

Impact of Contact Sensitization in Chronic Spontaneous Urticaria

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Abstract: *Introduction:* Patch testing is performed to diagnose allergic contact dermatitis to avoid exposure to the revealed contact allergens. Nevertheless, patch testing is not routinely performed in the evaluation of patients with chronic idiopathic (spontaneous) urticaria (CIU). The objective of this study was to determine the frequency of sensitization to patch test allergens in severe CIU and assess a role of the allergen avoidance in CIU remission. *Methods:* The cases of patients with severe CIU were retrospectively studied. The patients were patch tested using T.R.U.E. TEST. Three groups were studied: CIU with positive patch test group; CIU with negative patch test group and control group, which included the cases of not patch-tested patients with CIU. The groups were followed up monthly to assess changes in Chronic Urticaria Severity Score (CUSS) after allergen avoidance. *Results:* Forty-three subjects with severe CIU were patch tested. Nickel sulphate was positive in 4 (9.3%) cases, potassium dichromate in 2 (4.7%) cases, cobalt, balsam of Peru, paraphenylene diamine, fragrance mix and epoxy resin were positive in 1 (2.3%) case. Their baseline CUSS (5.4 ± 0.5) improved significantly after 1 month of allergen avoidance (3.2 ± 1.1 ; $P < 0.001$); but similar improvement of CUSS (5.3 ± 0.5) was seen in 34 patients with CIU with negative patch test (3.2 ± 1.3 ; $P < 0.001$) and in 49 patients with CIU of control group (5.2 ± 0.4 to 3.4 ± 1.3 ; $P < 0 < 0.001$) after 1 month. *Conclusions:* There is no relationship between avoidance of contact allergens and the course of CIU. **Key Indexing Terms:** Contact; Sensitization; TRUE TEST; Chronic; Urticaria. [Am J Med Sci 2011;341(3):202–206.]

Recurrent urticaria for more than 6 weeks is called chronic urticaria, and in the majority of cases, no exogenous cause is determined, and the condition is termed chronic idiopathic (spontaneous) urticaria (CIU).¹ The average CIU duration is 3 to 5 years, and factors associated with longer disease duration include the positivity of autologous serum skin test (ASST), disease severity and presence of angioedema.²

Patch testing is performed to diagnose allergic contact dermatitis to avoid exposure to the revealed contact allergens. Nevertheless, patch testing is not routinely performed in the evaluation of patients with CIU. In a recent study of 121 Italian patients with CIU, 50 (41%) tested positive to contact allergens.³ The authors reported complete remission of CIU within 1 month in all patients after contact allergen avoidance. Although the study presents interesting results, it has several significant limitations. First, no control group was used to exclude a spontaneous remission of CIU without relation to contact allergens avoidance. Second, none of the patients underwent rechallenge with the revealed contact allergen that really limits a relevance of an exacting allergen as a cause of

CIU. In another study (not listed in PubMed), 21 French patients suffering from CIU with a positive nickel sulfate patch test underwent a positive placebo-controlled oral challenge test with oral nickel pidolate. Fifteen of them had a positive placebo-controlled oral challenge test, whereas a low-nickel diet improved CIU clinical severity in 11 patients.⁴

There were other reports of CIU, which were subsequently found to be caused by common contact sensitizers such as nickel, chromates, cobalt, balsam of Peru, rubber compounds, etc.^{5–8} Although patch testing is not recommended by recent guidelines, it is being sporadically used for diagnostic investigation of urticaria.⁹ The aim of the study was to determine a relationship between the avoidance of contact allergens and the course of severe CIU.

PATIENTS AND METHODS

The cases of patients referred to the outpatient allergy clinic from Ashdod region (Israel) between March 2004 and December 2009 because of a diagnosis of CIU and/or angioedema at least 6-week duration were retrospectively collected. Only the subjects with CIU were included. Exclusion criteria were any type of physical urticaria, cholinergic urticaria, contact urticaria, food- and drug-induced urticaria and urticaria related to other autoimmune disorders.

