

ORIGINAL ARTICLE

WILEY

Chronic inducible urticaria subtypes in children: Clinical features and prognosis

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Editor: Jon Genuneit

Abstract

Background: Chronic inducible urticaria (CIndU) is a subtype of chronic urticaria induced by a physical stimulus.

Objective: To evaluate the clinical features, prognostic factors, and natural course of childhood CIndU subtypes.

Methods: Patients (1-18 years old, n = 117) diagnosed with CIndU between March 2011 and March 2019 were analyzed. Patients (n = 101) were re-evaluated for the status of their CIndU at least 6 months after the initial evaluation.

Results: The study population comprised of 117 children with a median (inter-quartile range) age of 10.3 (6-14.8) years at admission and a male predominance (53%). Symptomatic dermographism was the most common type of CIndU, affecting 65% of the group, followed by cold urticaria and cholinergic urticaria, which affected 17% and 15.4%, respectively. Baseline serum tryptase levels in cholinergic urticaria and cold urticaria were higher than those in symptomatic dermographism [7.0 (3.3-10.7) µg/L, 4.2 (2.8-9.3) µg/L, and 2.7 µg/L (1.8-5.9), respectively; $P = .020$]. Recovery was observed in 9.6%, 25.3%, and 34.7% of the CIndU children after 12, 36, and 60 months, respectively. Of the patients with symptomatic dermographism, 40% had remission in 5 years, whereas this rate was only one-fifth in patients with cold urticaria. The worst prognosis was observed in patients with cholinergic urticaria.

Conclusion: This study concluded that nearly one-third of children with CIndU recovered within 5 years and symptomatic dermographism has the best prognosis. Cholinergic urticaria is the CIndU type with the worst prognosis, male dominance, and highest baseline serum tryptase levels.

KEYWORDS

baseline serum tryptase, children, chronic inducible urticaria, chronic urticaria, prognosis

Fatma Bal and Melike Kahveci contributed equally to this work.

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1 | INTRODUCTION

Chronic urticaria (CU) is characterized as the appearance of pruritic migratory wheals, angioedema, or both on most days of the week for more than 6 weeks.¹ The estimated prevalence of CU is 0.5%-5% and may affect up to 3% of children.^{2,3} CU is classified into two subgroups: chronic inducible urticaria (CIndU) and chronic spontaneous urticaria (CSU). Recurrent pruritic wheals and/or angioedema occur after exposure to a specific stimulus in CIndU that includes symptomatic dermographism, cold urticaria, cholinergic urticaria (ChU), solar urticaria, heat urticaria, delayed pressure urticaria, vibratory angioedema, aquagenic urticaria, and contact urticaria.¹

CIndU is observed in approximately 20%-30% of adults with CU.⁴ In a meta-analysis including children and adults, 14.9% of patients with CU were reported as having CIndU.⁵ There are few studies in the literature about CIndU in children, with most adult studies providing guidance. A retrospective study by Silpa-archa et al. noted that CIndU was diagnosed in 7.2% of patients with CU, and the most common form was symptomatic dermographism, followed by cold urticaria, delayed pressure urticaria, and ChU.⁶

In the literature, it was reported that nearly 13-16% of adult CU patients were in remission within 1 year and 50% after 5 years.^{6,7} In our previous studies, we demonstrated that CSU had a better prognosis in children than in adults.^{8,9} However, the data regarding the persistence and prognosis of CIndU in children and characteristics in different age groups are very limited.⁶ Kauppinen et al. reported that physical urticaria had a worse prognosis in children, with 47% of them in remission after 3.8 years.¹⁰ Thus, this study aimed to evaluate the clinical features, prognostic factors, and natural course of pediatric CIndU subtypes, thereby providing insights into this little-known topic.

