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Differences between adult and pediatric chronic spontaneous urticaria from a cohort of 751 patients: Clinical features, associated conditions and indicators of treatment response

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Abstract

Background: Chronic spontaneous urticaria (CSU) is a common disease both in the pediatric and in the adult population. However, there are differences between the two patient populations with respect to etiological factors, comorbidities, and treatment responses. Our aim was to determine differences between pediatric and adult CSU in terms of clinical characteristics, laboratory parameters, comorbidities, response to treatment, and indicators of response.

Methods: A retrospective analysis of CSU patients was performed. Data regarding differences between pediatric and adult CSU patients were analyzed. Indicators of treatment response were determined separately in both pediatric and adult patients.

Results: Of 751 CSU patients (162 pediatrics and 589 adults), female dominancy (48.8% vs. 69.6%) and rate of angioedema (19.1% vs. 59.8%) were lower, and disease duration (5 months vs. 12 months) was shorter in pediatric patients. Anti-TPO positivity (24.7% vs. 9%), elevated CRP (46.5% vs. 11.1%), eosinopenia (38.5% vs. 18.1%), and skin prick test positivity (39.3% vs. 28.8%) were significantly more frequent in adult patients. Response to antihistamines was higher in the pediatric group, and only 7% used omalizumab versus 20.8% in the adults. The comparisons were also performed between <12-year and ≥12-year patients and yielded similar results.

Conclusion: Pediatric CSU shows distinct characteristics such as lower incidence of angioedema and antithyroid antibodies, and it responds better to antihistamines. These suggest that CSU becomes more severe and refractory in adolescents and adults. Adolescent CSU shows features similar to adult CSU rather than pediatric CSU.

KEYWORDS
adolescent, adult, angioedema, antihistamine, children, chronic spontaneous urticaria, omalizumab, pediatric, treatment

1 | INTRODUCTION

Chronic urticaria (CU) is classified as chronic spontaneous urticaria (CSU) or chronic inducible urticaria (CIndU) depending on the existence of specific eliciting factors (cold, heat, solar radiation, pressure, or exercise) and is defined by the occurrence of wheals, angioedema, or both for more than 6 weeks.[1] It is a common disease and affects a significant proportion of the population worldwide; lifetime and point prevalence rates are reported as 1.4% and 0.7%, respectively.[2,3] Although CU has been considered less prevalent in children than in adults, a Korean survey on children who were aged 4–13 found a prevalence of 0.7%.[4] Likewise, in a multicenter European study, the annual prevalence of CU and CSU in pediatric patients was 1.38% and 0.75%, respectively.[5]

The guidelines for the treatment of urticaria recommend limiting laboratory work-up and adopt a history and examination-based diagnostic workup in CU patients. The goal of pharmacotherapy is to completely eliminate symptoms of wheals and/or angioedema. Since the main mediator released from mast cells upon degranulation is histamine, antihistamines are the mainstay of treatment.[6] According to the EAACI/GA2LEN/EDF/WAO urticarial guideline, a stepwise approach is recommended starting with monotherapy of a second-generation H1 antihistamine (sg-AH) and then increasing the dose up to fourfolds and if symptoms persist, adding omalizumab.[1] Cyclosporine is the fourth step of treatment in patients who do not respond to omalizumab. Even though there are many national and international guidelines on the management of CU, pediatric population is addressed under "treatment of special populations" rather than having a separate treatment algorithm. Nonetheless, a group of pediatricians from Italy published a guidance for the management of children with CU.[7]

A recent study including 178 adult CSU patients concluded that H1-antihistamines are beneficial in less than 50% of cases;[8] however, the efficacy and need for second- and third-line treatments in children are yet to be determined. There is a definite lack of clear guidance on the management of CU in children, which stems from the sparsity of evidence-based knowledge retrieved from clinical trials or real-life studies on epidemiology, comorbidities, and treatment outcomes in the pediatric population. The need for real-life evidence addressing the discrepancies between pediatric and adult CU populations prompted us to perform this study, which aimed to determine differences between pediatric and adult CSU focusing on clinical characteristics, laboratory parameters, comorbidities, response to treatment, and indicators of response.

Key messages

Pediatric chronic spontaneous urticaria (CSU) and adult CSU show distinct features. CSU becomes more severe and refractory in adolescents and adults. Adolescent CSU shows similar features as adult CSU rather than pediatric CSU.

