

# Natural course and prognostic factors of chronic urticaria in Korean children: A single center experience

Hwanhee Park,<sup>1\*</sup> Ji Young Lee,<sup>2\*</sup> Ari Song,<sup>1</sup> Minyoung Jung,<sup>1,3</sup> Minji Kim,<sup>4</sup> Insuk Sohn,<sup>5</sup> Minji Kim,<sup>5</sup> Joongbum Cho,<sup>1</sup> Kangmo Ahn,<sup>1,3</sup> Jihyun Kim<sup>1,3</sup>

## Abstract

**Background:** Chronic urticaria (CU) has an adverse effect on academic achievement and psychosocial development in children.

**Objective:** We aimed to investigate the natural course of CU and to identify relevant factors associated with a poor CU prognosis in Korean children.

**Methods:** We retrospectively analyzed 253 children with episodes of wheals or angioedema at least 3 times a week that persisted for at least 6 weeks. Clinical data and laboratory results were obtained from medical records and parental telephone interviews. Kaplan-Meier survival analysis and log rank tests were performed to assess the median time to remission of CU and prognostic factors.

**Results:** Median age at onset was 5.0 years (interquartile range, 2.5-9.1) and median follow-up period was 7.6 months (interquartile range, 3.9-19.7). Of 253 patients, 68.8% had chronic inducible urticaria and 31.2% had chronic spontaneous urticaria. Physical urticaria was the only cause of chronic inducible urticaria, and the most common physical urticaria was dermographism. Median duration to remission of CU was 10.2 months (95% confidence intervals, 8.0-12.5 months). Kaplan-Meier analysis revealed that 33.4%, 53.0%, and 71.2% of children were in remission at 6, 12, and 24 months, respectively, after the onset of CU. The presence of allergic sensitization was significantly associated with a poor CU prognosis in univariable and multivariable analyses ( $P=0.010$  and  $P=0.014$ , respectively).

**Conclusion:** Half of children with CU were in remission 10.2 months after onset. Allergic sensitization was a risk factor associated with longer duration CU.

**Keywords:** Chronic urticaria; Etiology; Prognosis; Children; Korea

## From:

<sup>1</sup> Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

<sup>2</sup> Department of Pediatrics, Hallym University Hangang Sacred Heart Hospital, Seoul, Korea

<sup>3</sup> Environmental Health Center for Atopic Diseases, Samsung Medical Center, Seoul, Korea

<sup>4</sup> Department of Pediatrics, Hallym University Dongtan Sacred Heart Hospital, Hallym University School of Medicine, Dongtan, Gyeonggi-do, Korea

<sup>5</sup> Statistics and Data Center, Research Institute for Future Medicine, Samsung Medical Center, Seoul, Korea

\* These authors contributed equally to this work.

## Corresponding author:

Jihyun Kim

Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul, 06351, Korea

E-mail: jhlovechild@gmail.com

## Introduction

Chronic urticaria (CU) is defined as wheals with recurrent episodes lasting for at least 6 weeks. The prevalence of CU has been reported to be 0.5-5.0% in the general population and about 0.1-0.3% in children.<sup>1</sup> It is known that children have a lower prevalence than adults.<sup>1</sup> Impairment of quality of life in patients with CU is comparable to that experienced by patients with other chronic diseases such as ischemic heart disease, cystic fibrosis, and epilepsy.<sup>2,3</sup> CU impairs physical activity and lowers social function, which can adversely affect academic achievement and psychosocial development in children and adolescents.<sup>3-5</sup>

Acute urticaria is frequently associated with identifiable causes; in contrast, it is difficult to identify the etiology and to predict the occurrence or exacerbation of symptoms in patients with CU.<sup>3,6</sup> CU is classified into chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIU) according to

whether symptoms occur spontaneously or are induced by specific triggers. Although its pathogenesis is poorly understood, mixed Th1/Th2 immune response, mast cell activation, and autoimmunity are considered to play a role in the pathogenic mechanisms of CU.<sup>7</sup> There are also several types of evidence supporting that autoantigen is synthesized by specific triggers leading to mast cell degranulation in patients with CIU.<sup>8,9</sup> In general, the duration of CSU is 1-5 years, but is likely to be longer in more severe cases.<sup>10</sup> A previous Korean study reported that the mean duration of CU was 3.76 years in 641 adults.<sup>11</sup> The co-existence of angioedema, severity, and the presence of anti-thyroid antibodies were associated with longer disease duration in adult patients with CU.<sup>12,13</sup> However, few studies have investigated the clinical course or identified prognostic factors of CU in children.

