Characterization of chronic urticaria and associated conditions in a large population of adolescents

Yossi Rosman, MD,[a,b] Alon Y. Hershko, MD, PhD,[a,b] Keren Meir-Shafrir, MD,[a] Ron Kedem,[c] Idit Lachover-Roth, MD,[a,b] Yoseph A. Mekori, MD,[a,b] and Ronit Confino-Cohen, MD[a,b]
Kfar Saba, Tel-Aviv, and Tel HaShomer, Israel

Background: Although chronic spontaneous urticaria (CSU) affects all age groups, data regarding CSU in adolescents is scarce.

Objective: To characterize the epidemiology, demographics, and comorbidities associated with CSU in a large, cross-sectional nationwide population of adolescents.

Methods: Medical records of 16-year-old candidate conscripts to the Israeli Defense Forces were reviewed. Data were collected on the prevalence and severity of CSU, as well as the demographics, medical comorbidities, medication use, and blood test results of affected individuals.

Results: Medical records of 1,108,833 consecutive 16-year-old adolescents were reviewed. A total of 6617 (0.6%) adolescents received CSU diagnoses. CSU was increased in female conscripts (odds ratio [OR] 1.13, 95% confidence interval [CI] 1.07-1.19, $P < .001$) and adolescents with higher socioeconomic scores (OR 1.92, 95% CI 1.56-2.32, $P < .001$). Individuals with CSU were significantly more likely to have allergic diseases, including food allergy (OR 7.31, 95% CI 6.13-8.72), allergic rhinitis (OR 2.9, 95% CI 2.71-3.11), atopic dermatitis (OR 2.35, 95% CI 2.03-2.72), and asthma (OR 1.46, CI 1.35-1.57).

Conclusion: Our work provides an account of CSU in a large cohort of adolescents. We found a strong link between CSU and atopic diseases. Further investigation is needed to decipher the mechanism underlying this observed association. (J Am Acad Dermatol 2019;81:129-35.)

Key words: adolescents; allergy; atopy; chronic spontaneous urticaria.

Chronic urticaria is defined as daily or almost daily hives that last at least 6 weeks that might be accompanied by episodes of angioedema.[1] In chronic spontaneous urticaria (CSU), the hives are not evoked by physical or environmental stimuli. Although CSU affects all age groups, most studies on its epidemiology and comorbidities focus on adults or mixed populations.[2-7] Studies on CSU in pediatric patients often group children and adolescents, even though the latter might represent a distinct population.[8-21] For example, the results of a post hoc analysis of 39 adolescents included in trials of omalizumab for CSU showed high prevalence of allergic rhinitis and asthma (61.5% and 56.4%, respectively), and the authors emphasized the need for larger, controlled studies focusing on adolescents with CSU. The current guidelines on CSU diagnostic workup and treatment provides little reference to children in general or to adolescents in particular.[1,22] We investigated the epidemiology, demographics, and comorbidities of CSU in a large, nationwide population of adolescents.

METHODS

Patient selection and data collection

At the age of 16 years, all Israeli citizens undergo mandatory medical screening as part of military conscription. This includes review of medical

From the Allergy and Clinical Immunology Unit, Meir General Hospital, Kfar-Saba, Israel[a]; Sackler School of Medicine, Tel-Aviv University[b]; and Medical Corps Headquarters, Israel Defense Forces, Tel HaShomer.[c]

Funding sources: None.
Conflicts of interest: None disclosed.
Accepted for publication February 17, 2019.

Reprint requests: Yossi Rosman, MD, Allergy and Clinical Immunology Unit, Meir Medical Center, 44261, Kfar Saba, Israel. E-mail: yossi.rosman@clalit.org.il.

Published online February 21, 2019.
0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2019.02.034

evaluation forms from the primary care physician, history and physical examination by a military physician, and specialty consultations and additional testing as needed. Altogether, the detailed medical records of ~70% of 16-year-old Israeli adolescents were available for study; Muslim Arabs and Jewish women are exempt from military service for religious reasons, so these populations were not included in this study.[23]

The medical records of 16-year-old conscripts screened for inclusion in the Israeli Defense Force during 1996-2015 were reviewed. Demographic information, medical diagnoses, data on CSU severity, and medication history were collected, coded, and stored in a computerized database. The research protocol was reviewed and approved by the Human Trial Committee of the Israeli Defense Force Medical Corps.