2 | METHODS

2.1 | Study population and design

A retrospective analysis of CSU patients who referred to Pediatric Allergy Clinic and Dermatology Clinic of Istanbul Okmeydanı Training and Research Hospital between 2013 and 2019 was performed. These clinics are among the highly referred centers for the treatment of CSU with a high number of outpatients. The patients are referred by dermatologists to the Dermatology Clinic or by pediatrists to the Pediatric Allergy Clinic. There are no referral criteria with respect to treatment refractoriness or disease duration; every CSU patient is a potential candidate for referral.

This study was approved by the Ethics Committee of Istanbul Okmeydanı Training and Research Hospital (163–2021). Data on demographic features (age, gender, atopy, family history of atopy, disease duration, and angioedema) and laboratory values (serum eosinophil count [eosinopenia: $<0.05\times10^9$/L], serum total IgE levels [cutoff level for low IgE was 40 kU/L],[9] C-reactive protein (CRP) levels [elevated CRP (>5 mg/dL)], antithyroid peroxidase antibody [IgG-anti-TPO] levels, IgG-anti-TPO positivity [≥35 IU/mL], skin prick test, and autologous serum skin test (ASST) results) were retrieved from patient files.

Patients were treated according to the recommendations of the International Urticaria Guideline[1] and consisted of standard doses of sg-AH as first-line treatment, up-dosed sg-AHs as second-line treatment (exceptions were combinations of sg-AHs and leukotriene antagonists [LTRA] in some patients) and omalizumab as the third-line

treatment. Response to treatment in adult patients was determined by urticaria control test (UCT), which shows disease control when the score is ≥12,[10] while physician's assessment was used for the pediatric patients (treatment effective, treatment not effective). Patients with no response to standard sg-AH dose or higher dose sg-AH or sg-AH or LTRA combinations were considered as antihistamine refractory (AH-refractory). Also, patients who were already under treatment with omalizumab or cyclosporine were considered as AH-refractory. Clinical or laboratory indicators of treatment response (age, gender, atopy, family history of atopy, disease duration, angioedema, eosinopenia, low IgE, CRP, IgG-anti-TPO levels, IgG-anti-TPO positivity, skin prick test, and ASST) were determined in pediatric (<18 years), adolescent (12–17 years), and adult (≥18 years) patients. Pediatric urticaria was grouped as preschool period (0–7 years), school period (7–11 years), and adolescence period (12–17 years). Atopy was defined as having at least one atopic disease (atopic dermatitis, allergic rhinitis, or allergic asthma) and/or having prick test positivity.

2.2 | Statistical analyses

The statistical analyses were performed by the SPSS (Version 22 for Windows, SPSS Inc) package program. The suitability of the continuous variables to normal distribution was evaluated by the "Kolmogorov–Smirnov Test" and was expressed with a median (minimum and maximum value). Frequency data were expressed in percent (%) of the number. The Pearson's chi-squared test or Fisher's exact test were used when comparing the rates of gender, atopy, IgG-anti-TPO positivity, low IgE, elevated CRP, eosinopenia, ASST positivity, skin prick test positivity, and autoimmune thyroiditis between groups. Kruskal–Wallis test (with Bonferronni corrected) and Mann–Whitney *U* tests were performed for comparing age, disease duration, and levels of laboratory parameters. Binary logistic regression analysis was performed to determine the factors that affect treatment responses for ≥12 years. Statistical significance level was accepted as $p < .05$.

3 | RESULTS

3.1 | Demographic differences between pediatric and adult CSU patients

The analysis included a total of 751 CSU patients: 162 pediatric and 589 adults. Mean age was 10.7 ± 4.2 in pediatric and 40.3 ± 13.8 in adult patients. Male/female ratio was 83/79 (48.8% females) versus 179/410 (69.6% females; $p < .001$) in pediatric versus adult patients, respectively. Disease duration was significantly longer, and angioedema was more common in adults than in children (12 vs. 5 months and 59.8% vs. 19.1%, respectively), and there was a clear tendency towards increase by age in these figures ($p < .001$; Table 1). This trend prompted us to perform an analysis between patients <12 years and ≥12 years. Comparison of <12 years ($n = 91$) versus ≥12 years ($n = 660$) showed similar results with <18 years versus ≥18 years (Table 2).