2 | METHODS

2.1 | Study population

This study was conducted in the outpatient clinic of the Pediatric Allergy Department of Hacettepe University Ihsan Doğramacı Children's Hospital, which is a referral center for the entire country. Patients (1-18 years old, $n = 117$) who were diagnosed with CIndU between March 2011 and March 2019 were enrolled in the study. This study had both retrospective and prospective aspects. The study protocol was approved by the Hacettepe University School of Medicine Ethics Committee (GO 19/337), and informed consent was obtained from both patients and their parents.

CIndU was defined as wheals or angioedema that lasted >6 weeks and was provoked by a specific physical stimulus or other triggering factors. The classification for CIndU was based on the latest guidelines of the EAACI/WHO.¹ Demographic characteristics, including gender, age at admission and symptom onset, concomitant symptoms, accompanying allergic and chronic diseases, family history of atopy, triggering factors, duration of symptoms on admission,

Key Message

This study showed that nearly one-third of children with chronic inducible urticaria (CIndU) recovered within 5 years and symptomatic dermographism has the best prognosis. Baseline serum tryptase level may be important in disease pathogenesis in some CIndU subtypes.

and clinical follow-up, were recorded. Complete blood cell count, eosinophil percentage, absolute eosinophil count, total serum IgE, and baseline serum tryptase (BST), if available, were noted. All patients were interviewed using a detailed questionnaire regarding triggering factors such as sunlight, cold temperatures, water, pressure, vibrations, exercise, itching, foods, and drugs. Telephone interviews were performed to review the current disease status of each patient. Patients without urticaria for at least 6 months were considered in remission.⁸

2.2 | Skin prick testing

Skin prick tests (SPTs) were performed regarding the following common allergens¹¹: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Alternaria*, cat epithelia, dog epithelia, grass mix (*Phleum pratense*, *Poa pratensis*, *Dactylis glomerata*, *Lolium perenne*, *Festuca pratensis*, and *Avena elatior*), cockroach, *Cynodon*, *Cladosporium*, and histamine (10 mg/mL of histamine phosphate), with 0.9% saline used as a negative control. A positive SPT result was defined as a mean wheal diameter ≥ 3 mm above the negative control. In addition, SPT was performed in patients who had a suspected history of food allergy and elevated sIgE levels. In patients with dermographism, allergic sensitization was investigated by sIgE measurements for the allergens, as shown above.

2.3 | Challenge testing

Provocation tests were performed according to the EAACI/WHO guidelines to identify CIndU.¹² The diagnosis of dermographism was confirmed by stroking the skin of the volar surface forearm with a tongue blade. This procedure elicited a linear wheal with a flare and severe itching within minutes. For identification of cold urticaria, an ice cube test was performed in which a thin plastic bag was applied on the volar surface of the forearm for 10 minutes. The test was considered positive when a wheal appeared over the application site. For ChU, a treadmill exercise test was performed until the patient began to sweat and for up to 15 minutes after. If urticarial rashes with typical appearance occurred within 10 minutes after exercise, the test was considered positive. The diagnosis of aquagenic urticaria was confirmed by wetting a cloth with room temperature water and then applying this

damp cloth to the patient's skin for 20 minutes, with an urticarial reaction within 20 minutes indicating a positive test. For the diagnosis of delayed pressure urticaria, weighted rods were used, and test readings were done after 30 minutes and after 4, 6, 8, and 24 hours. The test was positive if red swelling was palpable 6 hours after provocation.

2.4 | Statistical analysis

All data were analyzed with SPSS for Windows 22.0 program (SPSS Inc, Chicago, IL). Descriptive statistics were used for demographic data, prevalence and type of CIndU, and laboratory findings. Data distribution was controlled using the Shapiro-Wilk and Kolmogorov-Smirnov statistical methods. Non-normally distributed data are presented as the median and inter-quartile range (IQR), and a Mann-Whitney or Kruskal-Wallis test was used for statistical analysis. The Kaplan-Meier analysis was performed for the prognosis. Prognosis curves were compared with a log-rank test. The risk factors affecting the prognosis of chronic inducible urticaria were evaluated by univariate and multivariate logistic regression analyses. *P*-values < .05 were considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics

The study group consisted of 117 children with a median (IQR) age of 10.3 (6-14.8) years at admission and a male predominance (53%). The median age at symptom onset was 9 (4.8-13) years, and the median duration of symptoms before diagnosis was 27 (15-56) months. Thirty patients (25.9%) had the concomitant allergic disease, most commonly allergic rhinitis (19%). A family history of atopy was observed in 47 (40.9%) patients, whereas urticaria or angioedema was observed in 17 (14.8%) patients. The characteristics of patients and laboratory findings are summarized in Table 1.