We use T.R.U.E. TEST patch test (Mekos Laboratories ApS, Hillerød, Denmark) routinely in severe CIU since 2004, and if contact allergen sensitization is diagnosed, the patient undergoes a detailed oral and written instruction how to avoid the revealed allergens (eg., in the case of nickel sensitization, the patient is instructed how to avoid, eg, nickel items, and also is put on a low-nickel diet). Each patient with severe CIU is followed up monthly to assess any changes in their urticaria, while they are advised to use oral antihistaminic medication in maximal doses on a daily basis. We do not add systemic steroids or any immunomodulator to oral antihistaminic medications at the first visit. As part of the standard practice in our allergy clinic, all subjects had been informed about any risks involved with testing and written informed consent for allergologic workup (Patch test, skin prick test, ASST) had been obtained. Because patch testing and ASST are part of routine diagnostic practice in our clinic, further ethical approval was not required. The following data were collected:

1. Demographic data, CIU Severity Score (CUSS).
2. Results of skin tests to common food allergens, ASST, if done.
3. Laboratory workup results: liver and renal function tests, complete blood count, erythrocyte sedimentation rate, stool analysis for parasite ova, thyroid function tests, antinuclear antibodies, antithyroglobulin and antiperoxidase antibodies, C3, C4 and total IgE.
4. Results of T.R.U.E. TEST patch test and contact urticaria test.

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Clinical Evaluation of Chronic Urticaria

Clinical and laboratory evaluation and classification of chronic urticaria were performed according to the EAACI/GA²LEN/EDF guidelines.¹⁰ Cold urticaria was excluded by application of an ice cube to the skin of the forearm for 20 minutes and checking for wheal appearance within 15 minutes at the test site.

Cholinergic urticaria was excluded after emergence of pruritic erythematous wheals within 5 to 15 minutes of a hot shower. Dermographism was assessed using firm stroking of the skin by a dermatographometer with a pressure of 4900 g/cm² and induction of linear itchy wheals within several minutes.

Solar urticaria was confirmed by exposure to natural sunlight. Screening for food allergy was investigated by means of medical history, skin tests to food allergens (ALK Abello, ALK, Hørsholm, Denmark) and an elimination diet for 3 weeks. Skin prick test was performed with a panel of 24 commonly consumed foods in Israel (using ALK-Abello allergens)—cows milk, egg white, peanut, soybean, hazelnut, almond, sesame, pecan nut, mixed fish, tuna, mixed shellfish, celery, wheat, tomato, beef, chicken meat, potato, orange, pea, mushroom, apple, peach, mango, kiwi and latex. When drug allergy was suspected, the relevant drug was discontinued or replaced with a chemically unrelated drug.

ASST was performed with 50 μ L of the patient's undiluted serum after blood centrifugation, which was then injected intradermally into the volar aspect of the forearm together with simultaneously injected controls, including saline and 10 μ g/mL histamine. The mean diameters of the wheals were measured at 30 minutes. The test was considered to be positive if the serum-injected site manifested a wheal with a diameter at least 1.5 mm greater than that of the saline.

Assessment of Urticaria Severity

CUSS, a simple semiquantitative assessment of disease activity was calculated as the sum of the number of wheals and itching—graded from 0 (none) to 3 (severe) according to EAACI/GA²LEN/EDF guidelines.¹⁰

Patch Testing

Usually, we used patch test in patients with CIU who had CUSS greater than 5 (severe CIU). The subjects were patch tested using T.R.U.E. TEST, which was applied to their upper back. The strips were removed after 2 days, and the reading was recorded after 30 minutes. The sites were reexamined after 4 days. The results were evaluated according to the standard scoring system recommended by the International Contact Dermatitis Research Group guidelines.¹¹

Test Performed to Detect Contact Urticaria

A 20-minute closed patch test was performed using IQ Chambers (Chemotechnique Diagnostics, Vellinge, Sweden) and the sensitizing contact allergens revealed by T.R.U.E. TEST. Allergens (European standard series) for a 20-minute closed patch test were purchased from Chemotechnique Diagnostics (Vellinge, Sweden). The test substances were undiluted and applied on the antecubital area of the arms. The occlusion time was 20 minutes. The tests were read at 20, 40 and 60 minutes after removal.