3.2 | Laboratory differences and comorbid conditions in pediatric and adult CSU Patients

As a comorbid disease, autoimmune thyroiditis was significantly more frequent in adults than in children (9.4% vs. 3.4%, $p = .02$, respectively). IgG-anti-TPO positivity (24.7% vs. 9%, $p < .001$), elevated CRP (46.5% vs. 11.1%, $p < .001$), eosinopenia (38.5% vs. 18.1%, $p < .001$), and skin prick test positivity (39.3% vs. 28.8%, $p = .03$) were significantly more frequent in adult patients, while low total IgE levels were more frequent in pediatric patients (29.5% vs. 17.5%, $p = .004$); IgG-anti-TPO positivity and eosinopenia rates were increasing by age (Table 3). Comparison of <12 years versus ≥12 years showed similar results with <18 years versus ≥18 years (Table 4, Figure 1). Furthermore, the comparison of pediatric patients aged <12 years versus 12–17 years (adolescent) also showed that IgG-anti-TPO positivity (2.6% vs. 18.5%; $p = .002$) and skin prick test positivity (23.8% vs. 39.6%; $p = .049$) were more frequent in adolescents, respectively (Table 5).

TABLE 1 Demographic characteristics of CSU patients compared between age groups.

	0–7 years ($n = 45$)	8–11 years ($n = 61$)	12–17 years ($n = 56$)	Adult (≥18 years) ($n = 589$)	*p*
Median age (min–max)	6 (2–7.5)	11 (8–12.5)	15 (13–17.5)	39 (18–85)	
Female/male ratio (*F* %)	18/27 (40%)	33/28 (54%)	28/28 (50%)	410/179 (69.6%)	<.001*
Median duration (months) of disease (min–max)	3 (2–36)	5 (2–60)	6.5 (2–120)	12 (1–600)	<.001**
Angioedema[a] *n* (%)	5 (8.9%)	8 (18.2%)	19 (26%)	330 (59.8%)	<.001*
Atopy[a] *n* (%)	6 (13.3%)	7 (20%)	5 (15.2%)	131 (25.3%)	.17

[a]Missing values are excluded from these analyses.

*The statistically significant difference is in only adult group.; **All groups are different from each other.

3.3 | Treatments for CSU in pediatric and adult patients

Distribution of given treatments was as follows in pediatric versus adult CSU patients, respectively; standard doses of H1-antihistamines (AH): 57.3% versus 40.1% ($p < .001$), high doses of H1-AH or combinations of AH and LTRA: 33.9% versus 25% ($p < .001$), and omalizumab: 7% versus 20.5% ($p < .001$). Distribution of treatments between ages 0–7 years and 8–11 years and between 12–17 years and ≥18 years were not significantly different from each other (Table 6), whereas there were significant differences between patients <12 years and ≥12 years; standard doses of H1-AH 60.2% versus 41.4%, high doses of H1-AH or combinations of AH and LTRA 37.3% versus 25.6%, omalizumab 2.4% versus 32.1% ($p < .001$), respectively.

TABLE 2 Demographic differences between CSU patients <12 years and ≥ 12 years.

	<12 years ($n = 91$)	≥12 years ($n = 660$)	*p*
Median age (min–max)	7.5 (2–11.5)	36 (12–85)	
Female/male ratio (*F* %)	43/48 (47.3)	446/214 (67.6)	<.001
Median duration (months) of disease (min–max)	3 (2–60)	12 (1–600)	<.001
Angioedema[a] *n* (%)	13 (14.4%)	348 (55.9%)	<.001
Atopy[a] *n* (%)	13 (15.9%)	136 (24.8%)	.076

[a]Missing values are excluded from these analyses.

3.4 | Factors that determine refractoriness to first- and second-step treatments in pediatric versus adult CSU patients: who are the antihistamine refractory patients?

