

Chronic Urticaria: Etiology and Natural Course in Children

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Key Words

Chronic spontaneous urticaria · Autoreactive · Urticaria · Children · Prognosis · Epidemiology · Autologous serum skin test

Abstract

Background: Chronic spontaneous urticaria (CSU) in childhood is infrequent, and information about the disease in children is limited. We attempted to investigate its etiologic factors, natural course, and predictors of prognosis. **Methods:** All children aged ≤ 18 years followed for CSU during an 8-year period were analyzed retrospectively, and the final outcomes were queried via a telephone interview. **Results:** One hundred patients (male/female ratio 1.27) with a median age of 9.2 years (range 0.7–17.2) at symptoms onset were evaluated. The median follow-up was 2.5 years (range 0.2–18.1). An autologous serum skin test was positive in 46.7% of the subjects ($n = 45$), with a female predominance (71.4%) ($p = 0.023$). In 13.8% of the children, ANA titers were over 1/100. Food allergy ($n = 1$), thyroid autoantibodies ($n = 3$), possible collagen disease ($n = 1$), and drug usage (deferioxamine) ($n = 1$) were found to be associated factors. Infections could not be confirmed as the cause of CSU. Recovery was seen in 16.5, 38.8, and 50.0% of the children after 12, 36, and 60 months, respectively. Though in multivariate analysis none of the factors, including age, gender, autologous serum skin test positivity, the presence of angioedema, or oth-

er allergic diseases, appeared to predict the prognosis, in univariate analysis being female and being older than 10 years of age predicted an unfavorable prognosis. **Conclusion:** The etiology of CSU in children is mainly related to an autoreactive background, as in adults. CSU has a favorable prognosis, and resolution is seen in half of the children within 5 years. Girls older than 10 years may have an unfavorable prognosis.

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Introduction

Urticaria is a common entity affecting 15–25% of the population with at least 1 episode in their lifetime [1]. It is divided into acute and chronic forms, with chronic urticaria (CU) defined as the presence of hives for more than 6 weeks. CU in children is generally known to be less common than in adults, affecting 0.1–3.0% of children [2], and it can be physical, spontaneous, or of a different nature. Physical urticaria is triggered by a specific physical stimulus and includes cold urticaria, solar urticaria, delayed pressure urticaria, localized heat urticaria, dermagraphic urticaria, and vibration urticaria. Chronic

This study was presented at the EAACI 2010 Congress in London (p511) with a slightly different conclusion because of the addition of new patients and an extra analysis.

spontaneous urticaria (CSU) is defined as the daily or almost daily occurrence of wheals for more than 6 weeks after the exclusion of physical urticaria and other urticaria types [3]. In contrast to the ease of its diagnosis, it is difficult to diagnose the etiologic factors responsible for CSU, and there are limited studies in children with CSU [4–7]. Reports of success in identifying a cause for CU in children (including physical urticaria in the classification of CU) range from 21 to 83% [5, 8]. In these studies, several etiologic factors were identified as possible causes, such as chronic infections, parasites, food allergies, and collagen vascular diseases [4–8]. In addition, recent publications have shown that in 30–50% of patients with CSU, the disease process is related to an autoimmune process with the presence of an immunoglobulin (Ig)G type autoantibody against either the high affinity receptor FcER1 α or IgE [9–11]. An autologous serum skin test (ASST) is used to screen for autoimmune pathology; however, it is regarded as a test for autoreactivity rather than a specific test for autoimmune urticaria. ASST has moderate specificity as a marker for functional autoantibodies against IgE or the high affinity IgE receptor (Fc ϵ RI), and it has a high negative predictive value for CU patients without them compared with the basophil histamine release test (BHRT), the gold standard for autoimmune pathology in urticaria [12, 13].

Knowledge about the natural course of CU is important to inform parents regarding their prognosis and for assessment of the social and economic burden of the disease. CU can cause significant morbidity in the form of school absences, low school performance, and poor quality of life, and patients rely heavily upon healthcare services compared to patients with other allergic diseases [14]. However, information about the natural course of the disease is drawn mainly from adult studies [15–17], and there is little information available regarding children [4, 18, 19].

