The persistence of chronic spontaneous urticaria in childhood is associated with the urticaria activity score

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ABSTRACT

Background: *There is little information regarding the etiology and natural course of chronic spontaneous urticaria (CSU) in childhood.*

Objective: *To investigate the etiology, prognosis, and the factors associated with the prognosis of CSU in children.*

Method: *Data from children with CSU who had been diagnosed between 1992 and 2015 were analyzed. A telephone interview was done to assess the current status of these patients. Remission was defined as the disappearance of urticaria for >6 months.*

Results: *A total of 222 children with CSU were evaluated. The median age of symptom onset was 8.8 years (interquartile range [IQR], 4.6–12.3 years), median duration of urticaria was 23 months (IQR, 7–48 months), and the median sum of the daily urticaria activity score of 7 consecutive days (UAS7) was 28 (IQR, 21–42). Accompanying angioedema was reported by 107 patients (48.2%), whereas 27.1% of the study population had autoantibody positivity. Autologous serum skin testing results were positive in 43 (34.1%); skin-prick testing results revealed atopy in 55 children (27.9%). Parasites (4.8%), pollen sensitization (1.5%), food allergy (0.9%), urinary tract infection (0.9%), and Hashimoto thyroiditis (0.5%) were determined as etiologic factors of CSU. The patients were followed up for a median time of 15 months (IQR, 5–36.5 months). Remission was observed in 10.6, 29.3, and 44.5% of the patients in 1, 3, and 5 years, respectively. In multivariate regression analysis, a UAS7 of >28 at admission was found to be a risk factor for persistence of urticaria (odds ratio 6.22 [95% confidence interval, 1.54–25.15; p = 0.010).*

Conclusion: *The etiology of CSU in children was mostly idiopathic despite detailed investigation. In childhood, the natural course of CSU was favorable, and nearly half of the patients recovered after 5 years of disease duration. A high UAS7 at admission seemed to be a significant risk factor for the persistence of symptoms.*

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Even though a lifetime prevalence of acute urticaria is as high as 20% in the general population,[1] relapsing or persistent urticaria is rare. Chronic urticaria is defined as daily or an almost daily appearance of urticarial symptoms, with or without angioedema, that lasted for >6 weeks,[1] which affects 0.5–1% of the general population.[2] There is no information regarding its true prevalence in childhood, but chronic urticaria is thought to be less common in children than adults. Chronic urticaria is classified as inducible chronic urticaria, which is triggered by specific physical stimuli, (*e.g.*, cold, heat, pressure) and chronic spontaneous urticaria (CSU), which occurs without any physical triggers.[1] Although CSU seems to be a benign disease; it has been shown that impairment of quality of life is comparable with children with other chronic diseases.[3]

CSU has been well documented in adults; however, there is limited knowledge regarding the underlying cause in childhood. The etiology could not be identified in more than half of children in the few published studies, which also include physical urticaria.[4] Also, the natural course of CSU in children within various age groups, follow-up periods or the definition of disease and/or remission criteria have not been investigated in detail.[5,6] Previously, we analyzed 100 children with CSU and found that girls >10 years of age may have an unfavorable prognosis.[5] In this study, we aimed to extend our study by including a larger number of patients with a longer duration of follow-up, and analyzed the factors associated with prognosis in childhood CSU. We also searched the severity of disease as a potential predictor of persistence.

METHODS

Study Population

This study was conducted in the Department of Pediatric Allergy, Hacettepe University School of Medicine, Ankara, Turkey, between 1992 and 2015, and had

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both retrospective and prospective aspects. Data from children who had been diagnosed as having CSU between 1992 and 2009 were collected and analyzed retrospectively; patients who were admitted to our department after 2010 and diagnosed as having CSU were evaluated prospectively. CSU was defined as the daily or almost daily spontaneous appearance of urticaria that lasted for >6 weeks.[1] Patients with physical urticaria, which was triggered by a specific physical stimulus, were excluded. The urticaria activity score (UAS) was used to assess the disease activity in all the participants according to the EAACI/GA^{2}LEN/EDF/WAO guideline[1], and was calculated by the sum of the daily scores for 7 consecutive days (UAS7) in patients before admission. This study was approved by Hacettepe University Ethics Committee.