Providing correct information about the etiology and prognosis of CU can reduce the anxiety of pediatric patients and their parents and help establish a therapeutic plan. Therefore, our aims in this study were to investigate the clinical features and natural course of CU and to identify factors associated with a poor CU prognosis in Korean children.

## Methods

### Patients

We retrospectively reviewed the medical records of patients 18 years or younger that were diagnosed with CU in Samsung Medical Center from January 2007 to October 2015. The definition of CU was wheals or angioedema that had lasted for more than 6 weeks and that occurred repeatedly (more than 3 times a week).

Demographic and clinical data were collected, including gender, age at onset, duration and frequency of symptoms, extent of skin involvement, presence of angioedema, and personal and familial history of allergic or autoimmune diseases. A family history of allergic diseases was defined as the presence of one or more family members diagnosed with atopic dermatitis, asthma, or allergic rhinitis by a physician.

All patients were interviewed using a detailed questionnaire regarding trigger factors such as sunlight, cold, water, pressure, vibration, exercise, scratching, foods, and drugs. Food or drug allergy was defined as a convincing history of reproducible symptoms within two hours after exposure to a single food or drug. Physical urticaria was diagnosed according to the criteria described by the Joint Task Force on Practice Parameters.<sup>14</sup> In addition, medication use for CU (H1 receptor antagonists, H2 receptor antagonists, leukotriene antagonists, oral corticosteroids, immunosuppressants, and biologic agents) was investigated.

For patients who did not have data regarding remission of clinical symptoms on their medical chart, a telephone survey was utilized based on a preformulated questionnaire. Complete remission of CU was defined as the absence of urticaria for at least 4 weeks without any medication.<sup>13</sup> This study was approved by the Institutional Review Board (IRB) of Samsung Medical Center (IRB No.2015-06-188).

### Laboratory test

Eosinophils in peripheral blood, erythrocyte sedimentary

rate (ESR), thyroid stimulating hormone (TSH), free thyroxine (T4), triiodothyronine (T3), thyroid auto-antibodies (thyroglobulin antibody, antimicrosomal antibody, and TSH receptor antibody), antinuclear antibody (ANA), serum C-reactive protein (CRP) levels, and serum total immunoglobulin E (IgE) levels were measured. The ANA test was performed by using the indirect immunofluorescence method with sera (Fluoro Hepana Test, MBL, Nagoya, Japan). Skin prick tests (Allergopharma, Reinbek, Germany) on the back or measurement of specific IgE levels with the immunoCAP system (Thermo Fisher Scientific Inc., Waltham, MA, USA) were performed regarding the following common allergens: *Dermatophagoides pteronyssinus*, *D. farinae*, egg white, cow's milk, wheat, soybean, and peanut. Positive sensitization was defined as a wheal diameter  $\geq 3$  mm or specific IgE levels  $\geq 0.35$  kU/L. Eosinophilia was defined as when eosinophils comprised more than 4% of total leukocytes.