Only 14 (8.6%) patients in the pediatric patient group did not respond to first- and second-step treatments (including standard dose of sg-AHs or higher doses of sg-AHs or combinations of sg-AH or LTRA –"antihistamine refractory"-), while 206 (35.0%) patients in the adult group were unresponsive to these treatments. Indicators of AH refractoriness were eosinopenia (13.6% in responders vs. 62.5% in nonresponders, $p < .001$), angioedema (19.4% in responders vs. 46.7% in nonresponders, $p = .01$) and IgG-anti-TPO positivity (7.3% in responders vs. 27.3% in nonresponders, $p = .002$) in the pediatric population, whereas angioedema (56.7% in responders vs. 65.6% in nonresponders, $p = .004$) and eosinopenia (32% in responders vs. 51.1% in nonresponders, $p = .003$) were markers for AH refractoriness in adults. But when we stratified the patient population into <12 years and ≥12 years, only two patients who were unresponsive to AHs remained in the <12 years of population. For this reason, indicators of AH refractoriness were determined only for ≥12 years as elevated CRP, angioedema, duration of disease, prick test positivity, and eosinopenia (Table 7). In the logistic regression analysis, only prick test positivity affected the AH response negatively in patients ≥12 years (beta = 0.23; B = −1.4 $p = .02$; %95 CI = 0.07–0.82).

4 | DISCUSSION

In the current report, we found distinct characteristics in pediatric versus adult CSU patients in terms of clinical presentation, disease

TABLE 3 Laboratory characteristics and comorbid conditions in pediatric versus adult patients.[a]

	0–7 years	8–11 years	12–17 years	Adult (≥18 years)	*p*
IgG-anti-TPO levels IU/mL Median (min–max)	1.2 (0.3–29)	1.1 (0.1–989)	1.8 (0.2–1103)	9.8 (0–1300)	<.001
IgG-anti-TPO positivity *n* (%)	0	2 (5.1%)	10 (17.9%)	54 (24.7%)	<.001
Total IgE levels (kU/L) Median (min–max)	84.8 (5.2–2111)	124 (8–1098)	121 (3–1300)	143 (1–7158)	.394
Low IgE *n* (%)	16 (35.6%)	13 (31.7%)	14 (23.3%)	61 (17.5%)	.01
CRP levels (mg/dL) Median (min–max)	0.9 (0.2–10)	0.9 (0.2–24.3)	0.7 (0.07–11)	4.3 (0.01–18.780)	<.001
Elevated CRP *n* (%)	5 (11.1)	6 (15.5)	5 (9.0)	120 (46.5)	<.001
Eosinophil levels Median (min–max)	200 (20–1450)	170 (1–790)	110 (14–740)	198 (1–1090)	.054
Eosinopenia *n* (%)	4 (8.9)	7 (17.5)	14 (26.4)	47 (38.5)	<.001
ASST positivity *n* (%)	3 (50.0)	2 (57.1)	7 (35.7)	149 (50.5)	.72
Skin prick test positivity[b] *n* (%)	11 (24.4)	9 (23.2)	20 (31.7)	96 (39.7)	.08
Autoimmune thyroiditis *n* (%)	0 (0.0)	1 (2.3)	4 (7.0)	32 (9.4)	.07

[a]Missing values are excluded from these analyses.

[b]Aeroallergen or food.

TABLE 4 Laboratory characteristics and comorbid conditions in CSU patients <12 years vs ≥12 years.[a]

	<12 years	≥12 years	*p*
IgG-anti-TPO levels IU/mL Median (min–max)	1.1 (0.2–986)	8.5 (0.0–1300)	<.001
IgG-anti-TPO positivity *n* (%)	2 (2.6)	64 (23.3)	<.001
Total IgE levels[b] (kU/L) Median (min–max)	90.7 (5–2111)	141.5 (1–7158)	.005
Low IgE *n* (%)	29 (32.0)	75 (19.0)	.012
CRP levels (mg/dL) Median (min–max)	0.9 (0.2–24.3)	3.4 (0.01–18.780)	<.001
Elevated CRP *n* (%)	11 (12.8)	125 (39.9)	<.001
Eosinophil levels Median (min–max)	165 (0–1450)	190 (1–1090)	.059
Eosinopenia *n* (%)	11 (12.8)	61 (35.1)	<.001
ASST positivity *n* (%)	6 (50.0)	155 (50.0)	1.000
Skin prick test positivity[b] *n* (%)	20 (23.5)	116 (38.9)	.009
Autoimmune thyroiditis *n* (%)	1 (1.1)	36 (9.0)	.012

[a]Missing values are excluded from these analyses.

[b]Patients who received omalizumab treatment were excluded from analysis since some of the total IgE levels were retrieved after omalizumab treatment.