Demographic features, including sex and age, the age at symptom onset, UAS7 at admission, whether or not angioedema was present, concomitant symptoms other than urticaria or angioedema, accompanying allergic diseases, chronic diseases, a family history of allergic diseases, and laboratory findings on admission and at follow-up were recorded. Telephone interviews were performed to review the current status of urticaria of the participants. We used a mini-questionnaire, which included the date of the last urticarial symptoms; the medications taken; and concomitant symptoms, such as gastrointestinal (*e.g.,* abdominal pain and/or cramp, diarrhea, mucus or blood in stool, anal pruritus, and emesis) or general (*e.g.,* loss of appetite, fatigue, and fever) in a telephone interview. Remission was defined as the disappearance of urticaria for at least 6 months.

Laboratory Investigations

All the children underwent extensive laboratory investigations, including a complete blood cell count; C-reactive protein level; erythrocyte sedimentation rate; total immunoglobulin E (IgE) level; C3 and C4 levels; thyroid hormones, including thyroid stimulating hormone and free T4 levels; thyroid autoantibodies (antithyroid peroxisomal, antithyroglobulin, and anti–thyroid stimulating hormone antibodies); antinuclear antibody; anti–double-stranded DNA antibody; urine analysis; and stool examination for parasites. Urine analysis was performed as automated urinalysis and direct microscopy. In case of any abnormality in these tests, further tests or consultation with relevant departments were performed as indicated. If a specific disease was diagnosed based on the laboratory tests mentioned above, then specific treatment was given by the consultant department, and treatment response was observed for relevance between test abnormality and urticarial symptoms. If there was no specific underlying disease, then second-generation antihistamines were given and treatment was organized according to the current guidelines.[1]

Skin-Prick Test Procedure

A skin-prick test (SPT) was performed with common allergens: *Dermatophagoides pteronyssinus, Dermatophagoides farinae, Alternaria,* cat epithelia, dog epithelia, *Blattella germanica,* grass mixture (*Phleum pratense, Poa pratensis, Dactylis glomerata, Lolium perenne, Festuca pratensis,* and *Avena elatior*), tree mixture (*Betula verrucosa, Alnus glutinosa,* and *Corylus avellana*), *Olea europaea,* cow's milk, soya, wheat, peanut, hazelnut, egg white, egg yolk, and histamine (10 mg/mL of histamine phosphate) as the positive control; and 0.9% sterile saline solution as the negative control. The SPT result was considered positive if the mean wheal diameter was ≥3 mm compared with the negative control. When there was suspicion of another food that was not listed above as a trigger of urticaria in patient's history, SPT was also performed with that culprit food. All positive SPT results were evaluated for relevance to urticarial symptoms. In the case of aeroallergen sensitization, the patients were queried about an increase of symptoms by allergen exposure. In case of any positivity with SPT results and/or specific IgE levels with culprit food, oral food challenge was performed to confirm a food allergy. When there was a suspicion of a drug as a trigger in the patient's history, the SPTs and/or intradermal tests were applied, if available, and oral provocation tests were performed to investigate the drug allergy.

Autologous Serum Skin Test Procedure

An autologous serum skin test (ASST) was performed with 0.05 mL of sterile, fresh autologous serum, and 0.9% sterile saline solution as a negative control. Thirty minutes after the intradermal injection of serum, wheal and flare reactions were measured, and a wheal diameter of ≥1.5 mm than the control was considered as a positive result.[7]

Statistical Analyses

All data were analyzed with SPSS statistical software, version 18.0 (SPSS Inc, Chicago, IL). The proportions in different groups were compared by using the Pearson χ^2 test or the Fisher exact test, when appropriate. All numeric variables were compared with Mann-Whitney *U* or Kruskal-Wallis tests, when appropriate; the results are given as median and interquartile ranges (IQR). Kaplan-Meier analysis was performed for persistence of CSU in all of the patients by using the standard log-rank test. The factors related to the resolution of CSU were determined by a Cox regression. The risk factors for the persistence of CSU were determined by univariate analysis and then multivariate logistic regression analysis, and the results were given

