

ORIGINAL ARTICLE

The natural history of chronic urticaria in childhood: A prospective study

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Background: There are few prospective studies on the natural course of chronic urticaria (CU) in children.

Objective: We sought to examine the natural history of CU in children and to identify predictors for remission.

Methods: Children 4 to 15 years of age with CU were investigated with a complete blood cell count, erythrocyte sedimentation rate, antinuclear antibody titer, complement CH₅₀ level, thyroid studies, autologous serum skin test, skin-prick tests, food challenges, and stool examination for parasites. They were considered to be in remission if symptoms did not recur for at least 12 months without medication.

Results: In all, 92 children (53.3% female) with CU were recruited and followed up for a median duration of 4.3 years (range 2.5-5.8 years). Chronic autoimmune urticaria (CAU) was identified in 40% of the patients. Food allergy was found in 8.7% and parasitic infestations in 5.4%. Remission rates at 1, 3, and 5 years after the onset of CU symptoms were 18.5%, 54%, and 67.7%, respectively. The remission rate did not differ in CAU compared with non-CAU. No predictor of CU remission was identified.

Limitations: The basophil histamine release assay was not performed.

Conclusion: Children with CU have a favorable outcome. CAU did not have an intractable course. (J Am Acad Dermatol <http://dx.doi.org/10.1016/j.jaad.2014.05.069>.)

Key words: autologous serum skin test; autoreactivity; children; chronic spontaneous urticaria; chronic urticaria; food allergy; natural course; remission.

Chronic urticaria (CU) is defined as urticarial episodes lasting for 6 weeks or longer.¹ The major subgroups of CU are chronic spontaneous urticaria (CSU), urticarial vasculitis, and physical urticaria.^{2,3} Disorders identified as possible causes of CSU include food allergies, connective tissue diseases, chronic infections, and parasitic infestation.^{2,4-6} In recent studies more than 30% of adults and children with CSU had autoantibodies to the α -subunit of high-affinity IgE receptor (Fc ϵ RI α) and/or anti-IgE antibodies.^{5,7-14} These patients were classified as having chronic

Abbreviations used:

ANA:	antinuclear antibody
ASST:	autologous serum skin test
CAU:	chronic autoimmune urticaria
CSU:	chronic spontaneous urticaria
CU:	chronic urticaria
SPT:	skin-prick test

autoimmune urticaria (CAU). The presence of autoantibodies may be screened for by performing the autologous serum skin test (ASST) or by an

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in vitro basophil histamine release assay.¹⁵ The ASST has relatively high sensitivity, moderate specificity, and a high negative predictive value compared with the basophil histamine release assay.^{14,16,17} It is also a practical test to assess autoreactivity in patients with CU especially where the basophil histamine release assay is not available.¹⁴ This autoreactivity may indicate mast cell activating autoantibodies in patients with CSU who have positive ASST.¹⁶

In adults, there are associations between CAU and autoimmune diseases such as thyroid disease, rheumatoid arthritis, celiac disease, type 1 diabetes mellitus, and an increased frequency of autoimmune markers such as rheumatoid factor and antinuclear antibody (ANA).¹⁸⁻²² Approximately 14% of adults and 4% of children with CSU have positive antithyroid antibodies.^{1,5,18-20} A cause for CSU is not identified in approximately 60% of patients.¹

Studies of the natural history of CU show that 30% to 50% of adults achieve remission 1 to 3 years after the onset of symptoms.²³⁻²⁷ The objectives of this prospective study were to investigate the natural course of CU in children and to identify predictors of disease remission.

METHODS

Patients

The study was approved by the institutional review board of Siriraj Hospital in Bangkok, Thailand. It was performed in the pediatric allergy clinic, from March 2003 to March 2009. Children 4 to 15 years of age with daily or almost daily urticaria lasting for 6 weeks or longer were asked to participate. Informed consent was obtained from the parents. Exclusion criteria included isolated physical urticaria and other urticaria subtypes (including aquagenic, cholinergic, and exercise-induced urticaria), inability to attend for follow-up, pregnancy, and underlying conditions such as cardiovascular, hepatobiliary, and renal disease.

Investigations

All patients underwent a complete history, physical examination, and the following laboratory tests: complete blood cell count, erythrocyte sedimentation rate, ANA, CH₅₀, free-T₄, thyroid-stimulating

hormone, antithyroglobulin antibody, antimicrobial antibody, and stool examination for parasites. A skin biopsy specimen was obtained if there were clinical features of vasculitis and connective tissue disease such as fever, arthralgia, raised erythrocyte sedimentation rate, painful skin lesions, and lesions lasting more than 24 hours or with residual purpura or petechiae.

