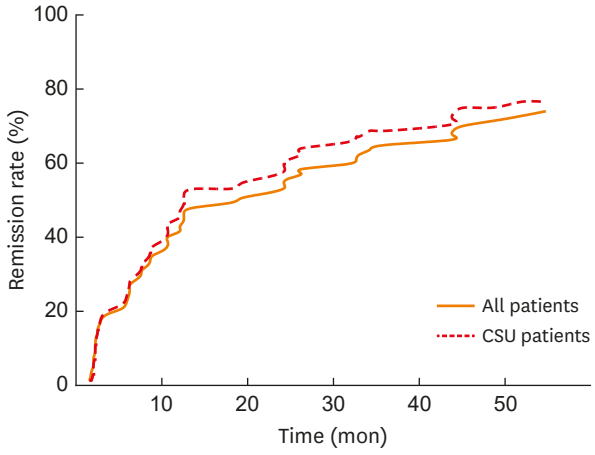

Fig. 1. Remission rates of chronic urticaria and CSU.
The remission rates at 6 months, 1 year, 2 years, 3 years, and 4 years after symptom onset were 22.1%, 40.3%, 52.0%, 63.7%, and 70.2%, respectively. In children with CSU, these values were 23.4%, 43.7%, 56.2%, 68.7%, and 75.0%, respectively.
CSU, chronic spontaneous urticaria.

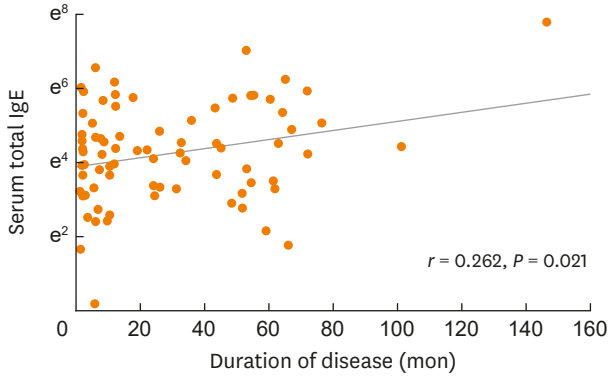

Fig. 2. Factors related to the remission of chronic urticaria. The level of total serum IgE was positively correlated with the duration of the disease.
IgE, immunoglobulin E.

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Table 5. Prognostic factors of remission of chronic spontaneous urticaria according to Cox analyses

Variable	HR	95% CI	*P* value
Sex	1.082	0.524–2.235	0.831
Age at onset	1.086	0.962–1.226	0.183
Duration of symptoms at the first visit	1.000	0.998–1.002	0.936
Frequency of urticaria at the first visit	0.833	0.663–1.046	0.116
Presence of angioedema	0.946	0.366–2.447	0.909
Presence of physical urticaria	0.392	0.150–1.025	0.056
Total IgE	0.997	0.994–0.999	0.019
Total eosinophil count	0.999	0.997–1.001	0.390
ECP	1.012	0.995–1.029	0.160
Vitamin D	0.998	0.954–1.045	0.947

HR, hazard ratio; CI, confidence interval; IgE, immunoglobulin E; ECP, eosinophil cationic protein.

DISCUSSION

Although CU is not uncommon in children, it still reduces the patients' quality of life, especially because of its unpredictable disease course. However, studies focusing on CU in children have been limited. The reported onset age of CU varies between 5 and 10 years in some international reports,[17,23,24] whereas it vares between 10 and 11 years in a domestic study.[25] Other recent local studies reported the median onset age of CU to be approximately 4–5 years.[21,26] In the present study, the median age of patients at diagnosis was 5–6 years, similar to recent findings.[21,26] In our study, CU cases were not correlated with age or prognosis, similar to other reports.[21,22,26] However, another study showed a higher remission rate in children below 8 years of age than those in older than 8 years[27]; the remission rate was also higher in children below the age of 10 years.[25]

Adult women more frequently had CU compared with adult men; however, in children, there was no significant difference in sex.[15] Some studies reported that the remission rate was higher in girls than in boys[27] and that prognosis was worse in girls below the age of 10 years[28]; however, recent studies reported no significant differences in remission rates according to the sex of the patients,[22,26,29] similar to our study results. Further studies are needed to investigate the association between prognosis and age or sex of pediatric patients with CU.

In this study, 83.1% of the subjects were classified as CSU because no definitive cause of CU was found. Although some subjects reported dermographism (n = 21; 32.8%) and food allergy (n = 15; 23.4%), the repeated urticaria observed in these subjects usually had a different shape from that of dermographism, with no relationship to specific foods. In this study, CU had several etiologies including food allergy (6.0%), aeroallergen allergy (3.6%), cold urticaria (2.4%), solar urticaria (1.2%), and mycoplasma infection (1.2%). Infection has been reported as an etiology of CU in pediatric patients[15,30]; however, in this study, all hepatitis B antigen tests and parasite fecal tests were negative. One patient infected with mycoplasma had respiratory symptoms accompanying urticaria for 4 weeks; urticaria persisted even after the improvement in respiratory symptoms, which was defined as CU, but gradually improved after 7–8 weeks without further urticaria development.

