Chronic Urticaria in Children – New Insights from a Large Cohort

idit Lachover Roth[1], Ahmad Rabie[2], Anat Cohen - Engler[1], Yossi Rosman[1], Keren Meir-Shafrir[1], and Ronit Confino-Cohen[1]

[1]Meir Medical Center
[2]Tel Aviv University Sackler Faculty of Medicine

October 20, 2020

Abstract

Background: Chronic spontaneous urticaria is well-described in adults, but less so in children. The aim of this study is to describe the demographics, clinical characteristics, comorbidities, and outcomes of children with chronic, spontaneous urticaria. Methods: This retrospective study followed children up to 18 years-old, diagnosed with chronic spontaneous urticaria, between the years 2002-2018 and treated in a tertiary referral allergy and clinical immunology center. Data including demographics, clinical characteristics, comorbidities, treatments and outcomes was extracted from electronic medical records. Results: Records of 380 children coded to have chronic urticaria were reviewed, of which 250 (65.8%) fulfilled the diagnostic criteria for chronic spontaneous urticaria. There were 136 females (54.4%). Mean age at diagnosis was 11.4 years, 122 (48%) were adolescents. The average duration of chronic spontaneous urticaria was 12.25±15.2 months. The urticaria in 208 children)83.2%) resolved within 24 months. Eighty-seven patients (34.8%) had at least one atopic disease. Atopic comorbidities included atopic dermatitis in 17.2%, allergic rhinitis in 16%, asthma in 13.2% and food allergy in 3.2%. Eighteen patients (7.2%) had a concomitant autoimmune disease. Nine (3.6%) had thyroid disease. Conclusions and clinical relevance: Chronic spontaneous urticaria in children is a self-limited disease with favorable prognosis. Atopic diseases are more prevalent in children with chronic spontaneous urticaria than in the general pediatric population; increasing the possibility of a special subgroup of TH2-related chronic urticaria in children.

Key Message:

The literature regarding the characteristics and underlining mechanisms of chronic spontaneous urticaria in children is limited.

This retrospective cohort study included 250 children with chronic spontaneous urticaria. Chronic spontaneous urticaria in children is a self-limited disease. Urticaria lasted up to 2 years in most of the children. One third had at least one atopic disease. Atopic dermatitis and allergic rhinitis were the most prevalent, and significantly more common than in the general pediatric population.

Introduction

Urticaria is a common phenomenon that affects 15-25% of the population at least once in a lifetime. While most episodes are acute[1,2], a minority are prolonged, hence termed chronic urticaria (CU). CU is defined as recurrent urticarial lesions, appearing most of the days of the week, for at least 6 weeks.[2-4]The prevalence of CU in adults is estimated to be 1.8%, affecting women more than men and with up to 50% remission rate within one to three years.[5] In adults, autoimmune or auto-allergy mechanisms are suggested as possible etiologies for CU. In most patients, no underline cause is found or can be proven, and the urticaria is termed chronic spontaneous urticaria (CSU).[6]

The literature regarding the characteristics and underlining mechanisms of CSU in children is limited.[2,5,7-14] It is estimated that its prevalence in children is 0.1-0.3%[15-18] with an equal distribution between genders, ex-

cept among adolescents.[5,13] However, a recent review demonstrated 1.1–1.5% prevalence of CU in children.[19] The remission rate of CSU in children after one year is reported to be low (16.5% - 37%).[2,5,18]

A few small studies demonstrated an association between pediatric CSU and atopic diseases, including asthma, allergic rhinitis (AR), atopic dermatitis (AD) and food allergy.[5,8-10] An overall, coexisting prevalence of 30% to 50% has been described.[5,10,13] Chansakulporn et al. followed a small group of 92 patients and reported that one-third of the children with CU had atopic diseases, with an unusually high prevalence of food allergy (15.2%).[5] Netchiporouk et al. reported that 28% of 139 children with CSU had atopy, but they did not distinguish between the different types of atopic diseases and age groups.[9] In addition to atopic diseases, autoimmune diseases, including thyroid diseases, celiac and systemic lupus erythematosus (SLE) were also found to be associated with CU in children.[20,21,22]

The aim of the current study was to describe the demographics, clinical characteristics, comorbidities, and outcomes of a large pediatric cohort with CSU.

Materials and Methods

This retrospective study included children up to age 18 years, with the diagnosis of CSU, treated at the Allergy Unit of Meir Medical Center, Israel, 2002–2018. CSU was defined in accordance with Sahiner et al.[2-4] Briefly, urticarial lesions appearing most days for at least 6 weeks, with or without accompanying angioedema.