CAPSULE SUMMARY

- Chronic spontaneous urticaria is usually regarded as an idiopathic entity, occasionally associated with autoimmune phenomena. The current work, however, shows that in adolescents it is related to atopy.
- Recognition of the association between atopy and chronic spontaneous urticaria might provide pathogenic insights and improve patient management.

CSU diagnosis and severity

The diagnosis of CSU was made according to accepted clinical criteria: the spontaneous appearance of well-defined hives with or without angioedema lasting 1-24 hours during most days of the week for at least 6 weeks.[1] Patients with urticaria induced by physical stimuli, environmental factors, or nonsteroidal anti-inflammatory drugs and individuals with isolated angioedema were not included in the study. Diagnosis of CSU was assigned by an allergist or dermatologist who evaluated the conscript as part of military intake. Assessment of urticaria severity was based on the use of antihistamines and systemic corticosteroids combined with specific questions on the duration, severity, and frequency of symptoms and impact on quality of life. Quality of life was determined by a local version of the Dermatology Life Quality Index questionnaire that shares the same principles (eg, embarrassment and effect on study, social life, and leisure). Severe CSU was defined as resistance to high-dose antihistamines, recurrent courses of systemic corticosteroids, and a significant effect on quality of life.

Epidemiology and socioeconomic state

Data regarding place of birth, education, and socioeconomic status were available. Socioeconomic status was stratified into low, intermediate, or high classes according to prespecified criteria on place of residence.[23]

Comorbidities

All medical files were evaluated for the presence of other medical conditions, with a specific emphasis on the following diagnoses: atopic dermatitis, asthma, allergic rhinitis, chronic sinusitis, food allergy, celiac disease, peptic disease, irritable bowel syndrome, inflammatory bowel disease, thyroid disorders, diabetes mellitus, systemic lupus erythematosus, Raynaud phenomenon, rheumatoid arthritis, and psychiatric disorders. All medical conditions were diagnosed by specialist physicians in the corresponding disciplines. Food allergy was diagnosed by allergy specialists on the basis of the accepted guidelines, which includes clinical history, skin tests or radioallergosorbent test analysis, and food challenges, when indicated.[24]

Blood tests and medication use

When available, blood test results were collected, with a specific focus on complete blood count, thyroid function tests, autoantibodies, and inflammatory markers. Post diagnosis data regarding prescription of antihistamines and corticosteroids were collected when available. Of note, some antihistamines are sold over-the-counter in Israel.

Statistical analysis

The association between CSU and other diseases was evaluated using both univariate and multivariate logistic regression analyses. Odds ratio (OR) and 95% confidence intervals (95% CIs) were calculated. For the multivariate analysis, all the independent variables were entered into the model in the first block by using the forward likelihood ratio method. Criterion for inclusion into the model was a score statistic of $P \leq .05$, while the exclusion criterion was a Wald statistic of $P \leq .05$. CSU was entered in the second block, and a P value of $<.05$ was considered as statistically significant. Statistical analyses were performed by using SPSS version 23.0.

RESULTS

Prevalence and epidemiologic data

The medical records of 1,108,833 consecutive 16-year-old potential conscripts to the Israeli Defense Force were reviewed. Of them, 6617 individuals (0.6%) had CSU. Within this group, 1958 (29.6%) had severe CSU. The yearly prevalence of CSU ranged

Abbreviations used:

CI: confidence interval
CSU: chronic spontaneous urticaria
OR: odds ratio

0.4%-0.8% during the 20-year study period, with no evidence of an overall trend. Epidemiologic and demographic data are summarized in Table I.

Multivariate analysis demonstrated a relationship between CSU and female sex (OR 1.13, 95% CI 1.07-1.19, $P < .001$), high socioeconomic score (OR 1.92, 95% CI 1.56-2.32, $P < .001$), and level of education (OR 1.21, 95% CI 1.00-1.51, $P = .07$ for 12 years of education).

Medical prescriptions were reviewed as part of the CSU severity score. The mean number of prescriptions per year for antihistamines (CSU 1 ± 2.1 vs control 0.28 ± 0.9) and oral corticosteroids (CSU 0.14 ± 0 vs control 0.03 ± 0.3) was significantly higher in the CSU group than the control group ($P < .001$, for both comparisons). Also, the mean number of prescriptions per year for antihistamines (CSU 1.43 ± 2.6 vs control 0.78 ± 1.43) and oral corticosteroids (CSU 0.25 ± 0.9 vs control 0.09 ± 0.4) was significantly higher in persons with severe CSU than mild CSU ($P < .001$ for both).

