

Received Date : 23-May-2016
Revised Date : 16-Dec-2016
Accepted Date : 02-Jan-2017
Article type : Research Letter

**Chronic Urticaria and Atopic Disorders:
a Cross-sectional Study of 11,271 Patients**

Running head: Chronic Urticaria and Atopic Disorders

Table number: 1

Figure number: 0

*G. Shalom, MD MHA^{1,2}, *E. Magen, MD^{3,4}, J. Dreier, MD MPH^{5,6},
T. Freud, PhD,⁵ B. Bogen, MD^{1,2}, D. Comaneshter MHA PhD⁷,
D.A. Vardy, MD MSc^{1,2,5}, R. Khoury, MD^{1,2},
*N. Agmon-Levin, MD^{8,9}, *A.D. Cohen, MD MPH PhD^{5,7}

***Equal contributors**

¹Department of Dermatology and Venereology, Soroka Medical Center, Beer-Sheva, Israel

²Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

³Medicine B Department, Allergy and Clinical Immunology Unit, Barzilai Medical Center,
Ben-Gurion University of Negev, Ashkelon, Israel

⁴Leumi Health Services, Israel

⁵Sial Research Center for Family Medicine and Primary Care, Faculty of Health Sciences,
Ben-Gurion University of the Negev, Beer-Sheva, Israel

⁶Hospital Administration, Soroka Medical Center, Beer Sheva, Israel

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bjd.15347

This article is protected by copyright. All rights reserved.

⁷Chief Physician's Office, Department of Quality Measurements and Research, Clalit Health Services, Tel Aviv, Israel

⁸Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

⁹The Zabłudowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel Aviv, Israel

Corresponding author:

Guy Shalom, MD MHA

Department of Dermatology and Venereology, Soroka Medical Center, P.O.B. 151

Beer-Sheva 84101, Israel

Phone: +972-8-640-0603; Fax: +972-8-627-1704

E-Mail: Guyshal@bgu.ac.il

Funding: The present research was sponsored by an unrestricted research grant from Novartis AG. The company was not involved in any part of the study or writing; the manuscript approval was not required prior to its submission.

Conflict of Interest Statement: Prof. Arnon Cohen: Relationships relevant to this manuscript: Prof. Cohen received research grants from Novartis. Other relationships: In the last 3 years Prof. Arnon Cohen served as a consultant, advisor, or speaker at Abbvie, Dexcel Pharma, Janssen, Novartis, Perrigo, Pfizer, and Rafa.
All other authors state no conflict of interest.

Key words: allergic rhinoconjunctivitis; asthma; atopic dermatitis; atopic disorders; chronic urticaria.

Abbreviations used

Atopic dermatitis	AD
Allergic rhinoconjunctivitis	AR
Chronic urticaria	CU
Clalit Health Services	CHS
Thyroid stimulating hormone	TSH

TO THE EDITOR

Chronic urticaria (CU) and atopic disorders such as atopic dermatitis (AD), allergic rhinoconjunctivitis (AR), and asthma are related to aberrant immune function. The relationship between atopic disorders and CU is controversial, mostly since epidemiological data are lacking.

The aim of our study was to investigate the association between CU and asthma, AD, and AR using a database of Clalit Health Services (CHS) - the largest healthcare provider organization in Israel.

Our study was designed as a cross-sectional study of CU patients and age- and sex-matched controls. CU was defined as 4 couples of urticaria diagnoses, each recorded within a period of 6 weeks, registered by physicians in the primary care setting or during hospitalization from January 2002 to December 2012. The control group consisted of age- and sex-matched patients without urticaria extracted from the general population of CHS enrollees. Asthma, AD, and AR are all available as independent codes in the CHS database

and are registered by a dermatologist, an immunologist, a pulmonologist, or a general practitioner.

Patient demographic characteristics at baseline and concomitant atopic morbidities were described and compared. Continuous variables were compared using t-tests; dichotomous variables were compared by Pearson's chi-square. A logistic regression model was used to assess the associations between CU and atopy in a multivariate analysis. Interaction terms for statistically significant effect modifiers were added to the multivariate model when appropriate. All statistical tests performed were 2-sided; p -value < 0.05 was considered statistically significant.

