

Evaluation of Patch Test Reactivities in Patients With Chronic Idiopathic Urticaria

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Chronic urticaria (CU) is clinically defined as the daily or almost daily presence of wheals on the skin for at least 6 weeks.¹ <http://www.sciencedirect.com/science/article/pii/S019096220602250X#bib1> Chronic urticaria severely affects patients' quality of life and can cause emotional disability and distress.² <http://www.sciencedirect.com/science/article/pii/S019096220602250X#bib2> In clinical practice, CU is one of the most common and challenging conditions for general practitioners, dermatologists, and allergists. It can be provoked by a wide variety of different causes or may be the clinical presentation of certain systemic diseases^{3,4}; thus, CU often requires a detailed and time-consuming diagnostic procedure that includes screening for allergies, autoimmune diseases, parasites, malignancies, infections, and metabolic disorders.^{5,6} In many patients (up to 50% in some case series), the cause or pathogenic mechanism cannot be identified, and the disease is then classified as chronic idiopathic urticaria (CIU).⁷

It has previously been shown that contact sensitization could have some relation with CIU,⁸ which was further explored in this study. This study sought to evaluate if contact allergy may play a role in disease development in CIU patients in Saudi Arabia and if patch testing should be routinely performed for CIU patients to determine if any allergens can be avoided.

Methods

This prospective study was conducted at the King Khalid University Hospital Allergy Clinic (Riyadh, Saudi Arabia) in patients aged 18 to 60 years who had CU for more than 6 weeks. It was a clinic-based study conducted over a period of 2 years (March 2010 to February 2012). The study protocol was approved by the local ethics committee at King Khalid University Hospital. Valid written consent was obtained from each patient.

Patients were excluded if they had CU caused by physical factors (eg, hot or cold temperature, water, physical contact) or drug reactions that were possible causative factors or if they had taken oral prednisolone or other oral immunosuppressive drugs (eg, azathioprine, cyclosporine) in the last month. However, patients taking antihistamines were not excluded because it was impossible for the patients to discontinue their urticaria treatment. Other exclusion criteria included CU associated with any systemic disease, thyroid disease, diabetes mellitus, autoimmune disorder, or atopic dermatitis. Pregnant and lactating women were not included in this study.

All new adult CU patients (ie, disease duration >6 weeks) were worked up using the routine diagnostic tests that are typically performed for any new CU patient, including complete blood cell count with differential, erythrocyte sedimentation rate, liver function tests, urine analysis, and hepatitis B and C screenings. Further diagnostic tests also were carried out when appropriate according to the patient's history and physical examination, including levels of urea, electrolytes, thyrotropin, thyroid antibodies (antithyroglobulin and antimicrosomal), and antinuclear antibodies, as well as a *Helicobacter pylori* test.

All of the patients enrolled in the study were evaluated by skin prick testing to establish the link between CU and its cause. Patch testing was performed in patients who were negative on skin prick testing.

Skin Prick Testing

All patients were advised to temporarily discontinue the use of antihistamines and corticosteroids 5 to 6 days prior to testing. To assess the presence of allergen-specific IgE antibodies, skin prick testing is preferred because it is more sensitive and specific, is simple to use, is inexpensive, and is not associated with any complications.⁹

Patch Testing

Patch tests were carried out using a ready-to-use epicutaneous patch test system for the diagnosis of allergic contact dermatitis (ACD).¹⁰ A European standard series was used with the addition of 4 allergens of local relevance: black seed oil, local perfume mix, henna, and myrrh (a topical herbal medicine used to promote healing). Patients with a negative skin prick test who had a positive patch test were enrolled in an allergen-avoidance program to avoid the offending allergen for 8 weeks.

Assessment of Improvement

Assessment of urticaria severity using the Chronic Urticaria Severity Score (CUSS), a simple semiquantitative assessment of disease activity, was calculated as the sum of the number of wheals and the degree of itch severity graded from 0 (none) to 3 (severe), according to the guidelines established by the Dermatology Section of the European Academy of Allergology and Clinical Immunology, the Global Allergy and Asthma European Network, the European Dermatology Forum, and the World Allergy Organization.¹¹ The avoidance group of patients was assessed at baseline and after 1 month to evaluate changes in their CUSS after allergen avoidance for 8 weeks.

Statistical Analysis

All of the statistical analyses were carried out using SPSS software version 16. Results were presented as the median with the range or the mean (SD). Descriptive statistics were used to describe the demographic data. The comparability of demographic and baseline characteristics

among CIU patients was assessed using the Student *t* test, and $P < .05$ was considered statistically significant.

Results

During the study period, a total of 120 CU patients were seen at the clinic. Ninety-three patients with CU met our selection criteria (77.5%) and were enrolled in the study. The mean age (SD) of the patients was 34.7 (12.4) years. Women comprised 68.8% (64/93) of the study population (Table 1).

Table 1.

General Characteristics of Chronic Idiopathic Urticaria Patients (N=93)

Characteristic	Participant Data ^a
Mean age (SD), y	34.7 (12.4)
Patient age, n (%)	
≤30 y	35 (37.6)
31–45 y	31 (33.3)
>45 y	16 (17.2)
Sex, n (%)	
Female	64 (68.8)
Male	29 (31.2)
Median disease duration (range), y	4 (0.6–20.0)
Disease duration, n (%)	
<1 y	12 (12.9)
1–5 y	42 (45.2)
>5 y	25 (26.9)
Employment status, n (%)	
Employed	22 (23.7)
Unemployed	50 (53.8)
Severity of symptoms, n (%)	
Very severe	25 (26.9)
Severe	50 (53.8)
Moderate to mild	1 (1.0)

^aValues for all characteristics do not equal 93, as data for all patients was not available.