Among adult patients with CU, 14%–33% were related to autoimmune diseases,[25] and the incidence rates of other autoimmune diseases, such as rheumatic arthritis, systematic lupus erythematosus, and inflammatory bowel disease has increased.[31,32] Research on the association between CU and autoimmune disease in pediatric patients is quite limited. In our study, we were unable to find a correlation with CU and autoimmune diseases, although there

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were three subjects with positive ANA. One patient with an autoimmune disease initially had a negative ANA, but was diagnosed during follow-up. Therefore, it may be important to follow-up and observe the development of autoimmune diseases in pediatric patients with CU, because CU could be an antecedent symptom of autoimmune diseases.[33]

In many recent guidelines, review articles, and clinical studies, the diagnosis of CU is based on recurrent urticaria for a minimum of 6 weeks. However, the actual frequency of urticaria is either not specifically determined[13,22,34] or varies between reports.[25,26,35] In some cases, the criteria was limited to patients with CU for 6 weeks or more, occurring almost every day,[35] 3 times a week,[26] 2 times a week, once a week or over.[25] In recent guidelines, CU is defined only as symptoms lasting for more than 6 weeks, without specifying a frequency.[1,4,36] The guidelines of the British Society for Allergy and Clinical Immunology mention that CU is traditionally referred to as a case with symptoms lasting for more than 6 weeks, with daily or almost daily symptoms, but patients with urticaria that recured after over several days to months and years were also included in the definition of CU.[7] Some studies used the classification of CCU and CRU according to their frequency,[8,16,18-20] and both were considered CU. According to Lee *et al.*,[16] in patients with CU, symptoms that appear daily or more than 3 times a week were defined as CCU, whereas symptoms occurring at least 1 week apart were defined as CRU. We used a similar classification and considered both groups CU; however, there was no difference between CCU and CRU in terms of disease duration. Likewise, a previous study reported the absence of a significant difference in severity according to frequency.[16]

In this study, peripheral blood total eosinophil count, serum ECP, and vitamin D levels were not associated with remission rate, similar to previous reports.[16,37,38] Higher total serum IgE levels were associated with longer disease duration, similar to the finding of Kessel *et al.*,[39] wherein total serum IgE levels were commonly high in adults with CU and was related to severity and duration of the disease. Although some pediatric studies reported no association between total IgE and disease outcome,[16,26] Cho *et al.*[29] reported longer duration of the disease in groups with high total serum IgE levels; however, these results were not statistically significant. A future large-scale studies are warranted to determine the association between total serum IgE and the remission rate of CU.

Atopic subjects positive to at least 1 allergen were not significantly different from nonatopic subjects who were negative to all allergen-specific IgE tests (data not shown). Other studies reported that patients, who were positive for allergen-specific IgE, showed slower improvement than those who were negative,[29] and that patients positive for multiple antigens had a longer duration of medication and more severe symptoms compared with those positive for only 1 antigen.[40] It is important to conduct more studies addressing the association between CU and allergen sensitization.

Comparison of the CSU group with the other CU group showed no significant difference in the natural course the disease, except for serum ECP, which was significantly higher in the CSU group. Choi *et al.*[41] reported higher ECP in the CSU group than in the control group, but no significant difference was reported between the atopic and non-atopic CU groups. Because increased ECP can be considered a factor that can induce skin lesions, in relation to the inflammatory response in CU, meaningful results about the effects of ECP are expected if large-scale studies focusing on ECP are conducted in the future.

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Considering that no definition for remission has been established in pediatric patients with CU, previous studies have adopted various criteria for assessing this. Our study defined remission as having no symptoms for more than 1 year without any medication. The remission rates of all subjects at 6 months, 1 year, 2 years, 3 years, and 4 years after symptom development were 22.1%, 40.3%, 52.0%, 63.7%, and 70.2%, respectively. In the CSU group, these values were 23.4%, 43.7%, 56.2%, 68.7%, and 75.0%, respectively. Although the remission rate 1 year after the onset of disease varied in previous studies, from 10%[17,28] to 50% more [21,26,42] in pediatric patients with CU, the 1-year remission rate in this study was 40%–50%, and no significant difference was found in the remission rates between the CSU and the other CU groups. In a recent study on remission, Park *et al.*[26] reported that the mean duration to reach remission was 8.0–12.5 months. In total, 77% of the patients showed remission within 2 years, and the 6-, 12-, and 24-month remission rates were 33.4%, 53.0%, and 71.2%, respectively, in CSU patients and 29.4%, 49.4%, and 67.8%, respectively, in other CU patients,. Although our study had relatively lower remission rates, similar to other reports, there was no significant difference in 1-year remission rate and remission rate according to the cause of urticaria.

This study has some limitations. The number of subjects was small because they were recruited from only one center. The provocation test was not performed to confirm the association between the allergy test results and CU. However, the causal relationship was confirmed by taking detailed medical history and eliminating or introducing the suspected antigen or physical stimulus. In this study, disease activity was not confirmed via the average urticaria activity score for 7 days (UAS7). Reports have shown that higher UAS7 levels at the first visit was correlated with longer duration of symptoms[43] and with the severity of CSU,[44] which is thought to be another factor predicting prognosis. The recent guidelines define CSU as either with unknown causes or due to autoreactivity with an autoantibody.[1] In this study, the autologous serum skin test (ASST) was not performed, and CU cases with autoreactivity with an autoantibody were not classified. However, the ASST has several limitations. The positive ASST results are not unique to patients with CSU,[45,46] and it is not useful in identifying patients who respond differently to treatment or whose disease follows a different clinical course.[47-49] A few reports have shown that unlike in adults, the detection of ASST in children does not affect the prognosis.[47,50] Therefore, the purpose of this study, which is to confirm the clinical characteristics and natural course of CU, will not be significantly affected.

In conclusion, most of the CUpediatric patients with unknown cause were classified as CSU, and the remission rate after 1 year was approximately 50%. In children with CU, higher total serum IgE was associated with significantly longer duration of the disease. However, this association should be further examined in large-scale studies. The results obtained from the current study will provide important data for the clinical assessment of the natural course of CU in pediatric patients.

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