The study included 11,271 patients with CU and 67,216 age- and sex-matched controls. CU patients were more likely to be females (66%) and had increased proportions of obesity (22.6% vs 18.8%, $p < 0.001$) and a higher Charlson's Comorbidity Index (2.03 ± 2.6 vs 0.95 ± 1.6 , $p < 0.001$) in comparison to controls. Additionally, CU patients were more likely to be of an Arab ethnicity (21.5% vs 20.9%, $p < 0.001$), and intermediate socioeconomic status (39.4% vs 37.6%, $p < 0.001$) compared to the control group. No other demographic differences were observed. Demographic characteristics of both groups are presented in Table 1.

Of 11,271 CU patients 1,215 (10.8%), 1,100 (9.8%), and 2,238 (19.9%) had had asthma, AD, or AR respectively versus 4,342 (6.5%), 2,471 (3.7%), and 6,807 (10.1%) of 67,216 controls, all significantly different. In a multivariate analysis CU was significantly associated with all of the investigated morbidities adjusting for age, sex, BMI, smoking status, and ethnicity (Table 2).

CU and atopy share some similarities. Atopy is associated with various autoimmune morbidities,¹⁻⁴ likewise CU.⁵ IgE sensitization is higher among CU patients compared to the general population, resembling many atopic conditions.⁶⁻¹⁰ Respectively, previous epidemiological observations reported an association between CU and atopy.¹¹⁻¹⁵ On the

other hand, other opposing epidemiological studies reported no such association.^{6,11}

Nevertheless, these inconsistent epidemiological studies were mostly limited by relying on small series, restricted pediatric populations, or applying non-validated questionnaires.

Moreover, some of the studies refer to urticaria diagnosis and not to CU explicitly. Thus our report augments the possibility of such an association. The association between CU and atopic disorders may reflect an aberrant crosstalk between T-helper cells and mast cells, an interaction which is not yet fully understood. For example, Shefler et al. reported that the activity of mast cells might be indirectly affected by remote T-cells.¹⁶ Perhaps delicate aberrations in this crosstalk may lead to cooccurrence of CU and atopy in the same patients.

Our study has some limitations. Case definition was strict and conservative with high specificity (4 couples of urticaria diagnoses, each recorded within a period of 6 weeks) thus may have led to an underestimation of the actual prevalence of CU in Israel. Specific screening tests such as peak flow meter, IgE sensitization, or prick tests were not a precondition to include the atopic diagnoses in our study and therefore overdiagnosis is possible and represents another limitation of our study. In light of this limitation we avoided the use of the term atopy for describing the investigated conditions rather than using the term atopic disorders. While not all asthma, AR, and AD in our study are truly atopic - i.e. IgE mediated, the extrapolation that most of them are atopic is reasonable. As in any cross-sectional study, incidence-prevalence bias and temporal bias are also potential limitations. In spite of these limitations the present study reveals important data regarding the association between CU and asthma, AD, and AR.

In conclusion, we observed an association between CU and asthma, AD, and AR. These observations may open new hatches in the understanding of the etiopathogenesis of CU and atopy, as well as impact the management of atopy in the setting of CU and vice versa.

Acknowledgments: None.

REFERENCES

1. Mittermann I, Aichberger KJ, Bänder R, et al. *Autoimmunity and Atopic Dermatitis*. Curr Opin Allergy Clin Immunol 2004; **4(5)**:367-71
2. Pedullá M, Fierro V, Papacčiuolo V, et al. *Atopy as a Risk Factor for Thyroid Autoimmunity in Children Affected by atopic Dermatitis*. J Eur Acad Dermatol Venereol 2014; **28(8)**:1057-60
3. Shah A. *The Pathologic and Clinical Intersection of Atopic and Autoimmune Disease*. Curr Allergy Asthma Rep 2012; **12(6)**:520-9
4. Rabin RL, Levinson AI. *The Nexus Between Atopic Disease and Autoimmunity: a Review of the Epidemiological and Mechanistic Literature*. Clin Exp Immunol 2008; **153(1)**:19-30
5. Confino-Cohen R, Chodick G, Shalev V, et al. *Chronic Urticaria and Autoimmunity: Associations Found in a Large Population Study*. J Allergy Clin Immunol 2012; **129(5)**:1307-13
6. Augéy F, Gunera-Saad N, Bensaid B, et al. *Chronic Spontaneous Urticaria Is Not an Allergic Disease*. Eur J Dermatol 2011; **21(3)**:349-53
7. Chang KL, Yang YH, Yu HH, et al. *Analysis of Serum Total IgE, Specific IgE and Eosinophils in Children With Acute and Chronic Urticaria*. J Microbiol Immunol Infect 2013; **46(1)**:53-8
8. Daschner A, Roderó M, De Frutos C, et al. *Chronic Urticaria Is Associated With a Differential Helminth-arthropod-related Atopy Phenotype*. J Dermatol 2010; **37(9)**:780-5