3.2 | Characteristics and differences of CIndU subtypes

The most common CIndU was symptomatic dermographism (65%), followed by cold urticaria (17%) and ChU (15.4%). Only two patients (1.7%) were diagnosed with aquagenic urticaria and one patient (0.9%) with delayed pressure urticaria (Figure 1). ChU was more common in male patients (77.8%), while symptomatic dermographism and cold urticaria were observed almost equally in male and female patients (Table 2). The median (IQR) age at symptom onset for the symptomatic dermographism, cold urticaria, and ChU subgroups was 8 (4.2-12.8) years, 10 (5.7-14.9) years, and 8.5 (4.9-11.4) years, respectively. The family history of atopy was significantly higher in the symptomatic dermographism subgroup than in the

TABLE 1 Characteristics of patients and laboratory findings in CIndU

Male, n (%)	62 (53)
Age at admission ^a , y	10.27 (6.03-14.84)
Age at symptom onset ^a , y	8.95 (4.81-13)
Duration of symptoms ^a , mo	27 (15-56)
Concomitant allergic diseases, n (%)	30 (25.9)
Asthma	16 (13.8)
Allergic rhinitis	22 (19)
Atopic dermatitis	3 (2.6)
Family history of atopy, n (%)	47 (40.9)
Family history of urticaria/angioedema, n (%)	17 (14.8)
Skin prick test or specific IgE positivity, n (%)	18 (20.9)
Eosinophil percentage ^a	1.7 (1.2-2.9)
Eosinophil count ^a (mm ³)	100 (100-300)
Total IgE level ^a (U/L)	79.1 (34.8-168)

^aMedian, IQR = inter-quartile range.

cold urticaria subgroup (*P* = .04). Interestingly, BST levels varied between different CIndU subtypes. BST levels in cholinergic and cold urticaria were higher than those in symptomatic dermographism [7.0 (3.3-10.7) µg/L, 4.2 (2.8-9.3) µg/L, and 2.7 (1.8-5.9) µg/L, respectively (*P* = .020)]. Total IgE values in patients with cold urticaria were significantly lower than those in other subgroups (*P* = .039). Characteristics and laboratory findings of CIndU subtypes are shown in Table 2.

In the univariate and multivariate logistic regression analyses, age at symptom onset was associated with the duration of symptoms in the symptomatic dermographism subgroup (odds ratio, 1.220; 95% confidence interval, 1.010-1.474; *P* = 0.040).

3.3 | Natural course and predictors

One hundred and two patients were called by phone, and only these patients were included in the prognosis analysis. The remission rates for CIndU at 12, 36, and 60 months were 9.6%, 25.3%, and 34.7%, respectively. In patients with symptomatic dermographism, approximately one-third of patients went into remission within 3 years and 40% of them recovered in 5 years. However, in patients with cold urticaria, only one-fifth of patients improved within 5 years. The worst prognosis was observed in patients with ChU. Out of 11 patients who had prognosis data, only one patient recovered in 54 months (Figure 2).

Out of 117 patients, 38 (32.5%) had chronic spontaneous urticaria. In these patients, 36 (30.8%) had CSU and symptomatic dermographism and 2 (1.7%) had CSU and ChU. Analysis between patients with CIndU with or without CSU (*P* = .432, log-rank test) and patients with symptomatic dermographism with or without CSU (*P* = .290, log-rank test) did not show any differences with respect to remission.