In the present study, we attempted to document the etiologic factors and natural course of CU in children.

Patients and Methods

Patients

The study was performed in the outpatient clinic of the Pediatric Allergy and Asthma Unit of Hacettepe University İhsan Doğramacı Children's Hospital, which is the largest pediatric asthma outpatient clinic in the country. While the clinic serves as a referral center for the entire country, patients may also be admitted upon request; thus, it functions as both a primary and tertiary health care service. The medical records of the patients who attended our clinic and were diagnosed with CU between January 1,

2002 and December 31, 2009 were evaluated retrospectively. Histories, physical findings, and diagnostic tests were all retrieved from the patients' medical records. A total of 113 files were evaluated. One and 12 files were excluded from the study because of insufficient data and the diagnosis of physical urticaria, respectively, and finally 100 patients with CSU were analyzed in the study. A database was formed and each patient was then contacted by telephone to inquire regarding their current disease status. All of the patients were reached by telephone by the third attempt. If a patient had been free of urticarial symptoms for at least 6 months, he/she was considered to be in remission. Reappearance of the symptoms after remission was considered relapse of the disease [4].

Laboratory Investigations

Laboratory investigations included a complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), anti-streptolysin O (ASO), *Helicobacter pylori* IgG antibody, hepatitis markers, complement levels including C3 and C4, total IgE levels, antinuclear antibody (ANA), anti-double stranded deoxyribonucleic acid (anti-DNA), thyroid-stimulating hormone (TSH), free T4, anti-thyroid peroxidase antibody, anti-thyroglobulin antibody, a purified protein derivative (PPD) test, urine analysis, a stool examination for parasites, and throat and urine cultures.

Skin Test Procedures

All participants presenting with a history of CU were skin prick tested (SPT) for *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Alternaria*, cat, grass mix (*Phleum pratense*, *Poa pratensis*, *Dactylis glomerata*, *Lolium perenne*, *Festuca pratensis*, and *Avena elatior*), tree mix (*Betula verrucosa*, *Alnus glutinosa*, and *Corylus avellana*), *Olea europaea*, horse dander, *Blattella germanica*, wheat, peanut, hazelnut, egg white, egg yolk, soya and cow's milk, and histamine (10 mg/ml of histamine phosphate) as positive subjects and 0.9% sterile saline as negative controls. The SPT was considered positive if the mean wheal diameter was ≥ 3 mm compared with the negative control. A positive SPT was taken as evidence of the presence of atopy in that patient.

In the case of suspicion of food allergy, an open food challenge was performed followed by either a double-blind placebo-controlled food challenge or an elimination diet.

In 45 of the patients (informed consent was received from patients and parents) an ASST was performed using an intradermal skin test with 0.05 ml of sterile, fresh autologous serum as well as 10 μ g/ml histamine and 0.9% sterile saline as positive and negative controls, respectively. Thirty minutes after the intradermal injection of serum, wheal and flare reactions were measured and a wheal diameter of ≥ 1.5 mm when compared with a control saline solution was considered positive [11].

Statistics

Results were expressed as medians (ranges); groups were compared using the Student t test or Pearson's χ^2 test for differences. For prognosis, Kaplan-Meier and Cox regression analyses were used, and recovery curves were compared with a logrank test. Statistical analyses included univariate and multivariate analyses, and odds ratios (ORs) with relevant 95% confidence intervals (CIs) were calculated for evaluating the potential associations between various predictors and CU. $p < 0.05$ was considered statistically significant. All analyses were performed using the SPSS 16.0 software program (SPSS, Inc., Chicago, Ill., USA).