### Statistical analysis

Data for continuous variables were shown as median and interquartile range. Prevalence rates were shown as percentages. Cumulative survival curves were estimated by the Kaplan-Meier method, and relationships between the cumulative probability of complete remission of CU and prognostic factors were analyzed using a log-rank test. The influence of prognostic factors on remission was evaluated by univariable Cox regression analyses. The relative importance of multiple prognostic factors on CU remission was analyzed using multivariable analysis in conjunction with the Cox proportional regression model. Variables with a *P* value of less than 0.2 in univariable analysis were chosen for multivariable analysis. Candidate variables for adjustment included gender, age at onset ( $< 5$  years old or  $\geq 5$  years old), clinical symptoms (with or without angioedema), past history of allergic diseases (presence or absence), past history of autoimmune diseases (presence or absence), family history of allergic diseases (presence or absence), inducible factors (presence or absence), sensitization (negative or positive), total IgE ( $< 200$  kU/L or  $\geq 200$  kU/L), eosinophils ( $< 4\%$  or  $\geq 4\%$ ), ESR ( $< 20$  mm/hr or  $\geq 20$  mm/hr), CRP ( $< 0.5$  mg/dl or  $\geq 0.5$  mg/dl), and ANA (negative or positive). CRP and ANA were excluded from the multivariate analysis because data were available for only 80 and 88 cases, respectively. Statistical analyses were performed using SAS (version 9.3, SAS Institute, Inc., Cary, NC, USA). Statistical significance was defined as a *P* value  $< 0.05$ .

## Results

A total of 253 patients (142 boys and 111 girls) with CU were included in this study. Median age at onset was 5.0 years (interquartile range, 2.5-9.1) and median follow-up period was 7.6 months (interquartile range, 3.9-19.7 months) (Table 1). Overall, 29 (11.5%) patients had wheals accompanied with angioedema, while 224 (88.5%) patients had wheals only without angioedema. Of 253 patients, 68.8% (174/253) had CIU, while 31.2% (79/253) had CSU. The only cause of 174 patients with CIU was physical urticaria, and the most common physical urticaria was dermographism (128/174, 73.6%), followed by cholinergic urticaria (76/174, 43.7%), cold urticaria (15/174,

**Table 1. Subject characteristics and laboratory results (n = 253).**

Characteristic	Number (%)
Gender	
Male	142 (56.1)
Female	111 (43.9)
Age (years)*	5.0 (2.5-9.1)
<1	15 (5.9)
1-4	111 (43.9)
5-9	78 (30.8)
≥10	49 (19.4)
Clinical symptoms	
Wheals only	224 (88.5)
Angioedema with wheals	29 (11.5)
Past medical history	
Atopic dermatitis	52 (20.1)
Allergic rhinitis	38 (15.0)
Asthma	24 (9.5)
Autoimmune disease	7 (2.8)
Family history of allergic diseases	
Atopic dermatitis	20 (7.9)
Allergic rhinitis	38 (15.0)
Asthma	8 (3.2)
Allergic sensitization**	90/219 (41.1)
Log(total IgE, kU/L)	2.0 ± 0.5

\*Data are presented as medians (interquartile range).

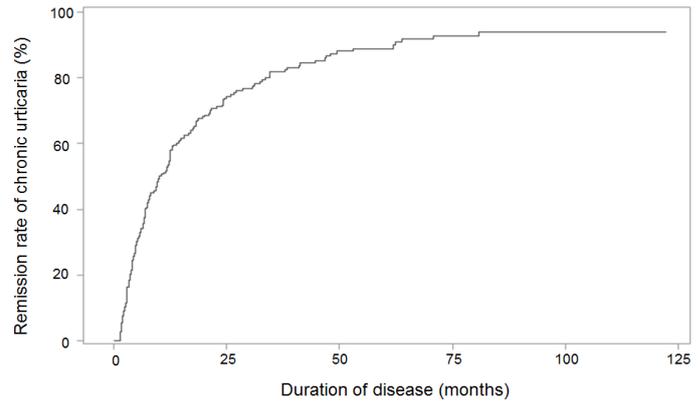
\*\* 219 patients underwent either a skin prick test or ImmunoCAP test.

8.6%), delayed pressure urticaria (9/174, 5.2%), solar urticaria (3/174, 1.7%), and aquagenic urticaria (2/174, 1.1%).