Table 1 **Characteristics of children with CSU**

Characteristics	CSU (*N* = 222)
Sex, no. (%)	
Boys	118 (53.2)
Girls	104 (46.8)
Age at symptoms onset, median (IQR), y	8.8 (4.6–12.3)
Duration of urticaria, median (IQR), mo	23 (7–48)
Age at admission, median (IQR), y	10.1 (6.4–13.2)
Period from the onset of symptoms until admission, median (IQR), mo	6 (3–18)
UAS7 at admission, median (IQR)	28 (21–42)
Angioedema, no. (%)	107 (48.2)
Concomitant allergic diseases, no. (%)	37 (16.7)
Asthma	19 (8.6)
Allergic rhinitis	18 (8.1)
Atopic dermatitis	7 (3.2)
Chronic disease without allergic disease, no. (%)	11 (5)
Family history of allergic disease, no. (%)	56 (25.2)

CSU = Chronic spontaneous urticaria; IQR = interquartile range; UAS7 = sum of the daily urticaria activity score of 7 consecutive days.

as odds ratio with relevant 95% confidence interval. A p value of <0.05 indicated a statistically significant result.

RESULTS

A total of 222 patients with CSU were evaluated. Baseline characteristics of patients are given in Table 1. The median ages of children at the onset of urticarial symptoms and at admission were 8.8 years (IQR, 4.6–12.3 years) and 10.1 years (IQR, 6.4–13.2 years), respectively. The median duration of urticaria was 23 months (IQR, 7–48 months), and the median UAS7 at admission was 28 (IQR, 21–42). At admission, 107 of patients (48.2%) also had angioedema and 37 (16.7%) had concomitant allergic diseases. A family history of allergic diseases was observed in 25% of the patients. The medians of the leukocyte and eosinophil counts were within normal limits: only 2.3% of the patients had a high eosinophil count, and 9.8% had a high eosinophil percentage in peripheral blood. Total IgE levels were >100 U/L in 65 patients (37.8%). Decreased levels of C3 or C4 were found in nine patients (4.1%), but none had an abnormal level or function of C1 esterase inhibitor (Table 2).

Ten patients (5.1%) had an abnormal urine test result, and three of them had positive urine culture results. However, only one patient's urticaria (0.9%) disappeared after antibiotic treatment and was considered urinary tract infection–associated urticaria. Parasites in stool were found in 19 patients (10.2%), and treatment was given according to the type of parasite. Urticaria resolved completely in nine patients (4.8%) and was considered to be parasite-associated urticaria. Detected causative parasites were *Blastocystis hominis* ($n = 5$), *Giardia lamblia* ($n = 3$), and *Dientomobea fragilis* ($n = 1$). Only nine children with CSU (4.9%) had abnormal thyroid function test results, and 13 (6.7%) had positive thyroid autoantibody results. Four patients were diagnosed as having Hashimoto thyroiditis, three of whom were euthyroid; therefore, treatment was not given. L-thyroxin regimen was indicated in only one patient (0.5%), and urticaria disappeared after treatment.

A total of 55 patients (27.1%) had positive autoantibodies. The patients with positive antinuclear antibody or anti–double-stranded DNA antibody results were evaluated for autoimmune diseases, but none of them were diagnosed as having a specific rheumatologic disease at the time of the analysis. Autologous serum skin testing was performed in 123 patients (55.4%), and 43 (34.1%) had positive results. SPTs were performed on 197 patients (88.7%) and 55 children (27.9%); the results were positive. Only three patients who were pollen sensitized developed urticaria exclusively during pollen season and was recognized as pollen-associated CSU. Four patients had positive SPT results with food. After 2 weeks of elimination diet by excluding offending food, oral food challenge revealed definite food allergies to cow's milk and egg in two of the children (0.9%). A total of 18 patients stated, in their history, a drug as a trigger of urticaria, and all of them were evaluated for drug allergy by skin tests, if available, and oral provocation tests, but none of them had been diagnosed as having a drug allergy.