Table 1. Characteristics of the study group

Male gender	56.0
Age at symptoms onset, years	9.2 (0.7–17.2) ^a
Follow-up duration, years	2.5 (0.2–18.1) ^a
Atopy (n = 98)	32.7%
Asthma (n = 99)	10.1%
Allergic rhinitis (n = 99)	7.1%
Atopic dermatitis (n = 99)	2.0%
Angioedema (n = 99)	42.4%
Family history	
Atopy (n = 99)	25.3%
CU (n = 99)	10.1%
Autoimmune disease (n = 99)	0.0%

^a Median (range).

Results

A total of 100 patients (56 male and 44 female) were evaluated for the study with a median age during symptoms onset of 9.2 years (range 0.7–17.2). The median age at admission, the current age, and the median follow-up durations and their ranges were 10.3 years (2.1–17.6), 13.6 years (3.9–22.5) and 2.5 years (0.2–18.1), respectively. The frequencies of asthma, allergic rhinitis, and atopic eczema were 10.1, 7.1, and 2.0%, respectively. Characteristics of the patients are shown in table 1.

An ASST was performed in 45 children (male/female ratio 0.87) and was positive in 21/45 (46.7%) of the patients (male/female ratio 0.40). Most of the patients with ASST positivity were female 71.4% ($p = 0.023$) (table 2). ASST results were not associated with ANA positivity and/or high levels of ESR or CRP ($p > 0.05$).

Thirty-two out of 98 patients had atopy. The numbers of patients sensitized were 18, 5, 4, and 4 for grass mix/tree mix, house dust mite, grass mix and house dust mite, and grass mix and cat, respectively. Only 1 of the patients showed food allergy (cow's milk) confirmed with an open oral challenge, and symptoms disappeared after the removal of cow's milk from the diet. Anti-thyroid peroxidase antibodies were positive in 3 of 82 (3.7%) patients. One of these patients was diagnosed with Hashimoto's thyroiditis. High antinuclear antibody titers ($>1/100$) were found in 13/94 (13.8%) patients, and 1 of them presented with persistent arthralgia. Abnormal laboratory results are shown in table 3. With the combination of case histories, physical examinations, laboratory results, and challenges, we determined that CU in our study group was associated with an autoreactive pathology in 46.7%

Table 2. Characteristics of the children according to the ASST results

	ASST negative n (%)	ASST positive n (%)
Male gender	15/24 (62.5)	6/21 (28.6)*
Presence of atopy	7/24 (29.2)	8/21 (38.1)
Age >10 years	11/24 (45.8)	12/21 (57.1)
Age at symptoms onset (range), years	8.1 (1–15.2)	10.1 (4–17)
Current age (range), years	13.4 (3.9–21.7)	13.3 (7.4–20.5)
Angioedema	9/24 (37.5)	11/24 (52.4)
Asthma	1/24 (4.2)	6/21 (28.6)*
Allergic rhinitis	2/24 (8.3)	2/21 (9.5)
Atopic dermatitis	1/24 (4.2)	0 (0)
Atopy in the family	6/24 (25.0)	6/21 (28.6)
Urticaria in the family	5/24 (20.8)	0 (0)
Autoimmune diseases in the family	0 (0)	0 (0)
ANA (+)	3/24 (12.5)	3/20 (15)
Abnormal C3	0 (0)	0 (0)
Abnormal C4	3/18 (16.7)	2/16 (12.5)
TPO (+)	0 (0)	1/20 (5)
Anti-thyroglobulin (+)	0 (0)	0 (0)
Abnormal FT3	0 (0)	1/18 (5.6)
Abnormal FT4	0 (0)	1/19 (5.3)
Abnormal TSH	0 (0)	1/19 (5.3)
Hepatitis markers (+)	0 (0)	0 (0)
Elevated <i>H. pylori</i> IgG	2/12 (16.7)	0 (0)
Elevated ESR	1/21 (4.8)	1/20 (5)
Increased ASO	6/14 (42.9)	2/14 (14.3)
Increased CRP	2/16 (12.5)	1/17 (5.9)
WBC >10,000	3/24 (12.5)	2/20 (10)
Eosinophil number (range)	135.0 (10–1000)	147.5 (30–317)
Eosinophils >4%	5/24 (20.8)	2/19 (10.5)
Total IgE >100	9/21 (42.9)	7/21 (41.2)
Parasites in stool	0 (0)	0 (0)
Positive PPD	1/4 (25)	2/8 (25)
Positive throat culture	1/19 (5.3)	0 (0)
Positive urine culture	0 (0)	1/19 (5.3)
Abnormal urine test	0 (0)	1/20 (5)

TPO = Thyroid peroxidase; WBC = white blood cells.