FIGURE 1 Distribution of chronic inducible urticaria patients according to different subtypes

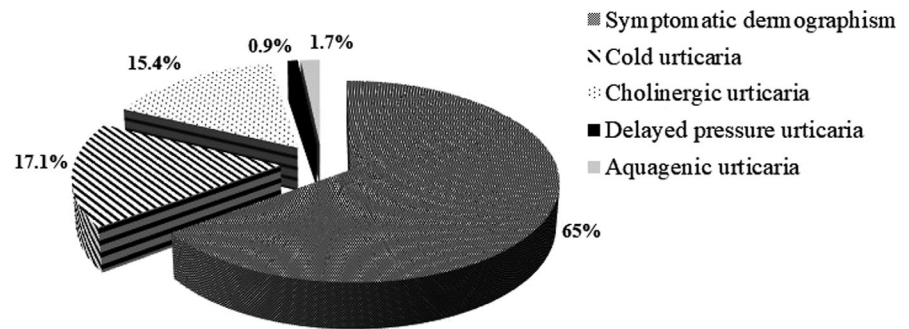


TABLE 2 Laboratory findings and characteristics of children with CI-U subtypes

	Symptomatic dermographism (n = 76)	Cold urticaria (n = 20)	Cholinergic urticaria (n = 18)	<i>p</i> ^c	<i>p</i> ^d	<i>p</i> ^e	<i>p</i> ^f
Gender ^a				.065	.834	.101	.034
Male	36 (47.4)	10 (50)	14 (77.8)				
Female	40 (52.6)	10 (50)	4 (22.2)				
Age at admission ^b , y	10.0 (5.7-14.9)	9.5 (6.4-14.1)	13.6 (6.9-14.8)	.426	.718	.217	.257
Age at symptom onset ^b , y	8.0 (4.2-12.8)	8.5 (4.9-11.4)	11.8 (6.6-14.4)	.339	.910	.186	.169
Duration of symptoms ^b , mo	25 (14-55)	32 (9-59)	54 (27-75)	.811	.606	.478	.854
Concomitant allergic diseases ^a				.765	.576	.709	.985
Asthma ^a	11 (14.7)	2 (10)	3 (16.7)	.812	.729	.653	1
Allergic rhinitis ^a	16 (21.3)	3 (15)	3 (16.7)	.768	.755	1	1
Atopic dermatitis ^a	2 (2.7)	0	1 (5.6)	.467	1	.474	.480
Atopy in the family ^a	35 (47.3)	4 (20)	7 (38.9)	.087	.04	.288	.521
Urticaria/angioedema in the family ^a	9 (12.2)	3 (15)	4 (22.2)	.575	.714	.687	.274
Skin prick test positivity ^a	13 (23.2)	1 (5.9)	4 (33.3)	.123	.165	.130	.477
Eosinophil percentage ^b	1.7 (1.1-2.9)	1.6 (1.2-2.5)	2.6 (1.8-3.4)	.183	.775	.068	.103
Eosinophil count ^b , mm ³	100 (100-300)	150 (100-200)	200 (100-300)	.262	.614	.308	.116
Total IgE ^b , IU/L	80.3 (39.4-232.5)	41.1 (14.8-95.5)	95.6 (57.8-162.3)	.039	.014	.041	.838
Tryptase ^b , µg/L	2.7 (1.8-5.9)	4.2 (2.8-9.3)	7.0 (3.3-10.7)	.020	.029	.720	.028

^an (%).

^bmedian (inter-quartile range).

^ccomparison among symptomatic dermographism, cold urticaria and cholinergic urticaria (Kruskal-Wallis test).

^dcomparison between symptomatic dermographism and cold urticaria (Mann-Whitney *U* test).

^ecomparison between cold urticaria and cholinergic urticaria (Mann-Whitney *U* test).

^fcomparison between symptomatic dermographism and cholinergic urticaria (Mann-Whitney *U* test).