Data for the entire cohort were retrieved from Clalit Health Services electronic record system. All medical records were reviewed by a specialist in allergy and clinical immunology from the date of CSU diagnosis to December 2018.

Data collected included: (a) Demographic parameters, (b) CSU duration, treatment, and relapses, (c) Laboratory tests, (d) Co-morbidities including asthma, allergic rhinitis, food allergy, atopic dermatitis, autoimmune thyroid diseases, celiac, SLE, diabetes mellitus, juvenile rheumatoid arthritis, inflammatory bowel disease, irritable bowel syndrome (IBS) and psychiatric disorders and (e) Chronic medications for other comorbidities.

Treatment modalities with antihistamines were defined as: Regular doses of antihistamines included 5 mg desloratadine daily or according to weight, 10 mg/day loratadine or according to weight, or 180 mg fexofenadine. High-dose antihistamines included up to 20 mg daily desloratadine or comparable dose of other antihistamine drugs.

Relapse was defined as a second episode of CSU with a gap of at least 6 months, without urticaria and without treatment for urticaria.

To analyze potential various age-related differences, patients were grouped according to age at CSU diagnosis: 0-3, 4-8, 9-12, and 13-18 years.

As CSU can be confused with AD, we analyzed the results with and without the patients diagnosed with both CSU and AD. Only data with significant differences are presented.

The study was approval by the Ethics Committee of Meir Medical Center.

Statistical analyses

Data are presented as numbers and percentage for nominal parameters and as mean and standard deviation for continuous variables. Two groups were compared using Student's t test for continuous variables and Chi-square or Fisher's Exact test for categorical variables, each when appropriate. Comparison with data from the literature was compared with Z scores. All tests of hypotheses were considered significant when two-sided probability values were $P<0.05$. All statistical analyses were performed using IBM, SPSS-25, Armonk, NY, USA.

Results

Patient demographics

During 2002-2018, 380 children with a diagnosis of CSU recorded in their medical records were evaluated. After reviewing the medical files, 250 patients (65.8%) had CSU according to the defined criteria and were included in the study. The remaining 130 were excluded either because they did not fulfill the criteria for CSU (113 children) or due to lack of follow-up data (17 children). Of the 250 patients included, 136 were females (54.4%). The mean age at diagnosis was 11.4 ± 5.1 years, median 12 years (range 0.9-18.0). Among the study group, 122 (48%) were adolescents (13-18 years old). There was no significant difference in the prevalence of CSU by sex; except for the adolescents, where females comprised 60% of the group (p=0.07) (Table 1).

Duration of CSU

The average duration of CSU was 12.3±15.2 months, median 6 months (range 1.5 – 84 months). A total of 135 patients (54%) had CSU for 12–24 months and overall, the urticaria resolved within 24 months in 208 patients (83.2%). Concomitant angioedema was present in 30% (n=75). No significant differences were found when comparing the duration of disease or the presence of angioedema between the various age groups or sexes (Table 1).

Relapse of CSU

The average follow-up time was 8.1 years (range 0.3-15.1). During this period, 24 patients (9.6%) had a relapse of CSU. Most (17 patients, 70.8%) were adolescents ($p< 0.05$, RR= 2.55). No relapses were documented in the youngest age group (0-3 years) (Table 1).

Comorbidities

A total of 87 patients (34.8%) had at least one atopic disease (Figure 1A): in 64.4% (56/87) the diagnosis of atopic disease was established before or concurrently with CSU. The atopic comorbidities found in the study cohort were: AD (n=43, 17.2%), AR (n=40, 16.1%), asthma (n=33, 13.3%) and food allergy (n=8, 3.2%). Thirty patients (12%) had more than one atopic co-morbidity. After excluding the patients diagnosed with AD, the prevalence of atopic comorbidities did not differ significantly: AR (n=27, 13% vs. 16.1% in the total cohort, p=0.36), asthma (n=21, 10.1% vs. 13.3% in the total cohort, p=0.3) and food allergy (n=7, 3.4% vs. 3.2% in the total cohort, p=0.9). Consequently, the rest of the analyses are presented for the entire group.

No correlation was found between the prevalence of AR, AD, asthma, or food allergy and the duration of CSU. Furthermore, there was no difference in the probability of relapse and the presence of atopic disease as a co-morbidity (9.8% vs. 9.2%, p=0.87).