* $p < 0.05$.

of the children, with food allergy in 1%, with thyroid pathology in 3.7%, with a possible collagen disease in 1%, and with drug usage (desferal) in 1%. We could not confirm the relationship of infections (4.1% of the patients), parasites (2.7% of the patients), or *H. pylori* (9.7% of the patients) with CU.

A total of 82 patients could be evaluated for the duration of symptoms with Kaplan-Meier analysis; 16.5, 38.8, and 50.0% of the patients recovered in 12, 36, and 60

Table 3. Abnormal laboratory results of the children with chronic urticaria

Parameters	Patients evaluated, n	% (n)
Age >10 years	100	42.0 (42)
Presence of atopy	98	32.7 (32)
Positive ASST	45	46.7 (21)
ANA positivity	94	13.8 (13)
Anti-DNA positivity	93	0 (0)
Abnormal C3	74	0 (0)
Abnormal C4	74	8.1 (6)
TPO (+)	82	3.7 (3)
Anti-thyroglobulin (+)	86	2.3 (2)
Abnormal FT3	75	2.7 (2)
Abnormal FT4	79	1.3 (1)
Abnormal TSH	80	2.5 (2)
Abnormal hepatitis marker	73	0 (0)
Elevated <i>H. pylori</i> IgG	31	9.7 (3)
WBC >10,000	99	17.2 (17)
Eosinophils >4%	97	13.4 (13)
Total IgE >100 kU/l	81	43.2 (35)
Elevated ESR	86	5.8 (5)
Increased ASO	46	34.8 (16)
Increased CRP	59	11.9 (7)
Parasites in stool	75	2.7 (2)
Positive PPD	21	19.0 (4)
Positive throat culture	73	1.4 (1)
Positive urine culture	74	2.7 (2)
Abnormal urine test	94	3.2 (9)

TPO = Thyroid peroxidase; WBC = white blood cells.

months, respectively. The same analysis was performed concerning gender, age groups (<10 years and ≥10 years), and ASST results (fig. 1). The median recovery time was 4.0 years for boys and 5.8 years for girls; however, the results were not statistically significant ($p = 0.351$). The median recovery times for the children with CU and <10 years of age compared to those with CU and ≥10 years of age were 4.59 and 5.0 years, respectively ($p = 0.218$). There was also no difference in prognosis with respect to the ASST results ($p = 0.762$).

Risk analysis regarding the prognosis was performed with univariate and multivariate analyses and group comparisons with the independent samples t test or Pearson's χ^2 test for differences between the groups. In Cox regression analysis, none of the factors, including age, gender, abnormal laboratory results, ASST positivity, a family history of autoimmunity, or the presence of angioedema or other allergic diseases, appeared to predict the prognosis in children with CU. However, when we com-

bined the 2 risk factors (being a girl and being older than 10 years) and made a comparison with the remaining group, an unfavorable prognosis appeared for 3–5 years of prognosis in univariate analysis (OR = 9.75, 95% CI = 1.21–78.32; $p = 0.016$ and OR = 8.40, 95% CI = 1.76–39.92; $p = 0.004$, respectively). However, it did not reach statistical significance in the multivariate logistic regression analysis, possibly due to a low number of subjects in the groups.