The patients were followed up for a median of 15 months (IQR, 5–36.5 months). Information about the current status of urticarial symptoms was obtained in 190 of the patients (85.6%); 60 (31.6%) were in remission. According to the Kaplan-Meier analysis, remission was seen in 10.6, 29.3 and 44.5% of the patients in 1, 3, and 5 years, respectively. The probability of persistence of urticarial symptoms was significantly higher in children with UAS7 of >28 at admission than children with ≤28 according to the Kaplan-Meier analysis ($p < 0.0001$, log- rank test, Mantel-Cox test) (Fig. 1 *B*). The risk factors for persistence of urticarial symptoms were investigated with univariate and multivariate logistic regression, and UAS7 of >28 at admission was significantly associated with persistence of urticaria (odds ratio 6.22 [95% confidence interval, 1.54–25.15; $p = 0.010$]) (Table 3).

Table 2 **Laboratory findings of children with CSU**

Laboratory Findings	No. Patients Evaluated	CSU (*N* = 222)
Leukocyte count, median (IQR), mm^3	214	7820 (6685–9575)
Eosinophil count, median (IQR), mm^3	214	124 (100–200)
Eosinophil count of ≥500 mm^3, no. (%)	214	5 (2.3)
Eosinophils, median (IQR), %	214	1.6 (0.9–2.7)
Eosinophils, percentage ≥ 4%, no. (%)	214	21 (9.8)
Total IgE level, median (IQR), IU/L	172	63.5 (26.3–152.5)
Total IgE level of ≥100 IU/L, no (%)	172	65 (37.8)
Elevated CRP level of >0.5 mg/dL, no. (%)	151	25 (16.6)
Elevated ESR level of >20 mm/h, no. (%)	189	15 (7.9)
Decreased C3–4 levels, no. (%)	161	9 (4.1)
Abnormal urine test, no. (%)	197	10 (5.1)
Parasite in stool, no. (%)	186	19 (10.2)
Abnormal thyroid function tests, no. (%)	185	9 (4.9)
Autoantibody positivity, no. (%)	203	55 (27.1)
Thyroid autoantibody	193	13 (6.7)
Antinuclear autoantibody	184	44 (23.9)
Anti–ds DNA	183	6 (3.3)
Autologous serum skin testing positivity, no. (%)	123	42 (34.1)
Skin-prick test positivity, no. (%)	197	55 (27.9)
Pollen		52
Mite		11
Animal epithelia		8
Mold		1
Food		4

CSU = Chronic spontaneous urticaria; IQR = interquartile range; IgE = immunoglobulin E; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; Anti-dsDNA = anti-double-stranded DNA.

DISCUSSION

Our study revealed some key information regarding the etiology, prognosis, and prognostic factors in childhood CSU within a large cohort and long-term follow-up. The underlying cause of CSU could be identified in 8.8% of our patients. In addition, the autoimmune background was determined in 34% of the children. Remission was attained in nearly half of the children after 5 years of symptom duration. A UAS7 of >28 at admission was a significant predictive factor that influenced persistence of urticaria.

Although there are many studies that investigated the etiology of chronic urticaria, most of data was related to adults. Among a few studies concerning childhood CSU, the proportion of patients whose underlying cause of chronic urticaria was identified varies between 6 and 55%.[5,8–12] However, inducible urticaria as an etiology was included in most of these studies. This rate was found to be low as 6–14% in a few studies that excluded physical urticaria.[5,12]

In our study, the etiology could be determined in only 8.8% of the patients, despite detailed clinical history, physical examination, extensive laboratory investigations, and challenge tests. Each suspected causative factor was evaluated carefully in terms of being a real trigger. If there was no clear relationship between abnormal tests or suspected factors and CSU, or was not confirmed by challenge tests or treatment response of diagnosed specific disease, then suspected factors or abnormal test were not accepted as a causative factor. This approach might be the reason for the low diagnosis rate of etiology in our study.