The prevalence of the different atopic diseases in CSU patients and the general pediatric population in Israel and in the world was compared (Figure 1B): The prevalence of AD in two age groups (4-8 years and 13-18 years) of the study population was significantly different compared to the general population in Israel[7,23,24] and in the world[25] ($p<0.01$). Differences in the prevalence of allergic rhinitis were statistically significant only in adolescents when compared to the general population of adolescents in Israel[7,23,26] and in the world[27]($p<0.01$). The differences in the prevalence of food allergy between participants in the current study and the general world population[28,29] were statistically significant in children age 4-8 years ($p<0.05$) but did not reach significance when compared to adolescents in the current study and adolescents in Israel[7,30] (p=0.83). Differences in the prevalence of asthma between the current study and the general population in Israel[7,24,26] and in the world [31]did not reach significance in any age group (p=0.46–0.99).

Overall, 18 patients (7.2%) had a concomitant autoimmune disease compared to 1.9% in the general adolescent population in Israel ($p<0.01$). Nine (3.6%) were diagnosed with thyroid disease, 7 with hypothyroidism and 2 with hyperthyroidism. Psoriasis was found in 6 patients (2.4%), type I diabetes mellitus in 2 patients (0.8%) and 1 patient was diagnosed with juvenile rheumatoid arthritis (0.4%). Celiac disease, irritable bowel disease and SLE were not diagnosed in our cohort. IBS was diagnosed in 5 patients (2%).

Seven patients (2.8%) had psychiatric disorders, including depression, anxiety, bipolar disorder, and schizophrenia. All were diagnosed after the first CSU episode.

Treatment of CSU

Treatment protocols were available for 213 patients (85.2%) (Table 2). Monotherapy was given to 161 (64.4%) and 52 (20.8%) received a combination of at least two medications. Of the 161 treated with monotherapy, 153 (95%) received antihistamine in the regular recommended dose and 7 (4.35%) received high dose antihistamines. One patient was treated with corticosteroids only. Of the 52 children treated with combination therapies, 32 (61.5%) received a regular dose of antihistamine and oral corticosteroids. Six patients needed a combination of three medications, 1 (16.66%) was treated with a combination that included omalizumab. Details regarding the treatment regimens are listed in Table 2.

Relapses were treated with regular dose antihistamines in 41.6%. However, relapsing patients used high dose antihistamine, or combination therapy more often (8.3% and 29.1%, respectively vs. 2.8% and 20.8% for the first episode, p=NS). Three of six patients who were treated with a combination of three medications in the first episode, suffered from relapse during the following years; significantly more than those treated with monotherapy or a combination of two medications (50% vs. 10.14%, $p< 0.01$, RR = 4.93).

Medications used for co-morbidities

Thirty-six patients (14.4%) used methylphenidate (or other comparable drugs) as a chronic medication for attention deficit disorder with or without hyperactivity. Although not statistical significantly, the percentage of patients who used methylphenidate increased parallel to the duration of CSU (11% of patients with CSU <12 months, 15.6% of patients with CSU for 12-24 months and 20% of patients with CSU > 24 months).

Laboratory tests

Complete blood count was available for 202 patients (80.8%) at the initial diagnosis of CSU. Eosinophilia (defined as eosinophil count > 500 cells/μL) was found in 29 patients (14.4%, range 500-1800 cells/μL) and was more common in children < 13 years (27.6% vs. 6.2% $p< 0.01$). Eosinophilia did not correlate with CSU duration or the presence of atopic diseases.

Total IgE was available for 60 patients (24%). High total IgE (defined as IgE > 100 IU), was found in 32 (53.3%). No correlation was found between high total IgE and atopic diseases or duration of urticaria.

C-reactive protein was measured in 109 patients at CSU presentation and was within the normal range in all cases. Antinuclear antibody was measured in 51 patients and found abnormal in 6 (11.8%). Of them, in the following years, one patient was diagnosed with hyperthyroidism, 1 with hypothyroidism and IBS, and 1 with Alport's syndrome.

Discussion

Chronic urticaria is a common medical condition, well-described in the adult population. Data regarding CSU in children is scarce. In the current report, we aimed to better characterize this disorder in a large cohort of children with a long follow-up period. We found that pediatric CSU is frequently accompanied by atopic diseases and has a favorable outcome.

