

Assessment of atopic dermatitis as a risk factor for chronic spontaneous urticaria in a pediatric population

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ABSTRACT

Background: Atopic dermatitis (AD) and chronic spontaneous urticaria (CSU) represent two of the most common chronic inflammatory pruritic skin diseases. Any relationship between atopic skin disorders and CSU is controversial, mostly due to the paucity of relevant epidemiologic and pathogenetic data.

Objective: To evaluate whether a history of AD in early childhood represents a risk factor for the subsequent occurrence of CSU in a pediatric population.

Methods: Retrospective data of new cases of patients who visited the outpatient allergy unit of a tertiary pediatric hospital in Athens, Greece, between June 2014 and August 2016, were analyzed. Diagnoses of CSU and AD were based on diagnostic criteria proposed by the European Academy of Allergy and Clinical Immunology and the Hanifin and Rajka criteria, respectively. The data analyzed included CSU and AD diagnoses and the association with gender and season of birth as well as a personal and family history of allergy-related diseases (e.g., asthma, allergic rhinitis, AD, and food and drug allergies).

Results: Records from 2261 children were included in the analysis (1365 boys; mean $\pm$ standard deviation [SD] age, 8.7 ± 5.8 years). Fifty-one children (31 boys; mean $\pm$ SD age, 9.1 ± 4.6 years) were diagnosed with CSU, whereas AD was reported in 761 children (466 boys; mean $\pm$ SD age, 5.2 ± 3.8 years). Multivariate data analysis showed that the children with a history of an early diagnosis of AD were at increased risk for later CSU occurrence (odds ratio 2.923 [95% confidence interval, 1.647–5.189], $p < 0.001$). No significant associations were observed with respect to other demographic and atopy-associated characteristics of the patients.

Conclusion: Results of our study indicated that AD may constitute an important risk factor to the subsequent occurrence of CSU. This notion warrants further study with well-designed prospective cohorts.

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Chronic spontaneous urticaria (CSU) is a debilitating disease characterized by the development of wheals (hives), angioedema, or both, for >6 weeks. Circulatory autoantibodies, such as immunoglobulin G (IgG) autoantibodies against IgE or the high-affinity IgE receptor and/or autoreactive cell populations, i.e., autoreactive CD4⁺ T cells against high-affinity IgE receptor α ,¹ have been implicated in the pathogenesis of the disease. More recently, synergistic or additive interactions with abnormal filaggrin (*FLG*) expression have also been reported.² Atopic dermatitis (AD) represents a chronic, relapsing, inflammatory pruritic skin disease, frequently attributed to different degrees of loss-of-function mutations of *FLG*.³ In addition, a pos-

itive family history for atopy and environmental exposure factors during early infancy, such as the month of birth and climate conditions, have also been associated with disease occurrence.⁴

It is well established that pruritus pathophysiology and disease characteristics between CSU and AD are distinct; however, any relationship between atopic skin disorders and CSU is controversial, mostly due to the paucity of relevant epidemiologic and pathogenetic data. The aim of this study was to assess whether early AD is associated with an increased risk of CSU occurrence later in childhood. Secondary outcomes included potential associations of CSU occurrence with the patient's gender, season of birth, and personal and family history of allergy-related diseases.

METHODS

Retrospective data on new cases of patients who visited the outpatient allergy unit of a tertiary pediatric hospital in Athens, Greece, between June 2014 and August 2016, were analyzed. The patients with CSU were diagnosed based on a positive history for persistent development of wheals, angioedema, or both, for >6 weeks, as proposed by EAACI/GA(2)LEN/EDF/

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WAO guidelines.⁵ These patients were grouped as the CSU group. The determination of patients with chronic inducible urticaria (CIndUs) was based on a reported clinical history and corresponding testing when indicated; these patients were not included in the CSU group. Patients with CSU and concomitant CIndUs were also included in the CSU group.

The AD diagnosis was based on a diagnosis given by a specialized physician (an allergist, a dermatologist, or a pediatrician) according to the diagnostic criteria of Hanifin and Rajka.⁶ Associations between CSU and AD diagnoses with respect to gender, season of birth, and personal and family history of allergy-related diseases (e.g., asthma, allergic rhinitis [AR], AD, and food and drug allergies) were analyzed. The study was approved by the General Children's Hospital Panagiotis and Aglaia Kyriakou Ethics Committee (1055).