Discussion

In the present study, we found that the etiology of CSU in children is mainly related to an autoreactive background as nearly half of the children tested with the ASST showed positivity. In contrast to acute urticaria, CSU is not frequently related to infections (bacterial, viral, and parasitic). Thyroid diseases do not appear to be an important bystander as is the case in adults. CSU has a favorable prognosis and half of the children with CSU recover without any relapse. Although in univariate analysis the coexistence of female gender and being older than 10 years of age appears to predict a poor prognosis, in multivariate analysis none of the risk factors (or any of their combinations) such as demographic characteristics, atopy, family history, and the presence of an allergic disease or laboratory abnormalities predicted the prognosis.

It is difficult to compare and discuss the etiologic factors responsible for CSU in children with the available related literature because of the lack of standardization. Variations in the rates of specific etiology reported in the previous studies are mainly due to the different criteria for the confirmation of suspected etiologies as well as the different populations studied. CSU is known to be predominant in females in different studies [7, 8, 14]. However, in the present study, as in the study by Volonakis et al. [5], males were predominant in the CSU group (56%). The frequencies of allergic diseases and atopy in the patients did not differ from those in the general Turkish population, and atopy was not associated with CSU, which suggests that atopy is not related to CSU [20].

Studies concerning the autoimmune nature of CSU discuss mainly adult populations [10, 21, 22]. In children, the number of studies concerning the autoimmune nature of CSU is limited and ranges between 30 and 40% for CSU [7, 12]. In the present study, a 46.7% ASST positivity was found. Our result is comparable with those of previous studies because we excluded the physical urticaria cases from the study group. One can speculate that the