The study cohort had an encouraging clinical course. CSU was not accompanied by angioedema in most children and there was a good clinical response to regular doses of antihistamines, without need for additional medications. In most cases, hives persisted for no longer than two years and relapses were rare. These findings are supported by previous smaller series that found CSU in children is a disease with good prognosis.[2,9,13] In accordance with the favorable outcome, laboratory tests in our cohort were within the normal range. Probably, indicating that routine laboratory tests in children with CSU are not essential. This notion is supported by Grattan et al. who left the decision to perform laboratory tests in cases of CSU to the discretion of the treating physician.[4]

Traditionally, CSU is considered a disease of unknown etiology. Nonetheless, in some patients, an underlining autoimmune mechanism may be present. This concept is supported by the fact that, in adults, autoimmune diseases, mostly affecting the thyroid gland, frequently accompany CSU.[6] Moreover, a canonic work by Hide

et al. [32] reported autoantibodies against IgE and its receptor, as a potential trigger for the disease. These findings established the notion that CSU is a TH1 derived phenomenon. Atopy, including AD, AR, food allergy and asthma are considered TH2-related diseases. In the current study, one-third of the children with CSU had at least one atopic disease. AD and AR were significantly more prevalent in children with CSU, as compared to the general pediatric population in Israel and in the world. Food allergy was significantly more prevalent in children ages 4 to 12 years, with CSU, as compared to the general pediatric population. An exception is the difference in the prevalence of asthma; although higher in children with CSU than in the general pediatric population, it did not reach significance.

It can be speculated that the high prevalence of atopic comorbidities can be attributed, in part, to confusion between CSU and AD. When patients with AD were excluded from the analysis, the prevalence of other atopic diseases and the significant differences between patients with CSU and the general pediatric population remained similar.

High levels of IgE were found in more than half of the results. This finding did not overlap with the patients with clinical atopy. This laboratory abnormality might provide additional support to the underling atopic background accompanying these children.

The co-existence of atopic diseases had no effect on the likelihood of relapsing or on the duration of CSU. These findings are in concordance with other studies that showed a similar prevalence of atopic diseases in smaller cohorts of pediatric patients with CSU.[5,8,9] Recently, one large cohort, that included Israeli adolescents, showed a robust link between CSU and atopic diseases.[7] These publications all support the assumption that there is a subgroup of CSU patients with TH2-driven disease.

This study is subject to the limitations inherent to any retrospective work; some of the data were incomplete. As the follow-up period was very long, changes in the treatment modalities for CSU were inevitable. Treatment with anti-IgE was approved for children with CSU older than 12 years of age, only at the end of the follow-up period. As such, its effect on childhood CSU was not evaluated in this study.

In conclusion, CSU in children is mostly a mild disease. It does not tend to relapse and can be managed with antihistamines alone. Atopy was found to be prevalent in children with CSU. However, these atopic diseases did not influence the duration or severity of the disease. Whether CSU in children should be part of the spectrum of atopic diseases requires further investigation in larger, prospective studies.

References

1. Kanwar AJ, Greaves MW. Approach to the patient with chronic urticaria. *Hosp Pract (1995).* 1996;31(3):175-179,183-174,187-179.

2. Sahiner UM, Civelek E, Tuncer A, et al. Chronic urticaria: etiology and natural course in children. *Int Arch Allergy Immunol.*2011;156(2):224-230.

3. Zuberbier T, Bindslev-Jensen C, Canonica W, et al. EAACI/GA2LEN/EDF guideline: management of urticaria. *Allergy.* 2006;61(3):321-331.

4. Grattan CE, Humphreys F, British Association of Dermatologists Therapy G, Audit S. Guidelines for evaluation and management of urticaria in adults and children. *Br J Dermatol.*2007;157(6):1116-1123.

5. Chansakulporn S, Pongpreuksa S, Sangacharoenkit P, et al. The natural history of chronic urticaria in childhood: a prospective study. *J Am Acad Dermatol.* 2014;71(4):663-668.

6. Kaplan AP. What the first 10,000 patients with chronic urticaria have taught me: a personal journey. *J Allergy Clin Immunol.*2009;123(3):713-717.

7. Rosman Y, Hershko AY, Meir-Shafrir K, et al. Characterization of chronic urticaria and associated conditions in a large population of adolescents. *J Am Acad Dermatol.* 2019;81(1):129-135.

8. Goldstein S, Gabriel S, Kianifard F, Ortiz B, Skoner DP. Clinical features of adolescents with chronic idiopathic or spontaneous urticaria: Review of omalizumab clinical trials. *Ann Allergy Asthma Immunol.* 2017;118(4):500-504.