Statistical Analysis

The Pearson χ^2 test of independence was used to identify univariate dependences among categorical variables and logistic regressions (simple and multiple) were used to estimate the probability of later CSU occurrence in relation to gender, season of birth, AD diagnosis, and family history of allergy-related diseases. Respective odds ratios (OR) and corresponding 95% confidence intervals (CI) were recorded. The mean $\pm$ standard deviation (SD) was used for quantitative variables. Data normality was assessed by using the Kolmogorov-Smirnov test. SPSS v20.0 (IBM, Chicago, IL) statistical software was used for data analyses; all tests performed were two-sided and α was set to 0.05. Data power was calculated *via* a *post hoc* power analysis by using the Fisher exact test between two independent groups with G*Power 3.1.⁷ Statistical significance was set at $p < 0.05$.

RESULTS

Records from 2261 children were included in the analysis (1365 boys [60.4%]; mean $\pm$ SD age, 8.7 ± 5.8 years). *Post hoc* analysis indicated that the power achieved with our sample was 94.4% ($p = 0.043$). Comorbid allergy-associated diseases in the whole population were reported as follows: AD in 761 children (33.6%), asthma in 521 (23%), allergic rhinitis in 454 (20%), food allergy in 707 (31.2%), and drug allergy in 9 (0.4%). A positive family history of allergy-related diseases was recorded in 1212 children (53.6%). Season of birth was equally distributed in the subjects. A male predominance in previously diagnosed AR ($p = 0.002$) and asthma ($p = 0.059$) was observed. Population characteristics are depicted in Table 1.

Physician-diagnosed AD was reported in 761 children (466 boys; mean $\pm$ SD age, 5.2 ± 3.8 years). Fifty-one children (31 boys; mean $\pm$ SD age, 9.1 ± 4.6

years) were diagnosed with CSU. Four patients were diagnosed with CIndUs, three with cold contact urticaria, and one with cholinergic urticaria. Within the CSU group, two children had concomitant cold contact urticaria, and three had symptomatic dermatographism. A positive history of AD was recorded in 30 patients with CSU (CSU group: 58.8%, $p < 0.001$); one had a positive history of AR, and two had a positive history of food allergy. Univariate correlations showed that gender ($p = 0.951$), family history of atopy ($p = 0.637$), and season of birth ($p = 0.362$) were not associated with later CSU occurrence. Multivariate data analysis showed that children with a positive history of AD presented an increased risk of later CSU occurrence (OR 2.923 [95% CI, 1.647–5.189], $p < 0.001$) (Table 2).

DISCUSSION

To our knowledge, this was the first study that indicated that AD at early life may represent a risk factor to later CSU occurrence in a pediatric population. Gender, season of birth, and family history of atopy were not associated with CSU. Our cohort was powered to evaluate the role of AD as a potential risk factor for a later occurrence of CSU, with an estimated β error equal to 5.6%. Recently, a positive association between AD and chronic urticaria occurrence in adults has been reported (OR, 2.77), without, however, further chronic urticaria phenotyping.⁸ Moreover, the positive association of a reported AD history with urticaria (chronic or acute) has been confirmed in cross-sectional population-based surveys.⁹

Although CSU is not an allergy-related disease, several recently reported concepts bolster the notion of a potential common pathogenetic mechanism between AD and CSU. Single nucleotide polymorphisms genotyping studies have shown that the *ORAI1* (ORAI Calcium Release-Activated Calcium Modulator 1) gene (rs3741595, rs3741596, and rs12320939) encoded calcium release-activated calcium channel protein 1, which is strongly associated with mast cell degranulation, has been associated with both increased AD and CSU susceptibility.^{10,11} Although data on the role of a disrupted epidermal barrier in CSU is scarce, recently, increased *FLG* gene expression has been noted in CSU lesional skin sites, both at a protein and an RNA level, compared with samples derived from patients with AD. Moreover, such an increase has been positively associated with the mean urticaria activity score.²

Increased levels of alarmins, such as thymic stromal lymphopoietin, interleukin (IL) 25 and IL-33 have been reported in AD and CSU skin lesions, which thus potentially indicates a role for altered T-helper type 2 (Th2) responses in both diseases.¹² Increased levels of other cytokines, such as IL-17 and IL-23, in the peripheral blood have also been reported in both entities.^{13,14}

Table 1 Demographics and reported personal and family history of allergy-related diseases of the cohort