Comorbidity

Allergic diseases and biomarkers for atopy. Patients with CSU had significantly more food allergy (3% vs 0.3%, $P < .001$), atopic dermatitis (3.9% vs 1%, $P < .001$), allergic rhinitis (24.1% vs 8%, $P < .001$), and asthma (18.5% vs 9%, $P < .001$) than the control population (Table II, Fig 1). Although not an allergic disease, chronic sinusitis is considered a common complication of allergic rhinitis. Accordingly, we found this condition to be significantly more prevalent in patients with CSU (CSU 0.4% vs control 0.2%, $P < .001$).

Eosinophil count was available for 337,547 (30.4%) people in the control group and 2403 (36.3%) people in the study group. Eosinophilia (eosinophil count >500 cells/μL), was more common in CSU patients (5.2%) than controls (4.4%, $P = .05$). Total IgE count was available for a minority of patients. High total IgE (>100 IU) was more common in CSU patients, albeit not reaching statistical significance (Table III).

Multivariate analysis (Table IV) further demonstrated a robust linkage between CSU and allergic diseases, including food allergy (OR 7.31, 95% CI 6.13-8.72, $P < .001$), allergic rhinitis (OR 2.9, 95% CI 2.71-3.11, $P < .001$), chronic sinusitis (OR 2.8, 95% CI 1.87-4.2, $P < .001$), atopic dermatitis (OR 2.35, 95% CI 2.03-2.72, $P < .001$), and asthma (OR 1.46, 95% CI 1.35-1.57, $P < .001$).

Autoimmune diseases and inflammatory markers. Single and multivalent analysis showed that CSU patients had a high prevalence of both thyroid disease (CSU 1.3% vs control 0.8%, $P < .001$) and Raynaud phenomenon (CSU 0.2% vs control 0.1%, $P = .003$; Table II). Other autoimmune diseases were comparable in both groups (Table II). No significant differences between the 2 groups were noted for C-reactive protein level, erythrocyte sedimentation rate, thyroid-stimulating hormone level, and antinuclear antibody (Table III).

Gastrointestinal diseases and markers. Irritable bowel syndrome was found to be more prevalent in the study group than in the control group in both the univariate (CSU 1.3% vs control 0.6%, $P < .001$) and multivariate models (OR 1.51, 95% CI 1.18-1.95, $P < .001$). Peptic disease, celiac disease, and positive testing for antitissue transglutaminase were more prevalent in the study group than the control group (Tables II-IV).

Psychiatric comorbidity. Psychiatric comorbidities, including depression and psychosis but not anxiety disorders, were found to be less prevalent in the study group (Table II). The multivariate analysis further confirmed these findings (depression OR 0.38, 95% CI 0.21-0.68, $P < .001$; psychosis OR 0.06, 95% CI 0.02-0.15, $P < .001$; Table IV).

DISCUSSION

Our study reveals a strong linkage between CSU and atopic diseases, including food allergy, asthma, allergic rhinitis, chronic sinusitis, and atopic dermatitis. These associations were even more prominent in patients with severe CSU. Limited data has been published on associations between CSU and atopy; most research has focused on adult patients in the Far East.[25-27] The few small studies focusing on pediatric patients have found atopic diseases in 13.5%-35% of children with chronic urticaria.[10,12,13,21,25] Goldstein et al published the only direct reference to teenagers, describing a high rate of co-existing asthma and allergic rhinitis in 39 adolescents with severe CSU.[16]

The current literature regards atopic diseases as T-cell helper 2 (T_H2) mediated and CSU as a T_H1 disease associated with autoimmunity. Approximately 40%-50% of children and adults with CSU have pathogenic mast cell— and basophil-activating autoantibodies.[21] However, autoimmune comorbidities are less well-recognized in children with CSU than in adults.[19,20,26,27] Our data for adolescents points toward selected associations,