In our cohort, parasitic infestation was the most common causative factor of CSU in 4.8% of children. Parasites in stool examinations of children with chronic urticaria was found in 2.4% by Kauppinien *et al.*,[9] 2.5% by Du Toit *et al.*,[13] 2.7% by Sahiner *et al.*,[5] 3.7% by Volonakis *et al.*,[10] and 5.4% by Jirapongsananuruk *et al.*[14]; however, improvement of symptoms after antiparasite treatment was only established in a few studies. In a recent systematic review that assessed the prevalence and relevance of parasitic infections in patients with CSU, it was stated that pediatric patients with parasites ranged from 0 to 37.8%.[15] Concurrent gastrointestinal symptoms, previous parasitic infection, traveling abroad, and unexplained peripheral eosinophilia might point out the presence of parasite infection in a patient with CSU. However, the types of parasites or

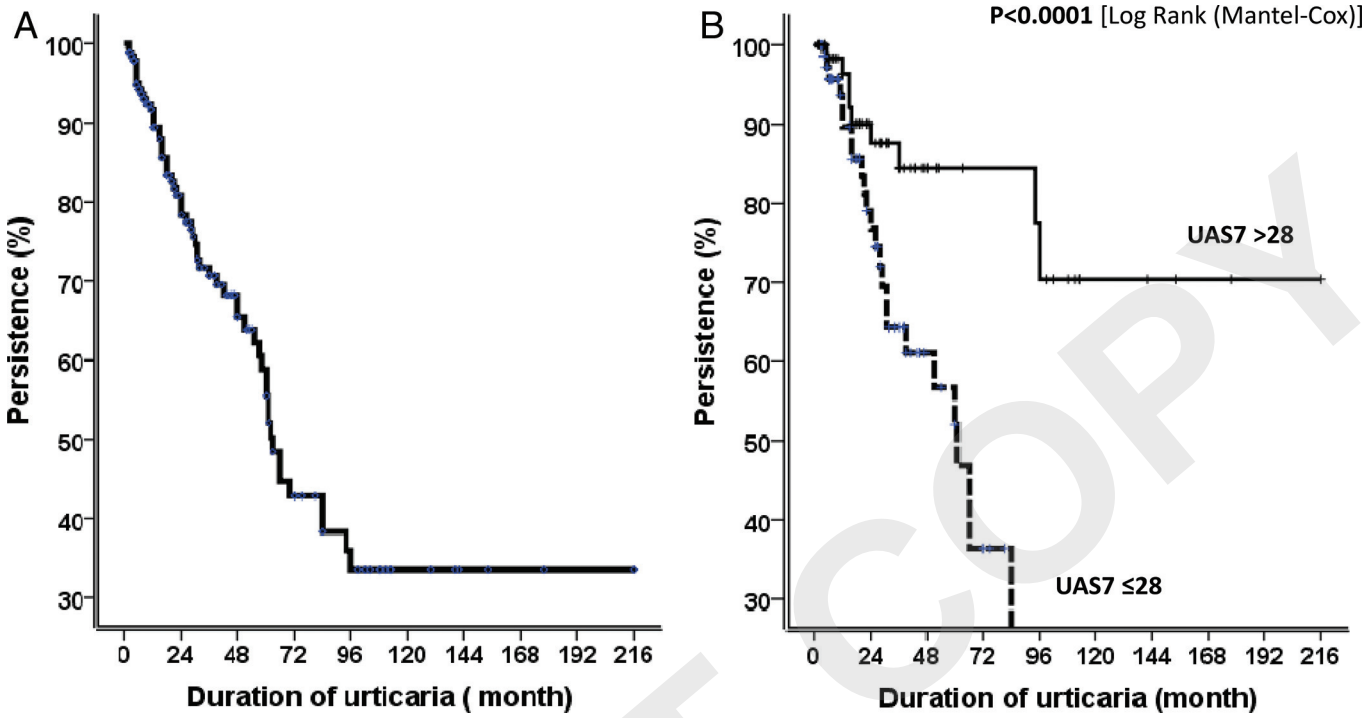

Figure 1. *The probability of the persistence of chronic spontaneous urticaria (CSU) according to the duration of urticaria. (A) The whole study population. (B) By urticaria activity score ($p < 0.0001$, log-rank test, Mantel-Cox test).*