FIGURE 1 Differences between pediatric and adolescent/adult CSU patients.

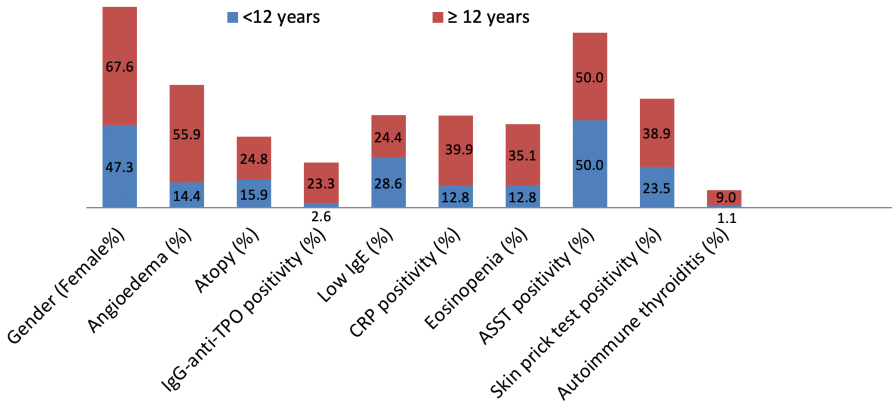

TABLE 5 Laboratory characteristics and comorbid conditions in pediatric CSU patients <12 years versus 12–17 years.[a]

	<12 years	12–17 years	*p*
IgG-anti-TPO levels IU/mL Median (min–max)	1.1 (0.2–986)	1.45 (0.1–1103)	.15
IgG-anti-TPO positivity *n* (%)	2 (2.6)	10 (18.5)	.002
Total IgE levels[b] (kU/L) Median (min–max)	90.7 (5–2111)	124.0 (3–1300)	.13
Low IgE *n* (%)	29 (32.0)	13 (22.8)	.13
CRP levels (mg/dL) Median (min–max)	0.9 (0.2–24.3)	0.7 (0.07–18.5)	.22
Elevated CRP *n* (%)	11 (12.8)	5 (9.6)	.58
Eosinophil levels Median (min–max)	165 (0–1450)	150 (14–740)	.25
Eosinopenia *n* (%)	11 (12.8)	12 (25.5)	.063
ASST positivity *n* (%)	6 (41.7)	7 (58.3)	.29
Skin prick test positivity[b] *n* (%)	20 (23.8)	21 (39.6)	.049
Autoimmune thyroiditis *n* (%)	1 (1.1)	3 (5.4)	.13

[a]Missing values are excluded from these analyses.

[b]Patients who received omalizumab treatment were excluded from analysis since some of the total IgE levels were retrieved after omalizumab treatment.

TABLE 6 Treatments for CSU in patient groups.

Treatment	0–7 years	8–11 years	12–17 years	Adult (≥18 years)	*p*
Standard dose sg-AH	30 (67.4)	20 (52.6)	39 (53.4)	234 (40.1)	<.001
Up-dosed sg-AG, sg-AH combinations or LTRA	15 (33.3)	16 (42.1)	22 (30.1)	147 (25.0)	<.001
Omalizumab	0 (0.0)	2 (5.3)	10 (13.7)	202 (34.4)	<.001
Others[a]	0 (0.0)	0 (0.0)	2 (2.7)	4 (0.7)	<.001

[a]Cyclosporine, dapsone, IVIG, phototherapy.

TABLE 7 Factors associated with refractoriness to first- and second-step treatments (standard dose sg-AH/high dose AH/sg-AH + LTRA) in ≥12-year old CSU patients.[a]

Indicators	Patients with response (*n* = 441)	Patients without response (*n* = 219)	*p*
IgG-anti-TPO positivity *n* (%)	53 (18.8%)	30 (25.9%)	.11
Elevated CRP *n* (%)	77 (31.3%)	46 (44.7%)	.017
Angioedema *n* (%)	219 (51.9%)	128 (64.3%)	.004
Disease duration			
Mean ± SD	35.3 ± 61.6	5.5 ± 74.3	.028
Median (min–max)	12 (1–600)	12 (1–480)	
Skin prick test positivity *n* (%)	75 (34.9%)	41 (50.0%)	.017
ASST positivity *n* (%)	110 (51.6%)	45 (46.4%)	.39
Eosinopenia *n* (%)	31 (26.1)	25 (49.0)	.004
Atopy *n* (%)	102 (25.3)	43 (23.4)	.61
Autoimmune thyroiditis *n* (%)	30 (10.8)	6 (4.9)	.059

Note: First and second step refractoriness= antihistamine refractoriness.