CAPSULE SUMMARY

- There are few prospective studies on the natural course of chronic urticaria in children.
- In this study of children aged 4 to 15 years, remission rates at 1, 3, and 5 years after the onset of symptoms were 18.5%, 54%, and 67.7%, respectively. There was no identified predictor of remission.
- Chronic urticaria has a favorable outcome in children.

Skin-test procedure

Skin-prick tests (SPT) to foods and ASST were performed in all patients. SPT with commercial food extracts (cow's milk, soy, egg white, chicken, pork, beef, mixed fish, shrimp, crab, clam, oyster, peanut, and wheat from Center Laboratory, Port Washington, NY) were performed with 10 mg/mL of

histamine phosphate and glycerinated saline as positive and negative controls. Oral antihistamines were discontinued for 7 days or longer before SPT. The SPT result was considered positive if the mean wheal diameter was 3 mm or greater compared with the negative control.

The ASST was performed using an intradermal skin test with 0.05 mL of sterile, fresh autologous serum. Histamine (10 µg/mL) and 0.9% sterile saline were used as positive and negative controls.¹¹ Wheal and flare reactions were recorded after 30 minutes. A wheal diameter of 1.5 mm or greater compared with that elicited by a control saline solution was considered positive.

Food-challenge procedure

Open food challenges to suspected foods were done in patients who had a positive SPT finding. The patients were asked to avoid all foods that elicited a positive SPT result and discontinue oral antihistamines for 7 days or longer before food challenges. Patients with asthma were asymptomatic and had forced expiratory volume in 1 second greater than 70% of predicted value. The food challenge was administered in the fasting state, beginning with a dose of 500 mg of lyophilized food. The dose was doubled every 15 minutes. A maximum dose of 10 g of lyophilized food was used, followed by open feeding.²⁸ Vital signs and any symptoms or signs were recorded every 15 minutes. Emergency resuscitation equipment and drugs were available.

Treatments and follow-up period

All patients were initially prescribed a second-generation H₁-antihistamine (cetirizine or loratadine). A stepwise approach of combination therapy was used if urticaria was not controlled: step 1, cetirizine/loratadine and hydroxyzine; step 2, cetirizine/loratadine and ranitidine; step 3, cetirizine/loratadine and ranitidine plus montelukast; step 4, cetirizine/loratadine and prednisolone. The medications were prescribed in the recommended doses (eg, cetirizine for children aged 4-5 years: 2.5-5 mg/d, ≥ 6 years: 5-10 mg/d). The patients were followed up every 3 to 6 months. Medications were tapered if they were free of urticaria. Remission was considered if symptoms did not recur for at least 12 months without medication.

Data analysis

Data were expressed as individual values or the median with the range for groups. Statistical analysis was done with χ^2 or independent *t* test to compare the demographic data and the abnormalities of investigation between patients with CAU and the non-CAU group. The Kaplan-Meier survival curves were used to analyze the probability of remission and displayed for the relation between the remission and each of the above variables and its statistical significance was determined by log rank test. *P* value of .05 or less was considered significant.

RESULTS

Patient characteristics

In all, 94 children with a diagnosis of CU were recruited. Two patients were lost to follow-up. The demographic data of 92 patients are shown in Table I. In all, 49 patients (53.3%) were female. The median age at inclusion was 8.4 years and the median age of onset of CU was 7.8 years. The median duration of urticaria was 2.7 years (range 0.3-11.3 years) and the median duration of urticaria before inclusion was 1.2 years (range 2-11.1 years). In all, 55 children (59.8%) had CU with angioedema. In all, 31 patients (33.7%) had a personal history of atopy and 28 patients (30.4%) had a family history of atopy. The step 1 medications were used in 75 patients (81.5%), step 2 in 14 patients (15.2%), and step 3 in 3 patients (3.3%). No patient required treatment with prednisolone.