Control Group

Control group included the cases of patients with severe CIU from the same outpatient allergy clinic who did not undergo patch testing attributable to several reasons.

Statistical Analysis

Results are presented as mean $\pm$ standard deviation. Descriptive statistics was used to describe the demographic

No.	Sex	Age (yr)	CIU duration (m)	ASST	Patch test results (T.R.U.E. TEST)	Contact urticaria test results (chemotechnique)	CUSS at patch testing	CUSS after allergen avoidance	CIU treatment
1	Male	35	5	—	Nickel sulphate	Negative	5	5	Fexofenadine (180 mg qd)
2	Male	42	11	+	Epoxy resin	Negative	6	3	Fexofenadine (120 mg bid)
3	Female	29	4	+	Fragrance mix	Negative	5	2	Fexofenadine (180 mg qd)
4	Female	47	9	—	Balsam of Peru	Negative	5	2	Fexofenadine (180 mg qd)
5	Female	51	6	+	Nickel sulphate and cobalt	Negative	5	4	Cetirizine (10 mg qd)
6	Male	48	4	—	Potassium dichromate	Negative	6	4	Fexofenadine (180 mg qd)
7	Female	39	7	—	Paraphenylenediamine	Negative	6	2	Fexofenadine (180 mg qd)
8	Female	21	5	+	Nickel sulphate	Negative	6	4	Desloratadine (5 mg bid)
9	Male	53	4	—	Potassium dichromate	Negative	5	3	Fexofenadine (180 mg qd)

Bid, twice daily; qd, every day; CIU, chronic idiopathic urticaria; CUSS, Chronic Urticaria Severity Score; ASST, autologous serum skin test.

TABLE 2. Demographics and CUSS in study groups

Characteristics	CIU with positive patch test (N = 9)	CIU with negative patch test (N = 34)	control group (CIU without patch test; N = 49)	<i>P</i> ^a	<i>P</i> ^b	<i>P</i> ^c
Sex: female, n (%)	5 (55.6)	36 (63.2)	28 (57.1)	0.59	0.34	0.82
Age (yr), mean ± SD	40.5 ± 10.7	43.8 ± 11.3	41.3 ± 12.1	0.93	0.68	0.89
CIU duration (mo), mean ± SD	6.1 ± 2.5	5.8 ± 3.2	6.7 ± 3.8	0.19	0.48	0.31
ASST positive, n (%)	4 (44.4)	13 (38.2)	21 (42.8)	0.24	0.57	0.94
Baseline CUSS, mean ± SD	5.4 ± 0.5	5.3 ± 0.5	5.2 ± 0.4	0.81	0.08	0.11
CUSS after 1 mo, mean ± SD	3.2 ± 1.1	3.2 ± 1.3	3.4 ± 1.3	0.79	0.26	0.49

^a *P* value between CIU with positive patch test and CIU with negative patch test groups.

^b *P* value between CIU with positive patch test and control groups.

^c *P* value between CIU with negative patch test and control groups.

CIU, chronic idiopathic urticaria.

data and CUSS. Comparability of demographic and baseline characteristics among study groups was assessed using Student *t* test, and a *P* value <0.05 was considered significant. All statistical analyses were performed using the software Statistica 6 (StatSoft, Inc. Tulsa, OK).

RESULTS

During the study period, 447 patients with CIU were referred to our allergy clinic. Ninety-two (20.6%) patients were diagnosed to have severe spontaneous CIU, and 43 (46.7%) of them underwent patch testing using T.R.U.E. TEST. Forty-nine (53.3%) patients with CIU declined to undergo a patch test.