[a]Missing values are excluded from these analyses.

duration, associated conditions, laboratory findings, and treatment responses. Additionally, we recognized that some of these distinctive features appeared after the age of 12, and adolescent CSU shared similar features with adult CSU.

There was a clear female dominance in adult CSU patients, while this predominance was not valid for pediatric patients (females 69.6% vs. 48.8%). This finding is consistent with the findings of a recent meta-analysis, which reported a higher prevalence in females among adult CSU, while this difference was not significant in children younger than 15 years.[2] However, the female dominancy became apparent after the age of 18 in our study. This trend of female preponderance increasing by age suggests that more female patients are developing CSU while transition to adulthood. Although it is not known why CSU is more common in females, we might speculate on the effects of female hormones on the autoimmune and inflammatory processes. First, autoimmune diseases are more common in women, second mast cells express hormone receptors, and sex hormones can influence mast cell activation.[11]

Angioedema is an important indicator of severe and refractory CSU[12,13] and is reported in approximately 40% to 60% of adult CSU patients.[14,15] In contrast, in children with CSU, rates of angioedema were found considerably lower ranging from 5% to 14%, and it was reported that the frequency of angioedema was higher in the 12–17 age group than in the younger age groups (0–6 years 5% and 12–17 years 14%).[5]

In our study, the frequency of angioedema was lower in the pediatric group than adults (19.1% vs. 59.8%), and angioedema frequency showed a trend of increase by age (0–7 years 8.9%, 8–11 years 19.7%, and 12–17 years 26.8%). Additionally, having angioedema was associated with antihistamine refractoriness both in the pediatric and in the adolescent/adult patients as previously reported.[16] This supports the notion that CSU gets more severe and refractory by increasing age given that we also found antihistamine refractoriness higher in the adolescent/adult group.

Traditionally, CSU has been considered as an idiopathic disease and has been associated with persistent infections and consumption of food and/or food additives and drugs, but as with the progress in the understanding of disease mechanisms, autoimmunity has become the leading cause in approximately half of the cases.[6] Recently, two groups of autoimmune CSU patients have been identified and characterized: First one is autoimmune hypersensitivity, that is, type I autoimmunity (also called autoallergy) and second one is the type IIb autoimmunity. According to this classification, higher rates of concomitant allergic diseases, normal or high total IgE levels, and high response rates to omalizumab favor type I autoimmune CSU, whereas the presence of auto-IgG (against IgE, FcεRI), higher disease activity, longer disease duration, higher rates of concomitant autoimmune diseases such as Hashimoto, lower total IgE levels, higher rates of eosinopenia and basopenia, higher levels of CRP, higher rates of ANA positivity, low response rate or slower response to omalizumab, and good response to immunosuppressive treatment favors type IIb autoimmune CSU.[17] In our study, autoimmune thyroiditis, IgG-anti-TPO positivity, eosinopenia, high CRP levels, and skin prick test positivity were significantly higher in adult patients

than pediatric patients, while low IgE levels were more frequent in the pediatric population. Furthermore, comparison of pediatric patients showed that adolescent patients (12–17 years) had more frequent IgG-anti-TPO positivity than <12 years. The rates of ASST positivity were similar between the groups; however, ASST results were lacking in many of the pediatric patients. According to the abovementioned endotype classification, our findings may suggest that adult patients tend to show more of a type 2b autoimmune CSU profile, but it is not possible to suggest the autoimmune profile of the pediatric patients. The reason for that is the higher frequency of low total IgE levels, lower prick test positivity, and similar rates of atopy in the pediatric group. However, atopy and IgE sensitization are prone to change with age, and total IgE levels show a tendency to increase with aging with a trend more evident in females.[18] For sure, this has to be confirmed in multicenter studies, which evaluate the presence of autoantibodies such as IgG-against IgE and FcεRI or IgE against anti-TPO or anti-ds-DNA in pediatric and adult CSU patients.