Table 3 **Factors associated with persistence of CSU**

	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Sex	1.13 (0.61–2.09)	0.693		
Age at initial symptoms	1.02 (0.96–1.09)	0.504		
Angioedema	0.54 (0.29–1.01)	0.054		
Concomitant allergic diseases	0.42 (0.16–1.08)	0.072		
Skin-prick test positivity	0.65 (0.31–1.37)	0.257		
ASST positivity	0.80 (0.33–1.93)	0.620		
Autoantibody positivity	0.64 (0.31–1.33)	0.234		
Resolved with antiparasitic treatment	0.27 (0.03–2.24)	0.227		
Urinary infection	0.57 (0.06–6.53)	0.647		
Eosinophil	1.01 (0.83–1.23)	0.929		
Total IgE value	1.00 (0.99–1.00)	0.929		
UAS7 of >28 at admission	0.33 (0.14–0.77)	0.011	6.22 (1.54–25.15)	0.010

CSU = Chronic spontaneous urticaria; OR = odds ratio; CI = confidence interval; ASST = autologous serum skin testing; IgE = immunoglobulin E; UAS7 = sum of the daily urticaria activity score of 7 consecutive days.

effects of treatment of parasitic infection on CSU were not mentioned in most of the research.

The prevalence of food allergy in children with chronic urticaria was determined to be 1–2.7% in studies that performed confirmation of food allergy by oral food challenges after a period of food elimination.[5,8,10] In our study, food allergy was found to be the causative factor in only 0.9% of children based on double-blind placebo-controlled oral food challenge and remission criteria of CSU. The parents frequently thought that foods were responsible for chronic urticaria symptoms. Elimination of the culprit food from a child's diet was already done by most of parents at admission. Nevertheless, IgE-mediated food allergies rarely cause chronic urticarial symptoms. Occasionally, urticaria may persist when the allergic food consumption was continued even in trace amounts. For similar reasons, drug allergies also rarely cause chronic urti-

caria.[4] In our cohort, drug allergy was inquired by clinical history but was not determined as an etiologic factor of CSU after provocation tests.

Even though infections may frequently cause acute urticaria in childhood[16]; there is no clear evidence regarding the association between infections and chronic urticaria.[17,18] The prevalence of infections related to chronic urticaria in children was reported as 2% by Harris *et al.*[8] and as 4.4% by Volonakis *et al.*[10] In our study, only one child underwent remission after treatment of urinary infection. Therefore, infections seem to be a causative factor in a small number of children with CSU.

Aeroallergen sensitization–associated chronic urticaria has been assessed in a few studies. It was shown that adults with chronic urticaria had more skin test result positivity with aeroallergens compared with those adults without chronic urticaria.[19] Volonakis *et al.*[10] found that aeroallergen sensitization was relevant, with CSU in 2.2% of the children. Although SPT positivity with aeroallergens was detected in >50 patients in our cohort, sensitization was relevant to CSU symptoms in only three children. In addition, those patients also had allergic rhinitis symptoms. Therefore, it may be useful to investigate aeroallergen sensitization in case of urticarial symptoms with a seasonal pattern and the existence of allergic rhinitis symptoms.

Studies that indicated the association between autoimmune thyroid diseases and chronic urticaria mainly concerned adults.[20,21] Levy *et al.*[22] showed the increased levels of antithyroid antibodies in 4.3% of children and adolescents with chronic urticaria at admission or at their follow-up; however, none of these patients had remission of urticaria after treatment of their thyroid disease. Other studies on childhood chronic urticaria reported none or only one patient who had been associated with thyroid autoimmunity.[8,10,14] In our cohort, 4.9% of the patients had abnormal thyroid hormone levels and 6.7% had positive serum thyroid autoantibodies; but the causative association was revealed in only one patient who had been diagnosed as having Hashimoto thyroiditis. Thyroid disease–associated CSU seems to be rare in childhood, even in the case of abnormal thyroid tests.