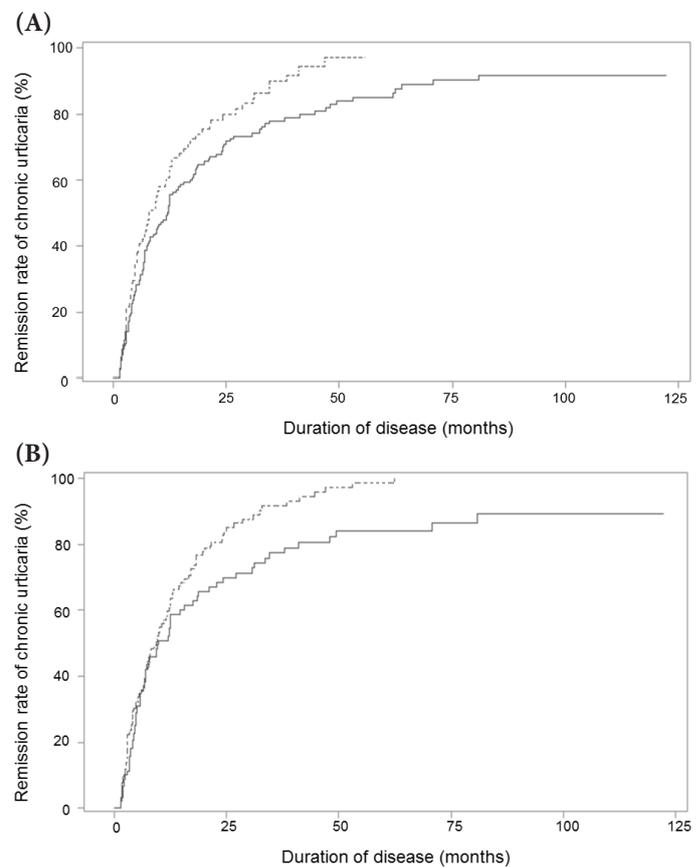
Twenty-two (25.0%) of 88 patients who underwent testing for ANA were positive. However, only one of these 22 patients had a history of autoimmune diseases such as systemic lupus erythematosus. TSH was elevated in only one of the 50 patients (2.0%) who underwent a thyroid function test, but her T3 and free T4 levels were normal.

During the observation period, 195 (77.0%) children had complete remission. In Kaplan-Meier survival analysis, 33.4%, 53.0%, and 71.2% of patients recovered at 6, 12, and 24 months after symptom onset, respectively (**Figure 1**). The median duration of CU was 10.2 months (95% confidence intervals, 8.0-12.5 months). A total of 190 patients (75.1%) were treated with H1 receptor antagonist alone, while 50 patients (19.8%) received two H1 receptor antagonists or more. In addition, nine patients (3.6%) were treated with both H1 and H2 receptor antagonists, and 21 patients (8.3%) were treated with an H1 receptor antagonist as well as a leukotriene receptor antagonist. No patients required systemic corticosteroids for ≥ 3 consecutive days or anti-IgE treatment.

Univariable analysis showed that patients who did not have inducible factors (CSU) or were not sensitized to common allergens had a better prognosis than those who had CIU or were sensitized to allergens ( $P=0.021$  and  $P=0.010$ , respectively) (**Table 2**). In Kaplan-Meier survival analysis, 40.7%, 60.9%, and 78.3% of CSU recovered at 6, 12, and 24 months after symptom onset, respectively. In addition, 29.4%, 49.4%, and 67.8% of CIU patients recovered at 6, 12, and 24 months,



**Figure 1. Kaplan-Meier survival analysis of children with chronic urticaria. Remission percentages at 6, 12, and 24 months after symptom onset were 33.4%, 53.0%, and 71.2%, respectively.**



**Figure 2. (A) Kaplan-Meier analysis of CIU (solid line) and CSU patients (dashed line). (B) Kaplan-Meier analysis of CU patients sensitized (solid line) and non-sensitized (dashed line) to allergens. CIU: chronic inducible urticaria, CSU: chronic spontaneous urticaria, CU: chronic urticaria.**

respectively (**Figure 2**). Median disease duration was 8.0 months for children with CSU and 12.1 months for those with CIU, and 9.4 months for non-sensitized patients and 9.8 months for sensitized patients. Median recovery time was 9.6 months for boys, 10.8 months for girls, 9.6 months for younger children (< 5 years old), and 12.0 months for older children (≥ 5 years