Table I. Epidemiology and demographic data

Characteristic	Control, N = 1,102,216, n (%)	Chronic urticaria, N = 6617, n (%)	Univariate *P* value	OR (95% CI)	Multivariate *P* value
Female sex	441,401 (40)	2882 (43.6%)	<.001	1.13 (1.07-1.19)	<.001
Socioeconomic score					
Low	46,907 (4.3)	107 (2)	<.001	NA	NA
Medium	561,818 (51.2)	2553 (46.6)		NA	NA
High	489,191 (44.6)	2820 (51.5)		1.92 (1.56-2.32)	<.001
≥12 years of education	1,056,148 (95.8)	6413 (96.9)	<.001	1.21 (1.00-1.51)	.07
Place of birth					
Israel	893,879 (81.8)	5231 (79.6)	<.001	NA	NA
Eastern Europe	154,522 (14.1)	1095 (16.7)		1.006 (0.99-1.02)	.4
Ethiopia	39,064 (3.6)	218 (3.3)		NA	NA

CI, Confidence interval; *NA*, not analyzed; *OR*, odds ratio.

Table II. Comorbidities and chronic urticaria univariate analysis

Comorbidity	Control, N = 1,102,216, n (%)	Chronic urticaria, N = 6617, n (%)	*P* value	Severe chronic urticaria, N = 1958, n (%)	*P* value*
Asthma	99,249 (9)	1222 (18.5)	<.001	449 (22.9)	<.001
Allergic rhinitis	88,669 (8)	1594 (24.1)	<.001	540 (27.6)	<.001
Food allergy	2758 (0.3)	198 (3)	<.001	137 (7)	<.001
Atopic dermatitis	10,557 (1)	256 (3.9)	<.001	104 (5.3)	<.001
Chronic sinusitis	1795 (0.2)	29 (0.4)	<.001	14 (0.7)	<.001
Thyroid disease	8929 (0.8)	85 (1.3)	<.001	33 (1.7)	<.001
Raynaud phenomenon	1156 (0.1)	16 (0.2)	.003	9 (0.5)	<.001
Rheumatoid arthritis	4273 (0.4)	32 (0.5)	.19	16 (0.8)	.005
Lupus erythematosus	712 (0.1)	4 (0.1)	1	4 (0.2)	.04
Irritable bowel syndrome	6976 (0.6)	87 (1.3)	<.001	32 (1.6)	<.001
Inflammatory bowel disease	3251 (0.3)	8 (0.1)	.009	2 (0.1)	.1
Celiac	2598 (0.2)	17 (0.3)	.7	7 (0.4)	.2
Psychosis	21,175 (1.9)	25 (0.4)	<.001	9 (0.5)	<.001
Depression	6901 (0.6)	27 (0.4)	.02	6 (0.3)	.08
Anxiety	17,514 (1.6)	95 (1.4)	.35	28 (1.4)	.35

**P* for comparison between severe chronic urticaria and control group.

in particular thyroid disease. Although a statistical association was found between CSU and clinical thyroid dysfunction, its magnitude was lower than that previously described in adults.[2]

Atopic diseases are more prevalent in highly educated individuals of higher socioeconomic status.[28] Thus, it is not surprising that we, as well as others, found that individuals from upper socioeconomic classes and persons with higher education levels were more prevalent in the CSU cohort than the control cohort.[29,30]

The underlying mechanisms that connect atopy and urticaria are likely to consist of factors such as mast cell activation that are common to both entities. Nonetheless, it is unknown whether the present findings suggest an underlying T_H2-mediated pathogenesis or whether the physiologic and hormonal changes inherent to this age group mediate this effect.

In addition to physical comorbidities, emotional conditions have been suggested to affect the occurrence or exacerbation of CSU.[1,31] Herguner et al found that anxiety and depression were more frequent in 27 children with CSU than matched controls.[32] Staubach et al recommend screening patients with CSU for mental disorders as a routine clinical practice.[31] Surprisingly, our data on adolescents does not lend support to this concept. We found no association between teenagers with CSU and emotional conditions including anxiety, depression, and psychosis. Interestingly, schizophrenia and depression were found to occur significantly less in patients with CSU. Because this age group is more susceptible to emotional lability and morbidity, the