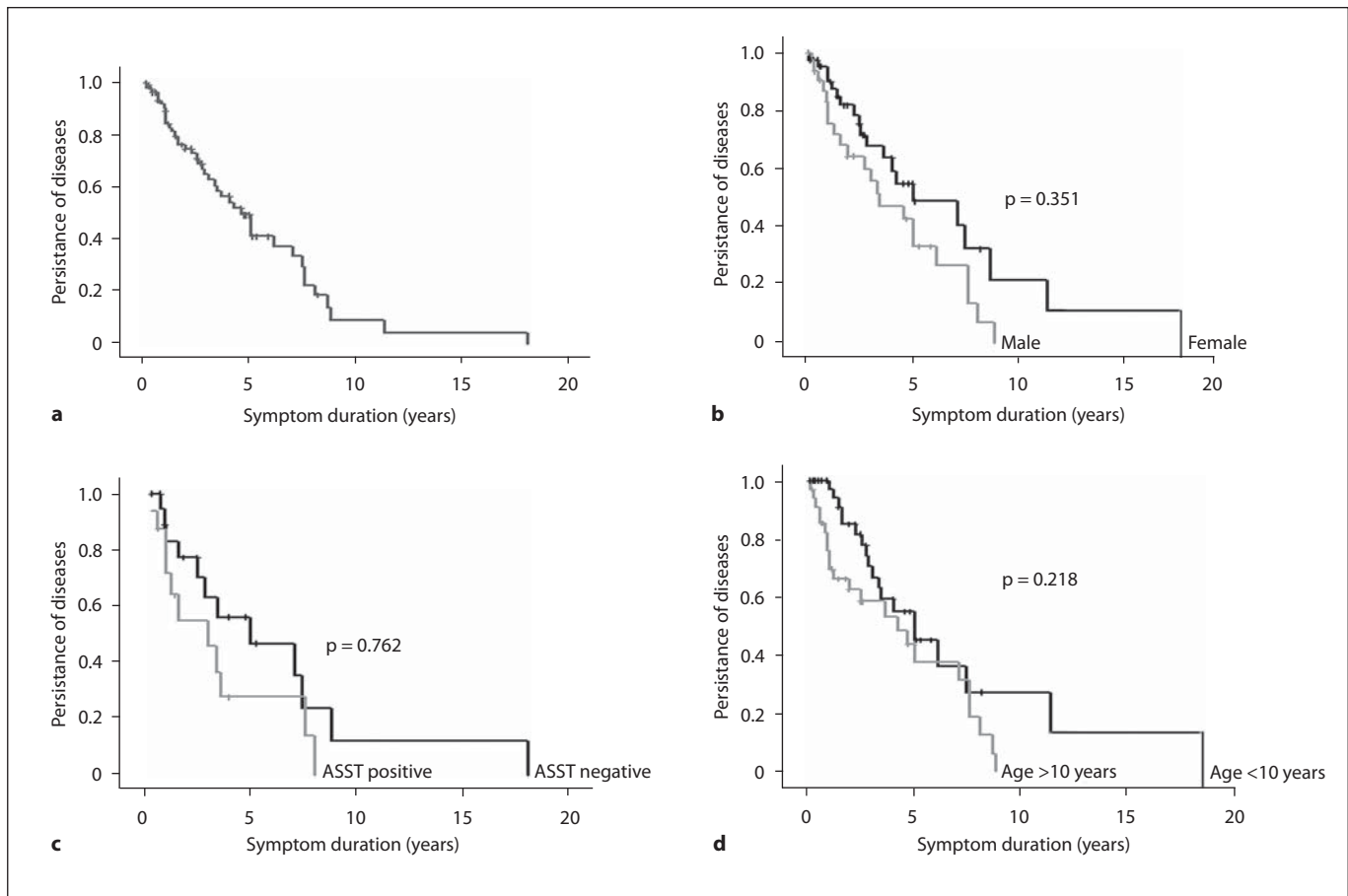


Fig. 1. Time to recovery in children with CU (median years to resolution). **a** The whole group. **b** By gender ($p = 0.351$). **c** By autologous serum skin test positivity ($p = 0.762$). **d** By age group ($p = 0.218$).

ASST is not a confirmatory test and does not show the autoantibodies but instead reflects that serum is able to induce histamine release from skin mast cells without knowledge of whether it is triggered by autoantibodies [23]. It is true, however, that ASST is a cheap, easy-to-perform, and practical method to diagnose the autoreactive nature of urticaria; it has a good sensitivity and an even better specificity compared to the BHRT, especially in developing countries where the BHRT is not available [12]. We think that children with ASST positivity should be followed for the development of new autoimmune diseases.

Thyroid pathology as a causative factor in CSU patients is based mainly on adult studies, and percentages as high as 25% have been reported [24, 25]. However, in studies in children, thyroid pathology does not appear to be an important associated factor. Neither Harris et al. [4] nor Volonakis et al. [5] mentioned thyroid abnormalities

in their papers. In addition, in a recent study, Jirapongsananuruk et al. [7] reported 1 out of 94 patients with thyroid autoimmunity. Levy et al. [26] evaluated 187 children with an age range of 7–17 years and found antithyroid antibody in 4.3%. In our study, we found that 3 children had antithyroid antibody positivity (3.7%); this result was similar to that from healthy Turkish children (1.2%) observed in a previous study [27]. One of these children was diagnosed with Hashimoto thyroiditis and this patient recovered from CU after the treatment. We think that children with ASST positivity should be searched for the presence of thyroid pathologies as mentioned in a recent guideline by Konstantinou et al. [13].

ANA positivity was present in 13/94 (13.8%) patients. One of them presented with persistent arthralgia. He is now under follow-up for the risk of a collagen vascular disease. Jirapongsananuruk et al. [7] showed an ANA positivity rate of 23%, but only 2 patients had a titration

of over 1/160, and no collagen vascular disease was diagnosed. Harris et al. [4] found 2/94 CU patients to have juvenile rheumatoid arthritis. In the case of ANA titers of 1/160 or over, it is important to follow patients for the development of systemic lupus erythematosus, whereas high ANA titers have no diagnostic utility in the diagnosis of juvenile rheumatoid arthritis [28].

Harris et al. [4] reported that in relation to history, 27% of children and/or parents considered food a causative factor for CSU, but food allergy was found to be related in only 2/94 (2.1%) of the children with CSU. Volonakis et al. [5] showed 6/226 (2.7%) children with CSU to have a related food allergy; Sackesen et al. [6] reported food-related urticaria cases (both acute and chronic) in 3/54 (5.5%) patients. We found 1 case of cow's milk allergy related to CSU. Although it is reported frequently by families, food allergy does not seem to be a major cause in children with CSU and should be confirmed by either an elimination diet or oral challenge tests.