Laboratory analyses

Eighteen patients (19.6%) had no laboratory abnormality. In all, 22 patients (23.9%) had eosinophilia; the median eosinophil count was

Table I. Demographic data of patients with chronic urticaria (n = 92)

Characteristics	
Female, n (%)	49 (53.3)
Median age (range), y	8.4 (4.0-15.5)
Median age at onset (range), y	7.8 (0.5-15.5)
Median duration of urticaria (range), y	2.7 (0.3-11.3)
Personal history of atopy, n (%)	31 (33.7)
Asthma	11 (12)
Allergic rhinitis	14 (15.2)
Atopic dermatitis	2 (2.2)
Food allergy	14 (15.2)
Family history of atopy, n (%)	28 (30.4)
Asthma	9 (9.8)
Allergic rhinitis	19 (20.7)
Atopic dermatitis	0
Food allergy	2 (2.2)

259 cells/mm³ (range 0-953 cells/mm³). Elevated erythrocyte sedimentation rate (>20 mm/h) was found in 12 patients (13%). No patient had an abnormal CH₅₀ level. Twenty patients (21.7%) had abnormal ANA titers ($>1:20$); however, only 2 patients (2.2%) had ANA greater than 1:160. No patient had symptoms of urticarial vasculitis such as fever, arthralgia, weight loss, lesions lasting more than 24 hours, painful lesions, or residual petechial hemorrhage, bruising, purpura, or hyperpigmentation. Skin biopsy was not performed in any patient. In all, 37 (40.2%) had a positive ASST result and were given a diagnosis of CAU or ASST-positive CSU. The 55 children (59.8%) with negative ASST result were given a diagnosis of non-CAU. In the CAU group, the mean wheal diameters from intradermal skin test with autologous serum and with saline were 7.7 ± 2.1 and 2.8 ± 3.2 mm, respectively. The demographic data, abnormal investigations, or medication usage of CAU and non-CAU groups were not significantly different (data not shown).

Parasitic infestations were found in 5 patients (5.4%) without gastrointestinal symptoms. The parasites were *Blastocystis hominis* (3 patients), *Dientamoeba fragilis* (1 patient), and *Giardia lamblia* (1 patient). There was only 1 patient with parasitic infestation and eosinophilia. All were treated with a 7-day course of oral metronidazole. Anthelmintic medications did not induce a higher rate of CU remission compared with patients who did not have parasites in the stool. Positive skin testing to foods was found in 33 patients (35.9%). Sixteen patients agreed to have food challenges and 8 of 16 (50%) had positive food challenges (3 to shrimp, 1 to crab, 2 to shrimp and crab, 1 to

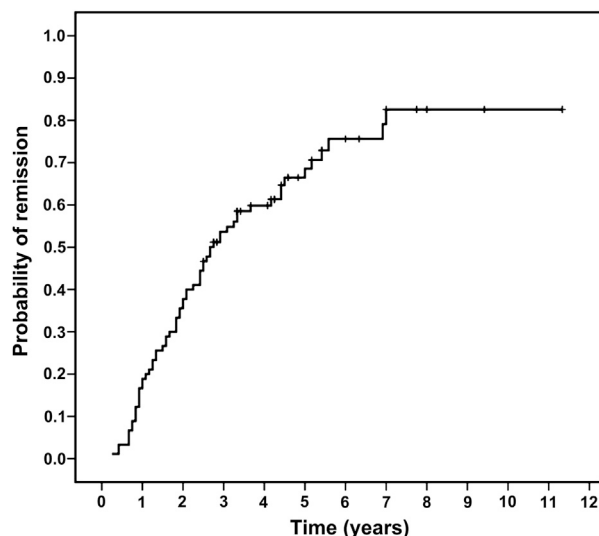


Fig 1. Remission of chronic urticaria (CU) in children. A Kaplan-Meier curve demonstrating duration of the disease in patients with CU (n = 92). CU remissions at 1, 3, and 5 years after the onset of symptoms were 18.5%, 54%, and 67.7%, respectively.

clam, 1 to oyster). Elimination of a specific food resulted in CU remission in 4 of 8 patients (50%).

No patient had abnormal thyroid function test results (free-T4 and thyroid-stimulating hormone). Antithyroglobulin and antimicrosomal antibodies were not detected.

Remission of CU during the follow-up period

The patients were followed up for a median duration of 4.3 years (range 2.5-5.8 years) from the diagnosis of CU. At 1, 3, and 5 years from the onset of symptoms, 18.5%, 54%, and 67.7% of the patients with CU were in remission (Fig 1). Patients with CAU had 18.9%, 63.1%, and 72.1% remission rates at 1, 3, and 5 years after the onset of symptoms, respectively. Patients with non-CAU had 18.2%, 62.5%, and 64.9% remission rates at 1, 3, and 5 years after the onset of symptoms, respectively. The remission rates for CAU and non-CAU groups were not significantly different (Fig 2). To determine predictors of CU remission, the Kaplan-Meier curves were plotted using different demographic data and abnormal investigations. There was no variable that could predict CU remission.