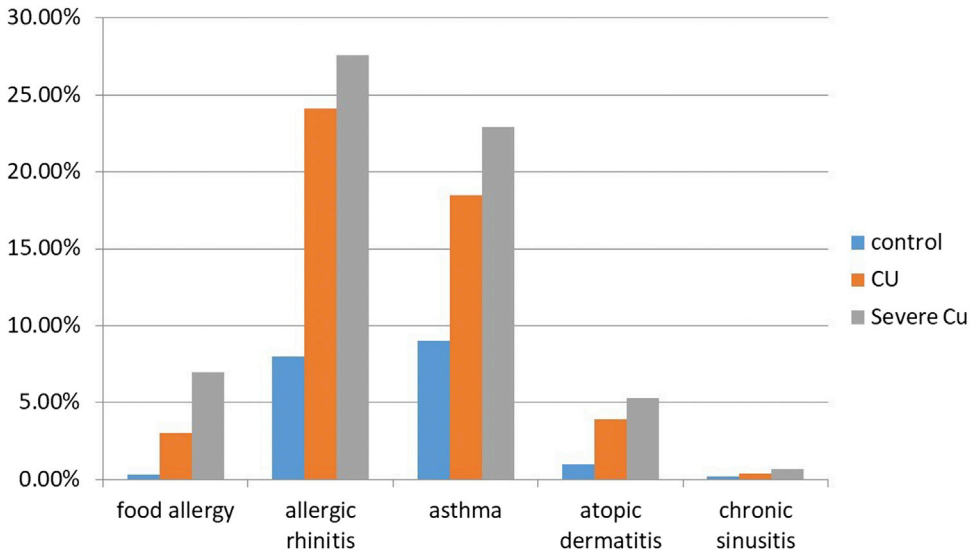

Fig 1. The prevalence of atopic diseases in the chronic urticaria, severe chronic urticaria, and control populations. All comparisons displayed are significant ($P < .001$). *CU*, Chronic urticaria.

Table III. Blood tests

Blood test result	Control, n/total (%)	Study, n/total (%)	*P* value
Eosinophil count >600 cells/μL	14,976/337,547 (4.4)	124/2403 (5.2)	.05
IgE >100 IU	2085/3809 (54.7)	50/80 (62.5)	.1
Erythrocyte sedimentation rate >20 mm/h	17,470/96,922 (18)	116/749 (15.5)	.08
C-reactive protein >0.5 mg/L	20,649/101,913 (20.3)	144/803 (17.9)	.1
Mean platelet volume >13 fL	50,039/346,708 (14.4)	358/2460 (14.6)	.4
Anitnuclear antibody positive	739/21,939 (3.4)	12/283 (4.2)	.2
Hemoglobin <12 mg/dL	41,663/350,908 (11.9)	261/2495 (10.5)	.01

lack of a correlation between psychosocial conditions and CSU is even more striking. A possible link between the low incidence of emotional illness and CSU found in our study might be explained by the relatively high socioeconomic status of the adolescents with CSU. This finding is in accordance with the recent evidence that social inequalities contribute to the pathogenesis of depressive disorders.[33] These findings seem to represent another unique feature of CSU in adolescents, which might distinguish them from other age groups.

The data presented herein also sheds light on the epidemiology and demography of CSU in adolescents. The few reports that pertain to the epidemiology of this disease entity in children estimate its prevalence as 0.1%-0.7% of the population, similar to the estimated prevalence in adults (0.6%).[4,14,21,29,34,35] Accordingly, the prevalence of CSU in our cohort was found to be 0.6%, with yearly prevalences of 0.4%-0.8%.

One strength of this study was the analysis of a large national registry; its size and nature render the data unbiased by patient origin, socioeconomic status, and place of residence or insurance status. Furthermore, medical records are based on specialists in relevant medical fields who diagnosed all comorbidities, including CSU, using well-defined diagnostic criteria. However, one should note that significant associations found in studies with extremely large numbers of patients must be interpreted carefully to determine their clinical relevance.

Because of its cross-sectional nature, this study does not provide information regarding the evolution of CSU over time or the emergence of new comorbidities. Moreover, despite the large sample size, the study excludes populations that are not obligated to serve in the military. This might compromise the diversity of the cohort, thereby restricting the applicability of its conclusions with respect to these populations.