**Table 2. Predictors of remission of chronic urticaria according to univariable and multivariable Cox analyses.**

Variables	Univariable analysis			Multivariable analysis		
	Hazard ratio	95% CI	P Value	Hazard ratio	95% CI	P Value
Gender						
Female	1					
Male	0.945	(0.712-1.255)	0.697			
Age						
<5 years	1			1		
≥5 years	1.276	(0.962-1.692)	0.092	1.006	(0.740-1.366)	0.970
Clinical symptoms						
Wheals only	1			1		
Angioedema with wheals	1.383	(0.861-2.222)	0.180	1.393	(0.837-2.320)	0.202
Past history of allergic diseases						
No	1					
Yes	1.171	(0.879-1.563)	0.281			
Past history of autoimmune diseases						
No	1			1		
Yes	2.451	(0.907-6.623)	0.077	1.698	(0.520-5.556)	0.381
Family history of allergic diseases						
No	1					
Yes	1.068	(0.770-1.479)	0.693			
Inducible factors						
No	1			1		
Yes	1.422	(1.054-1.919)	0.021	1.330	(0.965-1.835)	0.081
Sensitization						
Negative	1			1		
Positive	1.511	(1.104-2.070)	0.010	1.486	(1.083-2.037)	0.014
Total IgE						
<200 kU/L	1					
≥200 kU/L	1.093	(0.791-1.511)	0.590			
Eosinophils						
<4%	1					
≥4%	1.059	(0.756-1.486)	0.737			
ESR						
<20 mm/h	1					
≥20 mm/h	0.745	(0.436-1.274)	0.282			
CRP						
<0.5 mg/dl	1					
≥0.5 mg/dl	0.669	(0.398-1.122)	0.128			
ANA						
Negative	1					
Positive	1.733	(0.920-3.268)	0.089			

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ANA, anti-nuclear antibody.

old). However, there were no significant differences in disease duration with respect to gender or age ( $P=0.697$  and  $P=0.092$ , respectively) (Table 2). In addition, no differences were found in CU prognosis according to the presence of angioedema, past medical history, family history of allergic diseases, or laboratory findings such as total IgE level, eosinophilia, ESR, CRP level, or ANA status.

Multivariable analysis also showed that allergic sensitization was associated with the persistence of CU ( $P=0.014$ ), and a trend for an association between the presence of inducible factors and remission was seen ( $P=0.081$ ) (Table 2). There were no differences between patients who went into remission and

those that did not with respect to gender, age, the presence of angioedema, past medical history, family history of allergic diseases, or laboratory findings.

## Discussion

In our present study, we found that half of children with CU achieved remission at 10.2 months after disease onset. Overall, 33.4%, 53.0%, and 71.2% of patients achieved remission within 6, 12, and 24 months of disease onset. In addition, the symptoms of about 75% of subjects improved in response to avoiding inducible factors or taking a regular dose of H1 antihistamines, indicating a good response to conservative or

medical treatment. To our knowledge, this is the largest study to describe the natural course and prognostic factors of CU in Korean children. The percentages of patients in remission at different time points in the present study are inconsistent with those reported in previous studies.<sup>15-20</sup> Kang et al. reported a remission rate of 84.8% in Korean children with CU at the 1 year follow-up, which is a better prognosis than what we found in our study.<sup>15</sup> However, previous studies conducted in other countries reported poorer outcomes than those of our study and Kang et al.'s study. For example, a Turkish study reported that 16.5%, 38.8%, and 50.0% of children with CSU showed an improvement in symptoms within 1 year, 3 years, and 5 years after disease onset, respectively.<sup>20</sup> In Japanese and Thai studies, symptoms improved in 36.6% and 18.5% of patients, respectively, within 1 year.<sup>16,18</sup>