4 | DISCUSSION

In the present study, we defined the different characteristics and demographics of CI-U in children and showed the natural course of the disease and its subsets. There was a male predominance in ChU compared with symptomatic dermographism and cold urticaria. The prognostic analysis revealed that nearly one-third of children with CI-U went into remission within 5 years. Considering the different disease subtypes, symptomatic dermographism had the best

prognosis, followed by cold urticaria. In contrast, the worst prognosis accompanied ChU since only 9% (1/11) of ChU patients went into remission after 4.5 years of follow-up. The only risk factor defined in symptomatic dermographism patients for disease persistence was the age at symptom onset. Nevertheless, we could not identify any risk factors for the persistence of other disease phenotypes.

Few studies have discussed the epidemiology of CU in children. Variations in the prevalence of CU are mostly due to the heterogeneity of patient populations. The prevalence of CU in children is

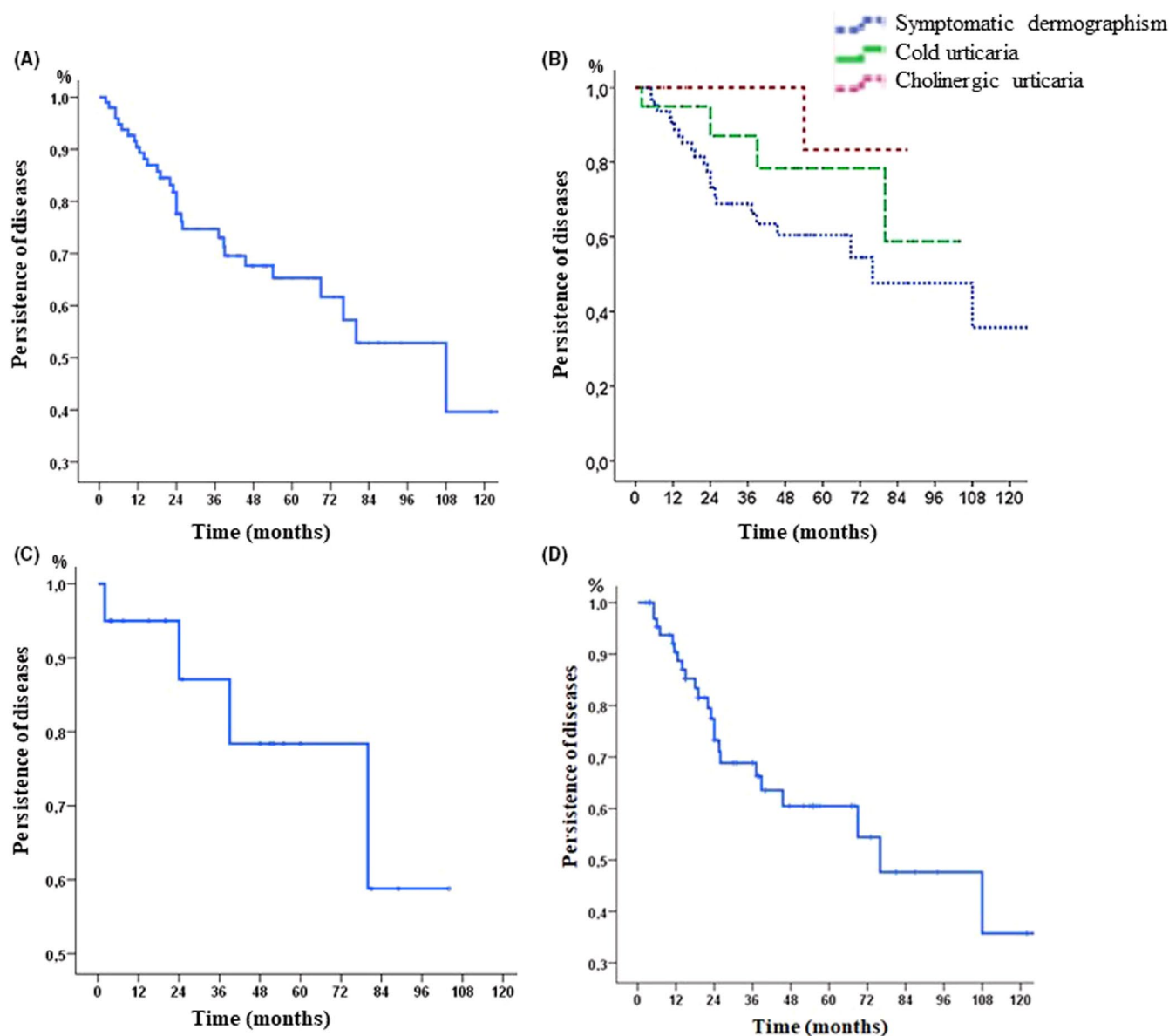


FIGURE 2 Time to recovery in children with CIndU. (A) Whole group (N = 101), (B) chronic inducible urticaria subtypes, (C) cold urticaria, (D) symptomatic dermatographism [Colour figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1111/pai.13324)]

<1%, and there is no significant difference among male and female patients.¹³ Chronic inducible urticarias are a subgroup of chronic urticaria and associated with a specific trigger that reproducibly leads to the immediate or delayed appearance of symptoms. Symptomatic dermatographism, ChU, and cold urticaria are believed to be the most common forms, though definitive data are lacking.¹⁴ In a study of 245 patients (>12 years old) diagnosed with CSU, symptomatic dermatographism was the most common type of CIndU, affecting 24.8% of subjects, followed by cold urticaria (13.4%).¹⁵ In a retrospective study of the 1200 chronic urticaria patients > 18 years old, 86 (7.2%) were diagnosed with CIndU and the most common type was symptomatic dermatographism (40.7%), followed by cold urticaria (23.3%).⁶ As in other studies, symptomatic dermatographism, cold urticaria, and ChU were the most common forms in this study population.