Demographics and baseline characteristics of patients with severe CIU are presented in Table 1. None of the 43 patch-tested patients with CIU had experienced contact dermatitis in their past. None of them had any surgical implants, pacemaker or dental braces.

An ASST was performed in 35 patients, and the test was positive in 19 (54.2%) of them. Of the 43 cases of CIU, 9

(20.9%) patients showed positive reactions to the patch test allergens. Nickel sulphate was the most common allergen: 4 (9.3%) of 43 patch-tested cases. All the nickel-positive patients had no previous history of reacting to nickel containing manufactured goods. Potassium dichromate was positive in 2 (4.7%) cases. Cobalt, balsam of Peru, paraphenylene diamine, fragrance mix and epoxy resin were positive in 1 (2.3%) each. Only 1 patient showed contact sensitivity to multiple allergens (nickel sulphate and paraphenylene diamine) in this series. Four (44.4%) patients were ASST positive, and 5 (55.6%) were ASST negative (Table 2). None of the patch-tested patients with CIU had a positive skin prick test to food allergens.

In 9 patients with CIU with positive patch test, baseline CUSS (5.4 ± 0.5) improved significantly after 1 month of allergen avoidance (3.2 ± 1.1; *P* < 0.001); but, similar improvement of baseline CUSS (5.3 ± 0.5) was seen in 34 patients with CIU with negative patch test (3.2 ± 1.3; *P* < 0.001) and in 49 patients with CIU of control group (5.2 ± 0.4 to 3.4 ± 1.3; *P* < 0 < 0.001) after 1 month (Figure 1).

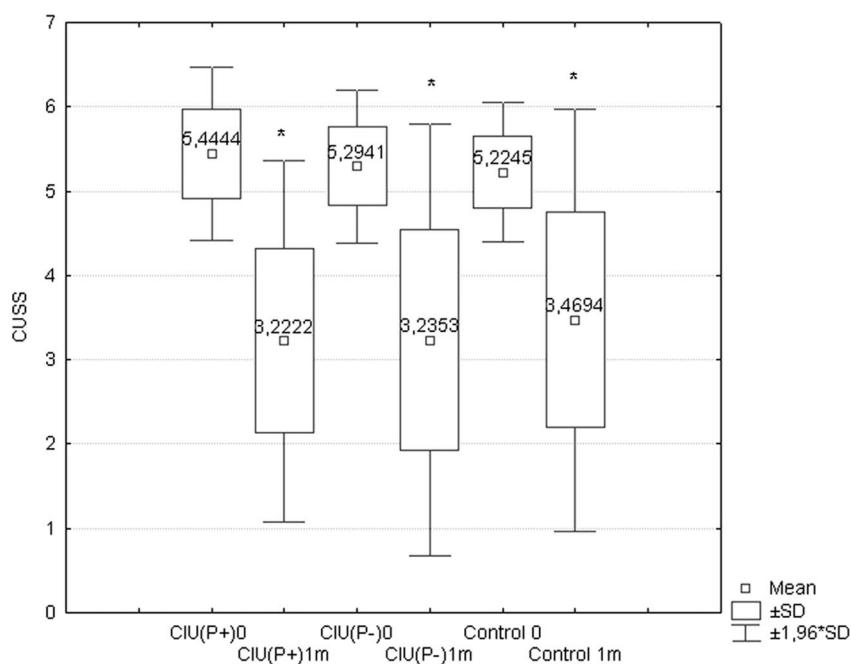


FIGURE 1. CUSS changes in study groups. CIU (P+), chronic urticaria patients with positive patch test; CIU (P-), chronic urticaria patients with negative patch test; Control, chronic urticaria patients not patch tested; 0, baseline, 1 m, 1 month. **P* < 0.001.