Nearly 40% of patients with chronic urticaria had circulating functional autoantibodies directed against IgE or epitopes in the α-chain of the high-affinity IgE receptor, which leads to mast cell degranulation and histamine release.[23] Brunetti *et al.*[11] demonstrated a good correlation between the ASST and the basophil activation test in children with chronic urticaria, whereas the ASST result was found to be positive in 38–47%.[5,11,13,14] However, there were differences in inclusion criteria regarding age ranges or the definition of disease, and some studies included physical urticaria. In our cohort, the ASST result was found to be positive in 34.1% of patients, and there was no association between ASST positivity and activity or persistence of CSU. ASST is a practical and reasonable test to assess the autoimmune background of CSU. However, it is still unclear whether or not it affects clinical symptoms and prognosis of the disease.

Differences about identified underlying causes in those studies may be due to differences in the methodology or inclusion criteria, such as the definition of disease and age ranges. In addition, to date, the proportion of patients with identified etiology is very low in studies of childhood CSU, including our study. These results supported the opinion that routine laboratory testing may not be required when investigating the etiology in all the patients.

Only a few studies investigated the natural course of CSU in children. However, there were many differences about the definition of the disease and remission criteria, and follow-up periods and age ranges of children. In a study in which remission criteria were considered as an urticaria-free period for >6 months, 58% of the children went into remission in a 1-year follow-up period, which also involved physical urticaria.[8] Previously, we reported that recovery was seen in 16.5, 38.8, and 50.0% of the children after 12, 36, and 60 months, respectively, with the same remission criteria.[5] In another study, with a remission criterion of 12 months and that included only 4–15-year-old children, the rates of remission were 8.5, 54, and 67.7% of children at 1, 3, and 5 years, respectively.[12] Hiragun *et al.*[6] retrospectively analyzed 117 children and adults with CSU that was insufficiently controlled by a standard dose of antihistamine. In that study, the remission criterion was considered as a 1-month urticaria-free period, and the remission rate was found as 36.6, 51.2, and 66.1% at 1, 2, and 5 years, respectively. Taken together, CSU has a better prognosis in children compared with adults. Although childhood CSU has a favorable natural course, no statistically significant prognostic factor could be identified in these studies. In our previous study, resolution rate was found to be worse in girls >10 years old at univariate analysis, but it was not statistically significant at multivariate analysis.[5] In a recent systematic review, plasma levels of prothrombin, D-dimer, and C-reactive protein were found to be probable markers of the severity and duration of CSU.[24]

In the present study, a UAS7 of >28 at admission was found to be a significant predictive factor relevant to the persistence of symptoms. Moreover, the probability of the persistence of CSU was significantly increased in children with a UAS7 of >28 compared with children with a score of ≤28. Until now, to our knowledge, there was no study that investigated the effect of severity of urticaria at admission on the natural course in childhood CSU. The UAS is proposed to assess the

disease activity in patients with CSU by using the recent guidelines.[1] The absence of the control group might be considered a limitation of this study. However, the primary aim of this study was to determine the etiologic factors in children in the CSU cohort. The lack of investigation of some diseases that were previously reported to accompany CSU, *e.g.*, celiac disease, may be considered as a limitation of the study. The rate of patients lost to follow-up was 14.4% in our cohort, but it was lower when compared with other studies. Nevertheless, this study included the largest cohort with wide age ranges in childhood.

CONCLUSION

The etiology of CSU in children remained idiopathic despite detailed investigation. The natural course of childhood CSU is favorable, with nearly half of the patients in remission after 5 years of duration. An increased UAS seemed to be a significant risk factor for the persistence of symptoms. To our knowledge, this was the first study showing UAS7 as a predictive factor on the prognosis of childhood CSU in a large cohort.

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