Chronic inducible urticaria and CSU may occur simultaneously or independently. In a study including 245 patients with CSU, 89 (36.3%) patients had a positive challenge test result, of which the most common type of CIndU was symptomatic dermatographism.¹⁵ The meta-analysis of Trevisonno et al. reported that 13% of patients with CSU also had CIndU.⁵ In our study, chronic spontaneous urticaria was observed in 38 (32.5%) patients who had symptomatic dermatographism (n = 36) and ChU (n = 2). Patients with both forms did not show different prognosis from those with CIndU only.

The sex distribution of CIndU in the literature is predominantly female,⁶ whereas in our study, male dominance was observed. However, this difference was due to a large number of male patients in the ChU subgroup. Regarding the sex distribution in ChU, there are contradictory results. Kim and colleagues noted that male predominance in ChU may be linked to the more frequent

documentation of young adult males who obtain medical reports for their mandatory military service.¹⁶ In a study from Korea that reviewed the medical records of 203 patients diagnosed with ChU, male predominance (93%) was observed.¹⁷ In our analysis, male patients were predominant in the ChU group (77.8%). It was hypothesized that male patients may have greater exposure to aggravating factors such as exercise, which may lead to their predominance.

The relationship between CIndU and atopy is not clear.⁶ Previous studies showed that the prevalence of atopy, defined as a positive skin test or history of allergic diseases, was 16.7%–33.7% in children with CU.^{9,18–20} We showed comparable results since the frequency of concomitant allergic diseases was 25.9% in our patients. Khakoo et al. reported a much higher prevalence of allergic conditions in children with CIndU (72.3%).²¹ This discrepancy may depend on the different characteristics of study cohorts. In a study by Azkur et al. that evaluated CU (including CSU and CIndU) in children, a family history of allergic disease and chronic urticaria was reported as 32.6% and 10.1%, respectively.²² In the present study, a family history of atopy (40.9%) and CU (14.8%) was similar to the literature.