9. Ye YM, Hur GY, Park HJ, et al. *Association of Specific IgE to Staphylococcal Superantigens With the Phenotype of Chronic Urticaria*. J Korean Med Sci 2008; **23(5)**:845-51
10. Altrichter S, Peter HJ, Pisarevskaja D, et al. *IgE Mediated Autoallergy Against Thyroid Peroxidase - a Novel Pathomechanism of Chronic Spontaneous Urticaria?* PLoS One 2011; **6(4)**:e14794
11. Nassif A. *Is Chronic Urticaria an Atopic Condition?* Eur J Dermatol 2007; **17(6)**:545-6
12. Bingeors K, Svensson Å, Isacson D, Lindberg M. *Self-reported Lifetime Prevalence of Atopic Dermatitis and Comorbidity With Asthma and Eczema in Adulthood: a Population-based Cross-sectional Survey*. Acta Derm Venereol 2013 6; **93(4)**:438-41
13. Zuberbier T, Balke M, Worm M, et al. *Epidemiology of Urticaria: a Representative Cross-sectional Population Survey*. Clin Exp Dermatol 2010; **35(8)**:869-873
14. Olze H, Zuberbier T. *Comorbidities Between Nose and Skin Allergy*. Curr Opin Allergy Clin Immunol 2011; **11(5)**:457-63
15. Lee HC, Hong JB, Chu CY. *Chronic Idiopathic Urticaria in Taiwan: a Clinical Study of Demographics, Aggravating Factors, Laboratory Findings, Serum Autoreactivity and Treatment Response*. J Formos Med Assoc 2011; **110(3)**:175-82
16. Shefler I, Salamon P, Reshef T, et al. *T cell-induced Mast Cell Activation: a Role for Microparticles Released From Activated T cells*. J Immunol 2010; **185**:4206

Table 1. Baseline characteristics of the study population and controls

Age group (years)		Chronic urticaria n=11,271 n, (%)	Control group n=67,216 n, (%)	p-value
Age, mean (SD)		47.4 (22.1)	47.4 (21.9)	0.988
Sex	Male	3,811 (33.8)	22,805 (33.9)	0.863
	Female	7,450 (66.2)	44,411 (66.1)	
Socioeconomic status	Low	4,600 (40.8)	27,476 (40.9)	<0.001
	Intermediate	4,436 (39.4)	25,270 (37.6)	
	High	1,889 (16.8)	13,573 (20.2)	
Arab Ethnicity		2,421 (21.5)	14,033 (20.9)	<0.001
Charlson's Comorbidity Index score; mean (SD) *		2.03 (2.6)	0.95 (1.6)	<0.001
Smokers		1,754 (15.6)	9,987 (14.9)	0.05
Obesity		2,544 (22.6)	12,653 (18.8)	<0.001

*Age adjusted

Table 2. Multivariate logistic regression models* for the association between asthma, allergic rhinitis, and atopic dermatitis in study population (n= 78,487)

	Allergic Rhinitis			Atopic Dermatitis			Asthma		
	OR	95% confidence interval	<i>p</i> -value	OR	95% confidence interval	<i>p</i> -value	OR	95% confidence interval	<i>p</i> -value
Chronic urticaria	2.03	1.89-2.18	<0.001	2.77	2.48-3.09	<0.001	1.62	1.48-1.78	<0.001
Female sex	0.81	0.76-0.87	<0.001	1.02	0.89-3.09	0.807	0.82	0.75-0.90	<0.001
Age	1.00	1.00-1.00	0.099	0.99	0.98-0.99	<0.001	1.01	1.01-1.01	<0.001
BMI	0.99	0.99-0.99	0.005	0.99	0.98-1.00	0.118	1.02	1.01-1.03	<0.001
Current smoker	0.69	0.63-0.76	<0.001	0.86	0.74-1.01	0.058	1.13	1.01-1.26	0.035

*Adjusted for age, sex, BMI, smoking status, and ethnicity.

Statistically significant p-values are presented in **bold**.