Table IV. Comorbidities and chronic urticaria multivariate analysis

Comorbidity	Chronic urticaria, OR (95% CI)	*P* value	Severe chronic urticaria, OR (95% CI)	*P* value
Food allergy	7.31 (6.13-8.72)	<.001	16.16 (12.9-20.25)	<.001
Allergic rhinitis	2.9 (2.71-3.11)	<.001	3.07 (2.71-3.47)	<.001
Chronic sinusitis	2.8 (1.87-4.2)	<.001	4.05 (2.22-7.38)	<.001
Atopic dermatitis	2.35 (2.03-2.72)	<.001	2.61 (2.04-3.34)	<.001
Asthma	1.46 (1.35-1.57)	<.001	1.66 (1.45-1.88)	<.001
Thyroid disease	1.4 (1.09-1.79)	<.001	1.87 (1.27-2.75)	.002
Raynaud phenomenon	2.06 (1.19-3.57)	.01	4.82 (2.4-9.35)	<.001
Rheumatoid arthritis	NA*	NA*	2 (1.1-3.55)	.01
Lupus erythematosus	NA*	NA*	2.3 (0.59-9.6)	.2
Irritable bowel syndrome	1.51 (1.18-1.95)	<.001	1.8 (1.2-2.7)	.004
Inflammatory bowel disease	0.34 (0.14-0.82)	.01	NA*	NA*
Depression	0.38 (0.21-0.68)	<.001	NA*	NA*
Psychosis	0.06 (0.02-0.15)	<.001	0.18 (0.05-0.74)	.02

CI, Confidence interval; *NA*, not analyzed; *OR*, odds ratio.
*Depression and inflammatory bowel disease were found to be nonsignificantly associated with severe chronic urticaria; hence, they were not inserted in the multivariate model. Rheumatoid arthritis and lupus erythematosus were found to be nonsignificantly associated with chronic urticaria; hence, they were not inserted in the multivariate model.

Another caveat that is inherent to our study includes the criteria for evaluation of disease severity. Whereas the Urticaria Activity Score summed over 7 days is commonly used in clinical trials, severity was assessed in this work by a different method; military allergy specialists instead focused on consumption of medications and on a medical interview. We strongly believe that this approach could also distinguish between mild and severe disease activities. Although antihistamines can be obtained as over-the-counter drugs in Israel, we expect that most antihistamines were purchased with prescriptions because these can be purchased at a reduced price and pharmacies are not allowed to sell high-dose antihistamines without a specialist-provided justification. Last, the biomarker information available in the database for our retrospective study were limited.

In conclusion, this study provides a comprehensive account of the epidemiology, demographics, and comorbidities associated with CSU in a nationwide cohort of adolescents. The present data establish a strong link between CSU in adolescents and atopic diseases with a less dominant role for T_H1-related diseases. Considering these new findings, we propose that atopy is associated with CSU in this age group. Further investigation into the association of atopy with chronic urticaria in this age group might provide pathogenic insights and improve management of these conditions.

The authors thank Maya Stein for her assistance in editing this paper.

REFERENCES

1. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy*. 2014;69:868-887.
2. Confino-Cohen R, Chodick G, Shalev V, Leshno M, Kimhi O, Goldberg A. Chronic urticaria and autoimmunity: associations found in a large population study. *J Allergy Clin Immunol*. 2012;129:1307-1313.
3. Greaves M. Chronic urticaria. *J Allergy Clin Immunol*. 2000;105:664-672.
4. Kaplan AP. Chronic urticaria: pathogenesis and treatment. *J Allergy Clin Immunol*. 2004;114:465-474. quiz 75.
5. Kolkhir P, Metz M, Altrichter S, Maurer M. Comorbidity of chronic spontaneous urticaria and autoimmune thyroid diseases: a systematic review. *Allergy*. 2017;72(10):1440-1460.
6. Lapi F, Cassano N, Pegoraro V, et al. Epidemiology of chronic spontaneous urticaria: results from a nationwide, population-based study in Italy. *Br J Dermatol*. 2016;174:996-1004.
7. Maurer M, Rosen K, Hsieh HJ, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med*. 2013;368:924-935.
8. Bakke P, Gulsvik A, Eide GE. Hay fever, eczema and urticaria in southwest Norway. Lifetime prevalences and association with sex, age, smoking habits, occupational airborne exposures and respiratory symptoms. *Allergy*. 1990;45:515-522.
9. Caffarelli C, Cuomo B, Cardinale F, et al. Aetiological factors associated with chronic urticaria in children: a systematic review. *Acta Derm Venereol*. 2013;93:268-272.
10. Caminiti L, Passalacqua G, Magazzu G, et al. Chronic urticaria and associated coeliac disease in children: a case-control study. *Pediatr Allergy Immunol*. 2005;16:428-432.
11. Cantarutti A, Dona D, Visentin F, et al. Epidemiology of frequently occurring skin diseases in Italian children from 2006 to 2012: a retrospective, population-based study. *Pediatr Dermatol*. 2015;32:668-678.
12. Chansakulporn S, Pongpreuksa S, Sangacharoenkit P, et al. The natural history of chronic urticaria in childhood: a prospective study. *J Am Acad Dermatol*. 2014;71:663-668.