DISCUSSION

Recent studies have suggested that contact allergen sensitization might have some role in the pathogenesis of CIU.^{3,4,12} In our study, 43 patients with severe CIU underwent patch testing, and 9 of them (both ASST positive and ASST negative) showed positive reactions to various allergens of T.R.U.E. TEST series. Nevertheless, we cannot judge whether these sensitizations are relevant, as a significant proportion of healthy general population is usually sensitized to one of the common allergens.¹³ These common allergens may possibly cause asymptomatic sensitization in general population^{14,15} and in some of our patients with CIU. Furthermore, the prevalence of sensitization to T.R.U.E. TEST patch test allergens in our patients are in general agreement with the previously published report on sensitization to T.R.U.E. TEST patch test allergens from the same region of Israel.¹⁶ Although Li and Wang¹⁷ revealed positive patch test reactions to various standard series allergens and aeroallergens in 52.4% of their patients with nonatopic chronic urticaria, it is well known that patients with allergic skin diseases are prone to develop sensitizations to various allergens, which are demonstrable on patch test.

CIU is now considered as an autoimmune disease, for which autoimmune basis has been evolved from the observations of increased prevalence of several autoantibodies¹⁸ in subjects with CIU and human leucocyte antigen-DR associations.¹⁹ Moreover, a significant number of subjects with CIU has serum IgG autoantibodies that target the IgE receptor alpha subunit (30%) or, less commonly, surface-bound IgE (10%).¹⁸ Subjects with autoimmune CIU are reported to have increased disease severity.^{19–21} An association of several contact allergens with urticaria is well recognized in contact urticaria syndrome (CUS).²² Since then, numerous reports of CUS caused by a variety of compounds, such as foods, preservatives, fragrances, plant and animal products and metals, continue to be reported. CUS includes 2 main categories: nonimmunologic CUS and immunologic CUS.²³ The mechanism of nonimmunologic CUS is incompletely understood, although evidence suggests that the disease may be mediated by prostaglandins²⁴ and inflammasomes.²⁵ Immunologic CUS is a type I hypersensitivity reaction mediated by IgE antibodies specific to the eliciting allergen and is less common in clinical practice than nonimmunologic CUS.^{26,27} Our patients with CIU with a positive patch test underwent a 20-minute closed patch test with the relevant allergen, and no 1 case of either nonimmunologic or immunologic CUS was revealed. Skin prick test to common food allergens and latex was also negative, which reliably excludes immunological contact urticaria caused by immediate-type hypersensitivity.

In summary, an association of spontaneous CIU and contact allergy sensitization remains questionable, and results of our study do not support the previous observations that contact sensitization has some role in CIU.^{3,4,12} Moreover, there was no relationship between avoidance of contact allergens and the course of CIU. The divergence of our results with the previous ones may be partly related to the fact that we patch tested only the subjects with severe CIU, whereas the other studies tested patients with CIU with a large spectrum of CIU severity.

We understand that the study has several limitations, although the main limitation is related to its retrospective nature with possible recording bias. Second, no controlled challenge test was done, which is important for confirmation of positive patch test relevance and implication of an exacting allergen as a cause of CIU.²⁸ In addition, we should assume that it is possible that the percentage of positive patch tests in

patients with CIU is similar to that in normal controls, therefore false positivity is possible.

Nevertheless, an avoidance of the revealed contact allergen was associated with the comparable improvement of CIU severity after 1 month, as was observed in both patch-tested negative CIU and not patch-tested control groups. Hence, we can speculate that an observed improvement of CIU severity was associated with the spontaneous remission of CIU and was not related to contact allergen avoidance. In general, such spontaneous remission of CIU is reasonable and well recognized from several epidemiological studies.^{2,29,30}

In conclusion, we can state that according to this study, patch tests are irrelevant in CIU. Well-designed prospective studies with controlled challenge test are needed to clarify a role of contact allergens in spontaneous CIU.

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