More than half of adult patients are reported to be refractory to even fourfold doses of sg-AH, while pediatric urticaria seems to show a higher response to antihistamine treatment, even controlled by lower doses and do not require up dosing as much as adults.[19] In a study from Singapore, only 11.4% of children required three or fourfolds of cetirizine.[20]

In our study, we observed a trend of decline in response to standard doses of antihistamines by age. Patients aged 0–7 years responded by 68%, while 7–11 years, 12–17 years, and >17 years responded by 60%, 48%, and 40%, respectively. In addition, there was a significant difference in terms of AH-refractoriness between pediatric and adult patients. Only 7% of pediatric patients required omalizumab, while 20% of adult patients required omalizumab and 14% needed other immunomodulatory therapies. This low omalizumab requirement in the pediatric group is consistent with the previous reports presenting that only 9.7% of pediatric CSU patients require omalizumab treatment.[21] We also observed that requirement of third-line treatment showed an increasing trend by age; that is, 17.9% of adolescents (aged between 12–17 years) required omalizumab treatment. This might be due to the fact that omalizumab has been approved for over 12 years of age in our country and may create a bias. A study from Italy reported omalizumab requirement in 18.2% of the pediatric CSU patients; however, they did not mention the average age of the patient population.[22]

In recent years, many biomarkers related to disease severity and resistance of AH treatment have come to the fore. Since we only had 15 pediatric patients who were refractory to antihistamines, it would not be appropriate to propose the indicators (eosinopenia, angioedema, and IgG-anti-TPO positivity) we found in our study as markers of AH-refractoriness. However, to our knowledge, indicators of antihistamine refractoriness in pediatric CSU have not been reported before.

For the adult group, we found that elevated CRP, presence of angioedema, longer disease duration, skin prick test positivity, and eosinopenia were associated with a poor response to antihistamines and requirement of omalizumab treatment. From these biomarkers, elevated CRP, presence of angioedema, longer disease duration, and eosinopenia have been reported in previous studies as indicators of both severe disease and antihistamine refractory disease.[23–29] The significance of skin prick test positivity remains to be clarified though it has been reported to be associated with a higher impairment in quality of life in CSU patients.[30]

Our study has several limitations: first of all, it has a retrospective nature and therefore some data are missing. Second, the presence of accompanying inducible urticarias was lacking in the pediatric patient files; therefore, we could not include this data as a parameter for comparison between groups. Third, since some of the total IgE levels in patient files might have been retrieved after the start of omalizumab treatment, we did not include total IgE levels for the comparison of treatment responses. Fourth, ASST could not be performed in many of pediatric patients and finally since UCT is not validated for use in children, assessment of treatment effectiveness might have been subjective in some pediatric patients.

As a conclusion, in our study, we showed that pediatric and adult CSU show distinctive features, and adolescent CSU shows similar pattern as adult CSU. These findings suggest that pediatric and adult CSU might reflect different endotypes of CSU, that is, adult form features Type IIb autoimmune endotype characteristics such as autoimmune thyroiditis, IgG-anti-TPO positivity, eosinopenia, and high CRP levels and shows high rates of antihistamine refractoriness which might be explained by the evolution of autoimmunity by age. This endotype approach might explain the reason for the different phenotypes in pediatric versus adult CSU; however, current literature lacks even satisfactory explanation for the pathomechanism of adult CSU. Chronic spontaneous urticaria patients are 6.5 times more likely to have IgG autoantibodies against FcεR1α, 2.4 times more likely to have IgG anti-IgE antibodies, and five times more likely to have anti-TPO antibodies than controls. While these findings indicate autoimmune basis for the disease, the clinical significance of the presence of such antibodies in CSU and its association with disease activity remains to be determined.[31] The lack of information is far more prominent for children; only two studies showed basophil activation test positivity in children with CSU, and none of them mentioned a link with the age of the patients.[32,33] The role of hormones in the evolution of autoimmunity and generation of IgG type antibodies by age remains to be determined. There is a certain need for molecular studies to identify the occurrence and significance of different types of autoantibodies in different age groups of CSU patients.

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CONFLICT OF INTEREST STATEMENT

EK served for advisory board and gave speak for Novartis, Sanofi, Menarini, Abdi İbrahim, and La Roche Posey. Other authors have no conflicts of interest.

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