Previous reports regarding the relationship between BST and CIndU type are mostly lacking, and the only paper we identified was about cold urticaria in children. In this study, Yee et al. evaluated the BST levels in only 10% of the study population and reported normal levels.²³ In our study, we found significantly higher BST levels in patients with ChU or cold urticaria; however, symptomatic dermographism patients showed normal BST levels. We do not know the exact reason for this, but it may be related to the disease pathogenesis as different CIndU forms may show distinct pathophysiologic processes.

Few data are available on the natural course of CIndU in children. Studies on representative pediatric populations showed that the remission rate of CSU at 1 year from onset ranged from 10 to 32%.^{9,13,20} However, the natural course of CIndU is not well known. A study in a pediatric population with CU reported that nearly half of the patients were in remission at 10.2 months, and the remission rates of children with CIndU were 33.4%, 53.0%, and 71.2% at 6, 12, and 24 months, respectively.²⁴ In an adult cohort, the remission rate of physical urticaria at the 1-year follow-up was 16.4%,⁷ whereas in the present study, only 9.6% of patients were in remission at 1 year. The lower remission rate may be related to the fact that patients referred to our center may have a more recalcitrant disease.

For symptomatic dermographism, the average disease duration is 6.5 years, with a large variance.^{25,26} Our results supported that the age at symptom onset was related to the duration of symptoms in symptomatic dermographism and the prognosis worsened as the age at symptom onset became older. However, Khakoo et al. found that the mean age of onset in the remission and non-remission groups was very similar. They suggested that age alone could not stratify patients who achieved remission.²¹ In a study of 415 pediatric patients diagnosed with cold urticaria, only 8.9% of patients

had documented disease resolution.²³ In other studies, disease resolution of cold urticaria in children was reported to be between 5% and 7.5%.^{27–29} In this study, one-third of patients with symptomatic dermographism achieved remission in 3 years, and 40% recovered in 5 years. However, only one-fifth of cold urticaria patients recovered within 5 years. Contrary to our study, in the literature, the prognosis of ChU is generally favorable. In a study including 203 patients diagnosed with ChU, about 25% had ChU for more than 5 years.¹⁷ Another study with 92 ChU patients showed that the mean disease duration was 48 months, and only 14 (15.2%) patients were presented at 5–10 years and four (4.4%) at ≥ 10 years.¹⁶ In our study, the worst prognosis has been observed in patients with ChU. This condition may be due to the low number of patients and lack of data on the prognosis of all patients.

Overall, the available data in pediatric CIndU are limited by small sample sizes and heterogeneous outcomes. Despite some limitations based on the partially retrospective and single-center nature of this study, we concluded that nearly one-third of children with CIndU recovered within 5 years and the natural course of children with CIndU was worse compared with those with CSU. Baseline serum tryptase level may be important in disease pathogenesis in some CIndU subtypes.

ACKNOWLEDGMENT

The authors would like to thank Hacettepe University Teknokent Technology Transfer Center for English editing service.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTION

Fatma Bal: Data curation (equal); Investigation (lead); Resources (equal); Writing-original draft (equal); Writing-review & editing (equal). **Melike Kahveci:** Data curation (equal); Resources (equal); Writing-original draft (equal); Writing-review & editing (equal). **Ozge Soyer:** Formal analysis (lead); Methodology (supporting); Software (lead); Writing-review & editing (supporting). **Bulent Enis Sekerel:** Formal analysis (equal); Methodology (equal); Project administration (supporting); Supervision (lead); Writing-review & editing (supporting). **Umit M Sahiner:** Conceptualization (lead); Formal analysis (equal); Methodology (lead); Project administration (lead); Writing-original draft (supporting); Writing-review & editing (equal).

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/pai.13324>.

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How to cite this article: Bal F, Kahveci M, Soyer O, Sekerel BE, Sahiner UM. Chronic inducible urticaria subtypes in children: Clinical features and prognosis. *Pediatr Allergy Immunol*. 2021;32:146-152. <https://doi.org/10.1111/pai.13324>