	Entire Population, no. (%)	Patients with CSU, no. (%)	Patients with AD, no. (%)	Patients with a History of AD and later CSU onset, no. (%)	Patients with a History of AD but not CSU, no. (%)
Patients	2261 (100)	51 (2.25)	761 (33.6)	30 (1.3)	731 (32.3)
Gender					
Boys	1365 (60.4)	31 (60.7)	466 (61.2)	17 (56.6)	449 (61.4)
Girls	896 (39.6)	20 (39.3)	295 (38.8)	13 (43.3)	282 (38.6)
Personal history					
Asthma					
Boys	333 (14.2)	1 (1.9)	85 (11.1)	1 (3.3)	84 (11.5)
Girls	188 (8.3)	0 (0)	51 (6.7)	0 (0)	51 (7)
AR					
Boys	303 (13.4)	1 (1.9)	103 (13.5)	0 (0)	103 (13.5)
Girls	151 (6.6)	0 (0)	60 (7.8)	0 (0)	60 (7.8)
Food allergy					
Boys	444 (19.6)	2 (3.9)	282 (37)	2 (6.6)	280 (38.3)
Girls	263 (11.6)	0 (0)	158 (20.7)	0 (0)	158 (21.6)
Drug allergy					
Boys	5 (0.2)	0 (0)	2 (0.2)	0 (0)	2 (0.2)
Girls	4 (0.17)	0 (0)	1 (0.1)	0 (0)	1 (0.1)
Positive family history of allergy-related diseases					
Boys	736 (32.5)	20 (39.2)	302 (39.6)	11 (36.6)	291 (39.8)
Girls	476 (21)	9 (17.6)	189 (24.8)	7 (23.3)	182 (24.9)

CSU = Chronic spontaneous urticaria; AD = atopic dermatitis; AR = allergic rhinitis.

Table 2 Logistic regression models (simple and multiple) of later CSU onset in relation to AD diagnosis, gender, family history of allergy-related diseases, and season of birth

	Patients with CSU (n = 51)			
	Simple Logistic Regression		Multiple Logistic Regression	
	OR (95% CI)	p	OR (95% CI)	p
AD diagnosis	2.89 (1.643–5.083)	<0.001	2.923 (1.647–5.189)	<0.001
Gender	0.982 (0.556–1.734)	0.951	1.005 (0.567–1.781)	0.986
Family history of allergy-related diseases	1.144 (0.653–2.004)	0.637	0.932 (0.526–1.652)	0.812
Season of birth*	—	—	—	0.373

CSU = Chronic spontaneous urticaria; AD = atopic dermatitis; OR = odds ratio; CI = confidence interval.

*Not defined as a variable with 3 degrees of freedom.

Increased serum IL-31 expression, an already established characteristic in AD, has also been noted in patients with CSU, although to a lesser extent, and is potentially associated with pruritus in both diseases.¹⁵ In support of this, it should be mentioned that therapeutic strategies, *e.g.*, anti-IgE, that suppress IL-31 levels have resulted in significant CSU improvement.¹⁵

Also, an autoreactivity profile has been observed in both diseases, through circulating either autoantibodies or autoreactive T-cell populations, although further investigation is required.¹ The possibility of an autoimmune association of AD with CSU seems a tempting idea due to their frequent coexistence with other autoimmune diseases, *e.g.*, alopecia areata, as it has recently been reported.¹⁶

An increased prevalence of CSU in the boys (60.7%) was noted in our cohort, which was not in line with most of the previous reports; however this notion emerged mainly from studies in adult patients.^{17,18} A recent Korean pediatric population-based study¹⁸ reports a male predominance (55.4%) in patients with CSU. It is plausible that ethnic and geographic differences might account for such discrepancies. No association between CSU and a family history of allergy-related diseases was recorded, in agreement with previous reports.^{19,20}

Certain limitations have to be considered in the present study. The retrospective design of the study and the data derived from a specialized department may potentially have led to an unavoidable selection, surveillance, and/or prevalence bias. This was clearly reflected by the high prevalence of AD and food allergy diagnosis (33.6% and 31.3%, respectively), thus, extrapolation cannot be applied to the general population. Furthermore, a family history of allergy-associated diseases was mainly based on parental reports, which are susceptible to recall bias and exposure misclassification. The lack of data regarding AD activity and/or severity did not allow further disease stratification. However, the notion that only an AD diagnosis was related to a later CSU onset as opposed to other allergy-associated diseases is of interest. In addition, the high number of children included and the extraction of data from medical files of specialized physicians increased the reliability of our results.

CONCLUSION

We presented evidence that indicated that AD may constitute an important risk factor to the subsequent occurrence of CSU. This notion warrants further exploration with well-designed prospective studies.

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