13. 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;44:537-541.
14. Khakoo G, Sofianou-Katsoulis A, Perkin MR, Lack G. Clinical features and natural history of physical urticaria in children. *Pediatr Allergy Immunol*. 2008;19:363-366.
15. Sahiner UM, Civelek E, Tuncer A, et al. Chronic urticaria: etiology and natural course in children. *Int Arch Allergy Immunol*. 2011;156:224-230.
16. 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;118:500-504.
17. Hide M, Suzuki T, Tanaka A, Aoki H. Efficacy and safety of rupatadine in Japanese adult and adolescent patients with chronic spontaneous urticaria: a double-blind, randomized, multicenter, placebo-controlled clinical trial. *Allergol Int*. 2019;68(1):59-67.
18. Greaves MW. Chronic urticaria in childhood. *Allergy*. 2000;55:309-320.
19. 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;167:186-192.
20. Kilic G, Guler N, Suleyman A, Tamay Z. Chronic urticaria and autoimmunity in children. *Pediatr Allergy Immunol*. 2010;21:837-842.
21. 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;153:1236-1242.
22. Zuberbier T, Asero R, Bindslev-Jensen C, et al. EAACI/GA(2)LEN/EDF/WAO guideline: management of urticaria. *Allergy*. 2009;64:1427-1443.
23. The Israely central bureau of statistics. http://www.cbs.gov.il/www1/skarim/stat_an.htm. Accessed August 31, 2017.
24. Sampson HA, Aceves S, Bock SA, et al. Food allergy: a practice parameter update-2014. *J Allergy Clin Immunol*. 2014;134:1016-1025.e43.
25. Kim BR, Yang S, Choi JW, Choi CW, Youn SW. Epidemiology and comorbidities of patients with chronic urticaria in Korea: a nationwide population-based study. *J Dermatol*. 2018;45:10-16.
26. Chiu HY, Muo CH, Sung FC. Associations of chronic urticaria with atopic and autoimmune comorbidities: a nationwide population-based study. *Int J Dermatol*. 2018;57:822-829.
27. Shalom G, Magen E, Dreiher J, et al. Chronic urticaria and atopic disorders: a cross-sectional study of 11 271 patients. *Br J Dermatol*. 2017;177:e96-e97.
28. Williams HC, Strachan DP, Hay RJ. Childhood eczema: disease of the advantaged? *BMJ*. 1994;308:1132-1135.
29. Lee SJ, Ha EK, Jee HM, et al. Prevalence and risk factors of urticaria with a focus on chronic urticaria in children. *Allergy Asthma Immunol Res*. 2017;9:212-219.
30. Xiao Y, Huang X, Jing D, et al. The prevalence of atopic dermatitis and chronic spontaneous urticaria are associated with parental socioeconomic status in adolescents in China. *Acta Derm Venereol*. 2019;99(3):321-326.
31. Staubach P, Dechene M, Metz M, et al. High prevalence of mental disorders and emotional distress in patients with chronic spontaneous urticaria. *Acta Derm Venereol*. 2011;91:557-561.
32. Herguner S, Kilic G, Karakoc S, Tamay Z, Tuzun U, Guler N. Levels of depression, anxiety and behavioural problems and frequency of psychiatric disorders in children with chronic idiopathic urticaria. *Br J Dermatol*. 2011;164:1342-1347.
33. Hoebel J, Maske UE, Zeeb H, Lampert T. Social inequalities and depressive symptoms in adults: the role of objective and subjective socioeconomic status. *PLoS One*. 2017;12:e0169764.
34. Church MK, Weller K, Stock P, Maurer M. Chronic spontaneous urticaria in children: itching for insight. *Pediatr Allergy Immunol*. 2011;22:1-8.
35. Tsakok T, Du Toit G, Flohr C. Pediatric urticaria. *Immunol Allergy Clin North Am*. 2014;34:117-139.