9. Netchiporouk E, Sasseville D, Moreau L, Habel Y, Rahme E, Ben-Shoshan M. Evaluating Comorbidities, Natural History, and Predictors of Early Resolution in a Cohort of Children With Chronic Urticaria. *JAMA Dermatol.* 2017;153(12):1236-1242.

10. Lee XH, Ong LX, Cheong JY, et al. A stepwise approach in the management of chronic spontaneous urticaria in children. *Asia Pac Allergy.* 2016;6(1):16-28.

11. Eser I, Yologlu N, Baydemir C, Aydogan M. The predictive factors for remission of chronic spontaneous urticaria in childhood: Outcome from a prospective study. *Allergol Immunopathol (Madr).*2016;44(6):537-541.

12. Kilic G, Guler N, Suleyman A, Tamay Z. Chronic urticaria and autoimmunity in children. *Pediatr Allergy Immunol.*2010;21(5):837-842.

13. Jirapongsananuruk O, Pongpreuksa S, Sangacharoenkit P, Visitsunthorn N, Vichyanond P. Identification of the etiologies of chronic urticaria in children: a prospective study of 94 patients. *Pediatr Allergy Immunol.* 2010;21(3):508-514.

14. Ozyilmaz-Bozat G, Sahiner UM, Buyuktiryaki B, Uysal-Soyer O, Sekerel BE. Children with chronic spontaneous urticaria: Recurrence after remission and its predictors. *J Allergy Clin Immunol Pract.*2020;8(2):796-798 e791.

15. Greenberger PA. Chronic urticaria: new management options. *World Allergy Organ J.* 2014;7(1):31.

16. Khakoo G, Sofianou-Katsoulis A, Perkin MR, Lack G. Clinical features and natural history of physical urticaria in children. *Pediatr Allergy Immunol.* 2008;19(4):363-366.

17. Caffarelli C, Cuomo B, Cardinale F, et al. Aetiological factors associated with chronic urticaria in children: a systematic review.*Acta Derm Venereol.* 2013;93(3):268-272.

18. Harris A, Twarog FJ, Geha RS. Chronic urticaria in childhood: natural course and etiology. *Ann Allergy.* 1983;51(2 Pt 1):161-165.

19. Saini S, Shams M, Bernstein JA, Maurer M. Urticaria and Angioedema Across the Ages. *J Allergy Clin Immunol Pract.*2020;8(6):1866-1874.

20. Levy Y, Segal N, Weintrob N, Danon YL. Chronic urticaria: association with thyroid autoimmunity. *Arch Dis Child.*2003;88(6):517-519.

21. Ferriani MP, Silva MF, Pereira RM, et al. Chronic Spontaneous Urticaria: A Survey of 852 Cases of Childhood-Onset Systemic Lupus Erythematosus. *Int Arch Allergy Immunol.* 2015;167(3):186-192.

22. Caminiti L, Passalacqua G, Magazzu G, et al. Chronic urticaria and associated coeliac disease in children: a case-control study.*Pediatr Allergy Immunol.* 2005;16(5):428-432.

23. Romano-Zelekha O, Graif Y, Garty BZ, Livne I, Green MS, Shohat T. Trends in the prevalence of asthma symptoms and allergic diseases in Israeli adolescents: results from a national survey 2003 and comparison with 1997. *J Asthma.* 2007;44(5):365-369.

24. Graif Y, Garty BZ, Livne I, Green MS, Shohat T. Prevalence and risk factors for allergic rhinitis and atopic eczema among schoolchildren in Israel: results from a national study. *Ann Allergy Asthma Immunol.* 2004;92(2):245-249.

25. Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI, Group IPTS. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. *J Allergy Clin Immunol.*2009;124(6):1251-1258 e1223.

26. Kivity S, Sade K, Abu-Arisha F, Lerman Y, Kivity S. Epidemiology of bronchial asthma and chronic rhinitis in schoolchildren of different ethnic origins from two neighboring towns in Israel. *Pediatr Pulmonol.* 2001;32(3):217-221.

27. Ait-Khaled N, Pearce N, Anderson HR, et al. Global map of the prevalence of symptoms of rhinoconjunctivitis in children: The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three. *Allergy.* 2009;64(1):123-148.