Disagreement among studies on the natural course of CU might be due to differences in the study population and the presence of inducible factors. In particular, a younger age is likely to be associated with a better prognosis.<sup>15,20</sup> In our study, the median age of patients was 5 years old, which is younger than the 8-9 years described in previous studies.<sup>18-20</sup> In addition, gender might affect the prognosis of CU, because sex hormones are involved in the action of mast cells, peripheral basophil cells, and dendritic cells.<sup>4,21</sup> In our study, the male to female ratio was 1.3: 1, which is a higher male predominance than in other studies.<sup>18,22</sup> According to previous reports, 50-80% of CU patients have CSU, and only 25-40% of CU patients have inducible factors, of which physical urticaria is the most common.<sup>22-24</sup> In our study, 31.2% of the patients did not have any cause of urticaria, despite detailed history taking and several tests. The only cause of CIU was physical urticaria, and dermatographism was the most common cause of physical urticaria, consistent with another domestic study that reported that 42.3% of CU patients have dermatographism.<sup>15</sup> In the present study, the proportion of CSU was lower than that reported in a previous study.<sup>15</sup> We should note that our study included dermatographism as an inducible CU factor, whereas previous studies did not.

Allergic sensitization was the only factor that was associated with a worse CU prognosis in our present study, although the importance of atopic status in the pathogenesis of CU is still a matter of debate. A previous Korean study showed that children with CU had a higher prevalence of sensitization against house dust mites and polysensitization compared to those with acute urticaria.<sup>25</sup> Several previous studies have reported a higher prevalence of sensitization to variable allergens in patients with CU than in normal healthy subjects,<sup>26-28</sup> while fewer studies have investigated the association between atopy and CU prognosis. Recently, Song et al. reported that house dust mite sensitization as well as a positive autologous serum skin test (ASST) result were related to more severe disease and a longer disease duration.<sup>26</sup> Furthermore, higher expression of CD63 was observed in basophils from patients with CSU, suggesting that spontaneous basophil activation may contribute to the relationship between CU and allergic sensitization.<sup>29</sup>

The presence of inducible factors and/or autoimmune antibodies have been considered poor prognostic factors in previous studies of patients with CU, although this is still controversial.<sup>15,22,23</sup> We found a trend for an association between

the presence of inducible factors and remission without statistical significance in the multivariable analysis. A previous study found that symptom duration was longer in autoimmune urticaria, which was defined in that study as positive ASST, than CSU.<sup>23</sup> In that study, 17% of patients with CU were ANA positive, and 16% and 12% of patients were positive for anti-thyroglobulin antibodies and anti-microsomal antibodies, respectively.<sup>23</sup> These autoantibodies could activate basophils and mast cells to induce histamine release by complement.<sup>30</sup> In our present study, the ANA-positive rate was 25.0%, which is higher than that reported previously for healthy children (6-14%).<sup>31,32</sup> However, we did not find an association between CU prognosis and autoimmune diseases, because the number of patients who received tests for autoantibodies was too small for robust statistical evaluation of this relationship. Further studies are required to identify additional prognostic factors in children with CU.

Our study had some limitations that must be considered. This study was performed in a single tertiary center, therefore selection bias might have occurred. Secondly, remission state was determined by telephone survey for some patients because of the retrospective nature of the study. There might be patients with persistent disease who were selectively missed, although the telephone survey was done with all caregivers whose children were lost to follow-up. In addition, the same laboratory tests were not performed in all patients. Therefore, some variables such as CRP and ANA were not included in the multivariable analysis. It also should be noted that the treatment in our present study followed Korean Expert Opinion Report on the Management of CU, not international guidelines.<sup>6</sup> Despite these limitations, we provide useful information regarding the natural course of CU in children, the response rates to medical treatment, and prognostic factors.

In conclusion, the median duration of CU in Korean children was 10.2 months, and half of the CU patients showed symptom improvement within a year, indicating that children with CU had a favorable outcome. Allergic sensitization was associated with a poor CU prognosis.

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