DISCUSSION

Information on the natural course of CU is scarce and most of the few studies were performed in adults, with variable results. Van der Valk et al²⁹ retrospectively identified the natural history of CU in 372 adults and found that 29% and 44% were in

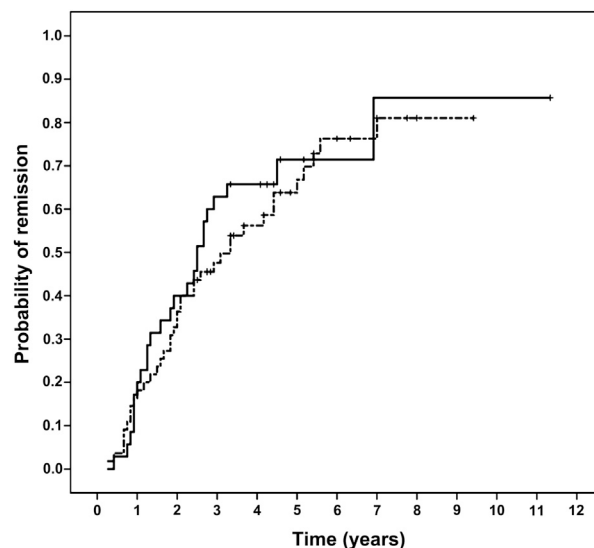


Fig 2. Remission of chronic spontaneous urticaria in children. A Kaplan-Meier curve demonstrating duration of the disease in patients with chronic autoimmune urticaria (CAU) (continuous line) versus non-CAU (dashed line). The remission rates of CAU at 1, 3, and 5 years after the onset of symptoms were 18.9%, 63.1%, and 72.1% and those of non-CAU at 1, 3, and 5 years after the onset of symptoms were 18.2%, 62.5%, and 64.9%, respectively.

remission after 5 and 10 years, respectively. The retrospective study of Champion et al,²³ in 554 adults with CU, found that 55% of patients with CSU were free of symptoms after 1 year. Kulthanan et al²⁷ revealed that of 337 adults with CSU, 34.5% were in remission after 1 year; within this group, 56.5% of patients with CAU were in remission after 1.2 years. Quaranta et al²⁴ investigated 86 patients with CU and reported 32% remission during a 3-year period. Kozel et al²⁵ prospectively followed up 220 adults for 3 years and found that 35% of patients with CU were free of symptoms after 1 year. The prospective study of Toubi et al²⁶ in 139 adults with CU revealed that symptoms lasted longer than 1 year in more than 70% of cases and that the duration of CU was significantly associated with positive ASST result and antithyroid antibodies. Taken together, the evidence reflected that 30% to 50% of adults with CU achieved remission within 1 to 3 years. A positive ASST finding and antithyroid antibodies seemed to be poor prognostic factors for remission of CU.

In pediatric populations, 3 studies were performed to identify the natural course of CU. The retrospective study of Harris et al³⁰ demonstrated that among 52 children with CSU, 37% were free of symptoms after 1 year and girls had a higher rate of resolution than boys. Du Toit et al³¹ reported that

25% of children with CU achieved remission in a 3-year cohort.¹ Sahiner et al³² did a retrospective study of 100 children with CSU during an 8-year period and found that remission of CSU in children was 16.5% after 1 year, 38.8% after 3 years, and 50.0% after 5 years. In our prospective study, the remission rates (18.5% after 1 year of the onset and 54% after 3 years) were not as high as those found in adult studies but similar to the 3 studies conducted in pediatric patients. One explanation for a low remission rate was that patients referred to our allergy clinic in a tertiary care center might have a more intractable course.

A positive ASST result did not determine a poorer prognosis. This result was supported by Kulthanan et al²⁷ who reported no difference between Thai adult patients with positive and negative ASST findings in the duration of CU symptoms. Our study did not demonstrate any effect of gender on the remission rate of CSU. This was in contrast to the study by Harris et al,³⁰ which indicated a better prognosis in females with CSU, and to the study of Sahiner et al,³² which concluded that the prognosis was unfavorable in girls older than 10 years. However, in both studies these findings were not statistically significant.

In conclusion, our study demonstrated that remissions occurred in 18.5%, 54%, and 67.7% of pediatric patients with CU after 1, 3, and 5 years of the onset of urticarial symptoms, respectively. There was no factor that could significantly predict the remission of CU in childhood.

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