28. Nwaru BI, Hickstein L, Panesar SS, et al. The epidemiology of food allergy in Europe: a systematic review and meta-analysis.*Allergy.* 2014;69(1):62-75.

29. Grabenhenrich L, Trendelenburg V, Bellach J, et al. Frequency of food allergy in school-aged children in eight European countries - the EuroPrevall-iFAAM birth cohort. *Allergy.* 2020.

30. Nachshon L, Schwartz N, Elizur A, et al. The Prevalence of Food Allergy in Young Israeli Adults. *J Allergy Clin Immunol Pract.*2019;7(8):2782-2789 e2784.

31. Akinbami LJ, Simon AE, Rossen LM. Changing Trends in Asthma Prevalence Among Children. *Pediatrics.* 2016;137(1).

32. Hide M, Francis DM, Grattan CE, Hakimi J, Kochan JP, Greaves MW. Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. *N Engl J Med.*1993;328(22):1599-1604.

Figures and tables

Table 1. Characterization of chronic urticaria in various age groups

		0-3 years	**4-8 years**	**9-12 years**	**13-18 years**	**Total**
Total (%)	Total (%)	19^{+} (7.6%)	71 (28.4%)	38 (15.2%)	122^{+} (48.8%)	250 (100%)
Sex (% of age group)*	Male	9 (47.4%)	38 (53.5%)	18 (47.4%)	49 (40.2%)	114 (45.6%)
	Female	10 (52.6%)	33 (46.5%)	20 (52.6%)	73 (59.8%)	136 (54.4%)
Duration of urticaria (% of age group)$^{*,++}$	<6 months	0	8 (11.6%)	1 (3%)	11 (9.4%)	20 (8.4%)
	6-12 months	3 (15.8%)	12 (17.4%)	11 (33.3%)	27 (23.1%)	53 (22.3%)
	12-24 months	13 (68.4%)	44 (63.8%)	17 (51.5%)	61 (52.1%)	135 (56.7%)
	>24 months	3 (15.8%)	5 (7.2%)	4 (12.1%)	18 (15.4%)	30 (12.6%)
Relapse of urticaria (% of age group)**	Relapse of urticaria (% of age group)**	7 (5.5%)	7 (5.5%)	7 (5.5%)	17 (13.9%)	24 (9.6%)

$^{+}$In the youngest age group (0-3 years) there were more patients with atopic dermatitis, while in the oldest age group (13-18 years) fewer patients had concomitant atopic dermatitis ($p<0.05$).

* p=Not significant for all comparisons

** $p< 0.05$

$^{++}$ In 12 patients (4.8%), data regarding the duration of urticaria were missing and they were excluded from this sub-analysis.

Table 2. Type of medication and number of drugs among 274 pediatric patients with chronic spontaneous

urticaria (CSU)

No. of medications	Type of medications	First CSU episode	Relapse of CSU
		No. of Patients (% of total cohort)	No. of Patients (% of total cohort)
1	Antihistamine regular dose	153 (61.2%)	10 (41.7%)
	Antihistamine high dose	7 (2.8%)	2 (8.3%)
	Steroids course	1 (0.4%)	0
	Montelukast only	0	1 (4.2%)
	Total	**161 (64.4%)**	**13 (54.2%)**
2	Antihistamine regular dose + Steroids	32 (12.8%)	2 (8.3%)
	Antihistamine high dose + Steroids	9 (3.6%)	0
	Antihistamine regular dose + Montelukast	2 (0.8%)	0
	Antihistamine high dose + Montelukast	3 (1.2%)	2 (8.3%)
	Montelukast + Omalizumab	0	1 (4.2%)
	Total	**46 (18.4%)**	**5 (20.8%)**
3	Antihistamine high dose + Steroids + Montelukast	5 (2%)	0
	Antihistamine high dose + steroids + Omalizumab	1 (0.4%)	0
	Total	**6 (2.4%)**	**0**
4	Antihistamine high dose + Steroids + Montelukast + Omalizumab	0	2 (8.3%)
No record of medications	No record of medications	37 (14.8%)	4 (16.7%)
Total of patients	**Total of patients**	**250**	**24**

CSU - Chronic spontaneous urticaria

Figure 1. Prevalence of atopic diseases in children with CSU compared to the general population. A. Prevalence of atopic diseases in CSU patients, by age groups. B. Atopic diseases in current study and the general pediatric population in Israel and in the world ($^{*}p<0.05$). Prevalence data in Israel and the world are incomplete due to lack of epidemiological studies.

Figure I: