
Role of contact sensitization in chronic urticaria

Laura Guerra, MD, Anthi Rogkakou, MD, Piera Massacane, MD, Cinzia Gamalero, BS,
Enrico Compalati, MD, Cristian Zanella, MD, Antonio Scordamaglia, MD,
Walter G. Canonica, MD, and Giovanni Passalacqua, MD
Genoa, Italy

We tested the hypothesis that contact allergy plays a role in chronic urticaria, and included the Italian series of patch tests in the diagnostic workup. Of 121 patients with chronic urticaria, 50 (41%) tested positive to contact allergens. In all patients, avoidance measures led to a complete remission within 1 month. We suggest that testing for contact sensitization can be helpful in the management of chronic urticaria. (J Am Acad Dermatol 2007;56:88-90.)

Chronic urticaria (CU) is clinically defined as the presence of wheals daily or almost daily for at least 6 weeks.¹ CU severely affects the quality of life of patients and can cause disability and distress.² In clinical practice, CU is one of the most common and challenging problems for general practitioners, dermatologist, and allergists. In fact, it can be provoked by a wide variety of different causes, or it may be the clinical presentation of systemic diseases.^{3,4} Thus CU often requires a detailed and time-consuming diagnostic procedure that includes screening for allergy, autoimmune diseases, parasitosis, malignancies, infections, and metabolic disorders. Finally, in many patients (up to 50% in some case series) the cause or pathogenic mechanism cannot be identified and the disease is then termed “chronic idiopathic urticaria.”

During recent years we have observed in our clinical practice that a not-negligible number of patients with CU were positive to patch tests, even without a clear clinical history or signs of contact dermatitis. Therefore we tested the hypothesis that contact sensitization to metals, additives, or related substances can sustain CU and, in turn, we verified whether appropriate avoidance exerts a beneficial effect. To do this, we included patch tests with the Italian standard series in the routine diagnostic workup for CU patients. A group of patients with allergic urticaria served as a control group.

Outpatients with CU seen at our unit during 2005 underwent a diagnostic procedure that included the following: clinical history; hemocytometry; erythrocyte sedimentation rate; blood chemistry; urinalysis; skin testing (prick-by-prick when appropriate) for foods; total IgE level, antibodies for viral hepatitis and HIV, thyroid hormones and autoantibodies, antinuclear antibodies; stool for parasites/eggs; breath test for *Helicobacter*, *Anisakis*- and *Echinococcus*-specific IgE; autologous serum skin test; and patch tests.⁵ Further diagnostic tests were also carried out when appropriate: C1q-inhibitor, complement, urine culture, thyroid or abdomen ultrasonography, chest radiography, urine electrophoresis, lymphocyte subpopulations, specific organ autoantibodies, and extractable nuclear antigens. Patch tests were carried out with the Gruppo Italiano Ricerca Dermatiti Contatto e Ambientali (GIRDCA) series including 39 “type IV” substances, belonging to the 4 main categories of metals, chemical compounds, cleaning agents, and cosmetics stabilizers/accelerators. The tests were performed with commercial diagnostics (Lofarma, SpA, Milan, Italy) and read at 2 and 4 days.⁶ A group of patients with urticaria due to food allergy/intolerance or drug reactions served as the control group.

Globally, 121 patients (28 men; mean age, 35 years; age range, 17-69 years) with CU were studied and patch tested. Their symptoms lasted between 3 and 24 months (mean, 6 months). All had been already treated with various antihistamines and systemic steroids, but they always relapsed when treatments were discontinued. Patch tests were negative in 71 patients. Among them, a disease associated with CU was identified in 50 patients (Table I). The appropriate treatment of thyroiditis or infections or diabetes led to remission in 39 of 50 patients, whereas the 6 patients referred to hematologists were lost to follow-up. In 21 subjects CU remained idiopathic. Patch tests with the GIRDCA series

From Allergy and Respiratory Diseases, Department of Internal Medicine, University of Genoa.

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Reprint requests: Giovanni Passalacqua, MD, Allergy & Respiratory Diseases, Dept of Internal Medicine, Pad. Maragliano, L.go R. Benzi 10, 16132 Genoa, Italy. E-mail: passalacqua@unige.it.

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Table I. Diagnostic results

Diagnosis	No. of patients	% Total	M/F (No.)	Details*	Patch test result [†]
<i>Helicobacter pylori</i>	14	11.0	3/11		Neg
Bacterial infection	10	8.2	2/8	Urinary tract, 8; chronic rhinosinusitis, 2	Neg
Hashimoto thyroiditis	7	5.8	2/5	Atrophic gastritis in 2 pts	Neg
<i>Anisakis</i> infestation	4	3.4	0/4		Neg
Diabetes mellitus	4	3.4	1/3		Neg
Immune, metabolic, or malignant disease	6	5.1	2/6	Multiple myeloma, 2; Waldenstrom macroglobulinemia, 1; common variable immunodeficiency, 1; hemochromatosis, 2	Neg
Autologous serum positivity	5	4.1	1/4		Neg
Idiopathic disease	21	17.4	10/11		Neg
Patch positive + other disease	3	2.9	1/2	Urinary infection, 1; diabetes, 2	Pos
Only patch positive	47	39.0	9/38	See Table II	Pos
Total	121	100.0	29/92		

*Numbers denote number of patients with diagnosis.

[†]Percentage of patients with negative patch test, 59%; testing positive, 41%.

Table II. Patch test results

Compound	No. of patients testing positive	M/F (No.)	Details
Metals	20	5/15	13 nickel, 6 cobalt + nickel 1 cobalt
Chemical	16	7/9	6 parabens, 3 colophony, 2 benzocaine, 1 thiuram mix, 1 bisulfites, 1 potassium dichromate
Cleaning agents/cosmetics	9	3/6	6 balsam of Peru, 1 fragrances mix 1 Kathon, 1 thimerosal
Stabilizers/accelerators	5	1/4	3 ethylenediamine 2 mercaptobenzothiazole

proved positive in 50 of 121 patients (41%), as shown in Table II, although none of the patients had actual signs of contact dermatitis. Of the 50 patients who tested positive, none had an urticarial response to patch tests, but 23 of them experienced an exacerbation of their urticaria. All patients with positive patch tests were prescribed appropriate avoidance measures for the sensitizing substances. In particular, patients with nickel sensitivity underwent a nickel-free diet⁵ for at least 8 weeks and nickel-free kettles and body products were also recommended. Of the 50 patch-test–positive patients, one had concomitant urinary infection and two had diabetes. These conditions were treated, before avoidance measures were prescribed, without benefit. On the contrary, in all 50 patients, avoidance measures led to remission between 10 days and 1 month. Patients with nickel sensitivity were subsequently allowed to ingest low amounts of nickel-containing foods after 8 weeks of a

totally nickel-free diet, and remission persisted. Five patients spontaneously ate larger amounts of the prohibited foods (eg, chocolate); a prompt relapse of urticaria occurred, which needed further weeks of elimination diet to be controlled. Eighty-one patients, matched for age and sex, with a clear diagnosis of urticaria due to food allergy/intolerance or drug adverse reaction, served as a control group. In none of these patients did patch tests prove positive.

The management of CU is a matter of debate among physicians and several diagnostic flow charts have been proposed.⁷ In general, patch tests for contact dermatitis are not recommended as an essential part of the diagnostic procedure, but our previous clinical observations suggested that contact allergy often plays a role in CU. The main finding of this study was that 41% of patients with CU had positive patch tests and that avoidance of the sensitizing substance was effective, as confirmed by

the remission of symptoms after avoidance. Metals were the most common sensitizing agents (20/50 patients), with nickel being frequently involved; in some cases, the intake of large amounts of nickel-containing food caused a relapse of urticaria. Contact dermatitis affects about 20% of the general population⁸; however, there has been little data, limited to nickel, on the relationship between contact allergens and chronic urticaria^{9,10} and the underlying mechanisms are unknown. We can hypothesize that small amounts of the substances (through the skin or the gut) are absorbed in the bloodstream over the long term and delivered to antigen-presenting cells in the skin, which provide the necessary signals for mast cell activation. Nonetheless, the reasons for a selective cutaneous localization of the reaction remain largely unclear. An interesting accessory finding of this study was that a cause or pathogenesis for CU could be identified in 79% of patients, thus showing that idiopathic urticaria occurs less frequently than commonly believed. In conclusion, we suggest that patch tests be included among the diagnostic procedures for CU since they allow effective diagnosis and treatment of a relevant number of patients.

REFERENCES

1. Greaves MW. Chronic urticaria. *J Allergy Clin Immunol* 2000; 105:664-72.
2. Staubach P, Eckhardt-Henn A, Dechene M, Vonend A, Metz M, Magerl M, et al. Quality of life in patients with chronic urticaria is differentially impaired and determined by psychiatric comorbidity. *Br J Dermatol* 2006;154:294-8.
3. Kaplan AP. Chronic urticaria: pathogenesis and treatment. *J Allergy Clin Immunol* 2004;114:465-74.
4. Sabroe RA, Fiebiger E, Francis DM. Classification of anti-FcepsilonRI and anti-IgE autoantibodies in chronic idiopathic urticaria and correlation with disease severity. *J Allergy Clin Immunol* 2002;110:492-9.
5. Uter W, Hegewald J, Aberer W, Ayala F, Bircher AJ, Brasch J, et al. The European standard series in 9 European countries, 2002/2003: first results of the European Surveillance System on Contact Allergies. *Contact Dermatitis* 2005;53: 136-45.
6. Von Krogh GV, Maibach HI. The contact urticaria syndrome: an updated review. *J Am Acad Dermatol* 1981;5:328-42.
7. Zuberbier T, Bindslev-Jensen C, Canonica W, Grattan CE, Greaves MW, Henz BM, et al. EAACI/GA2LEN/EDF guideline: management of urticaria. *Allergy* 2006;61:321-31.
8. Smart GA, Sherlock JC. Nickel in foods and the diet. *Food Addit Contam* 1987;4:61-71.
9. Abeck D, Traenckner I, Steinkraus V, Vieluf D, Ring J. Chronic urticaria due to nickel intake. *Acta Derm Venereol* 1993;73: 438-9.
10. Moneret-Vautrin DA. [Allergic and pseudo-allergic reactions to foods in chronic urticaria.] *Ann Dermatol Venereol* 2003; 130(Spec 1):1535-42. French.

CORRECTION

Resnik K. Subcutaneous sarcoidosis histopathologically manifested as fibrosing granulomatous panniculitis. *J Am Acad Dermatol* 2006;55:918-9.

In the letter above, Dr Resnik's e-mail address was misprinted. The correct e-mail address is kresnik@ameripath.com. We apologize to the author for the mistake.