The arguments concerning infections as an important causative factor for CSU are weak from an evidence-based viewpoint because variations in geographic regions, the kinds of settings, different diagnostic assessments, personal prejudices, and preconceived opinions of the investigators all affect the results; however, there are data suggesting a link [29]. Schuller [30] reported that infection, associated or not with drug intake, was defined as a major cause of acute urticaria in children. This is not the case in CSU patients, and infections are not as important as in acute urticaria. Infections were reported by Harris et al. [4] in 2% of the children with CSU, while Volonakis et al. [5] found a 1.3% association with infections. Our results were in agreement with these studies. We found high ESR, CRP, ASO, and PPD positivity in a number of patients, and throat and urine cultures were positive in 3 of them (table 3). However, no causal relationship was determined between these results and the clinical course of CSU since none of the patients recovered after the treatment of infections. We should mention that the viral etiology was not explored in detail in our study, and perhaps in a number of cases as reported previously from our center a viral causal relationship may be documented [7].

H. pylori has been suggested as a possible cause for CSU, but in most controlled prospective studies no relationship has been identified [31, 32]. The *H. pylori* serology positivity in our study was found to be less than that in the healthy children population (9.7 vs. 41.7%) [33]. We could not demonstrate a clinical correlation with CSU in our 3 patients diagnosed with *H. pylori* infection. Parasites

are rare causes of CSU in children. Harris et al. [4] and Sackesen et al. [6] did not report any case among 94 and 17 patients, respectively. Volonakis et al. [5] from Greece reported a rate of parasitic infestation of only 2.7% among 226 children, and even in a tropical country Jirapongsananuruk et al. [7] found 5 parasitic infestations in 94 children with CSU but there was no clinical correlation. In the present study, we found 2 patients with parasitic infestations and the urticaria persisted after the treatment.

Most of the information concerning the natural course of CU comes from adult studies. In 330 adult patients, the median duration of the symptoms with CU was between 2 and 4 years [34]. Quaranta et al. [15] found that the follow-up of 86 patients with CU for 3 years revealed a recovery rate of 56%. In another adult study with 153 patients, the recovery rates were 34 and 49% for 5 and 10 years, respectively [17]. There is little information available regarding children. Harris et al. [4] found a recovery rate of 58% in 94 children with CU after a 1-year follow-up. Mortureux et al. [19] reported a recovery rate of 94.7% in 57 children, most of whom had acute urticaria. Kauppinen et al. [18] reported a 47% recovery rate with a mean follow-up of 3.8 years, with physical urticaria having the worst prognosis. In our study, 1 out of 2 children were symptom free within 5 years. This shows that CSU in children has a favorable prognosis and that in half of the children CSU resolves without any relapse. The recovery rate seemed to be better for boys than girls and for children <10 years of age, but the results were not statistically significant. There was no difference with respect to the ASST results in contrast to the data mentioned in the EAACI/GA(2)LEN task force report. However, with a larger study group, these results may reach statistical significance. As in adults female gender was defined as a risk factor for poor prognosis [35], we considered being a female older than 10 years of age to be a risk factor and the analysis showed that being a girl older than 10 years of age may be a risk factor for a poor prognosis. However, we were not able to show any other predictors for prognosis, including age, gender, abnormal laboratory results, ASST positivity, a family history of autoimmunity, and the presence of angioedema or other allergic diseases.

In conclusion, the etiology of CSU in children is mainly related to an autoimmune background, and nearly half of the children who are tested show ASST positivity. In children, infections, foods, and thyroid diseases did not appear to be important causative factors for CSU. CSU has a favorable prognosis, with disease resolution in half of the children within 5 years, and being a girl older than 10 years of age may be related to a poor prognosis.

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