The duration of urticaria ranged from 0.6 to 20 years, with a median duration of 4 years. Approximately half of the patients (50/93) experienced severe symptoms of urticaria, but only 26.9% (25/93) had graded their urticaria as very severe.

Negative results from the skin prick test were reported in 62.4% (58/93) of patients and were subsequently patch tested. These patients also had no other etiologic factors (eg, infection;

thyroid, autoimmune, or metabolic disease). Patients who had positive skin prick test results (35/93 [37.6%]) were not considered to be cases of CIU, according to diagnostic recommendations.¹² Of the 58 CIU patients who were patch tested, 31 (53.4%) had positive results and 27 (46.5%) had negative results to both skin prick and patch tests (Figure).



Univariate analysis revealed significant associations between age, gender, and duration of urticaria and patch test positivity (χ^2 test, $P<.05$). Twenty of 31 (64.5%) patch test–positive patients were aged 30 to 45 years. Positive patch test results were observed in 31 of 43 female patients (72.1%; $P<.001$). Of the patch test–positive patients, disease duration was greater than 5 years in 16 of 31 patients (51.6%).

Of the 31 patients with positive patch tests, there were 20 positive reactions to nickel, 6 to formaldehyde, 4 to phenylenediamine, 3 to cobalt, and 3 to a fragrance mix (Table 2). Some patients showed patch test reactivity to more than 1 allergen concomitantly. Overall, these 31 patients had positive reactions to 16 allergens. None of the patients showed actual signs of contact dermatitis (Table 2).

Table 2. Patch Test Results in Patients With Chronic Idiopathic Urticaria (n=31) ^a		
Compound	No. of Patients Testing Positive	Details
Metals	20	Nickel (n=20), cobalt (n=3), potassium dichromate (n=1)
Cleaning agents/ cosmetics	15	Formaldehyde (n=6), fragrance mix (n=3), isothiazolinone (n=2), thiomersal (n=2), balsam of Peru (n=1), isothiazolinone (n=1)
Chemicals	10	Phenylenediamine (n=4), rosin (n=2), benzocaine (n=1), parabens (n=1), thiram mix (n=1)
Stabilizers	4	Ethylhexylamine (n=2), mercaptobenzothiazole (n=2)

^aEight patients who had a negative skin prick test underwent patch testing. Of them, 31 had positive patch test results. Some patients showed patch test positivity to >1 allergen concomitantly.

Of the 31 patch test–positive patients, 10 were enrolled but only 8 (25.8%) agreed to take appropriate avoidance measures for the sensitizing substances; 5 (62.5%) showed excellent improvement in their baseline symptoms at a 1-month follow-up visit.

Comment

Chronic idiopathic urticaria is the diagnosis given when urticarial vasculitis, physical urticaria, and all other possible etiologic factors have been excluded in patients with CU. Our study was designed to assess patch test reactivity in patients with CU without any identifiable systemic etiologic factor after detailed laboratory testing and negative skin prick tests.

Chronic idiopathic urticaria can be an extremely disabling and difficult-to-treat condition. Because the cause is unknown, the management of CIU often is frustrating. The efficacy of performing patch tests in CIU has not yet been proven, as there are conflicting results regarding the role of contact sensitization in CIU. Prior studies in this field have shown that contact allergy can play a role in the etiopathogenesis of CU; these findings have stimulated new approaches for investigation of CIU.^{8,12} There were no details of how a common allergen such as nickel was avoided, which caused remission in the majority of patch test–positive patients.

Patch testing is commonly performed to diagnose ACD, and if contact allergens are found via patch testing, patients can often be cured of their dermatitis by avoiding these agents. However, patch testing is not routinely performed in the evaluation of patients with CIU. It is a relatively inexpensive and safe procedure to determine a causal link between sensitization to a specific agent and ACD. In patch test clinics, agents often are tested in standard and screening series. Sensitization that is not suspected from the patient's history and/or clinical examination can be detected in this manner. Requirements for the inclusion of a chemical in a standard series have been formulated by Bruze et al.¹³ In addition, ready-to-use materials relevant to the specific leisure activities and working conditions also can be selected for patch testing.

A study conducted in Saudi Arabia showed that the European standard series is suitable for patch testing patients in this community¹⁴; however, 3 allergens of local relevance were added in our study: black seed oil, local perfume mix, and henna. Moreover, in our study we added a local allergen known as myrrh, which is a topical herbal medicine used to promote healing that has been reported to cause ACD in some cases.¹⁵ We sought to determine if contact allergens can be identified with patch testing in patients with CU and if avoiding these contact allergens would resolve the CU.

Urticaria was once considered an IgE-mediated hypersensitivity reaction, but recent studies have demonstrated the existence of different subgroups of urticaria, some with an autoimmune

mechanism.^{1-4,11} In CU, skin prick tests are recommended for etiologic workup, while patch testing generally is not recommended.¹⁶

It has been observed in clinical practice that a substantial number of patients with CU are positive to patch tests, even without a clear clinical history or signs of contact dermatitis.¹⁷ In 2007, Guerra et al¹⁷ reported that of 121 patients with CU, 50 (41.3%) tested positive for contact allergens. In all of the patch test–positive patients, avoidance measures led to complete remission within 10 days to 1 month. Therefore, this result suggested that testing for contact sensitization could be helpful in the management of CU. Patients with nickel sensitivity were subsequently allowed to ingest small amounts of nickel-containing foods after 8 weeks of a completely nickel-free diet, and remission persisted.¹⁷

Contact dermatitis affects approximately 20% of the general population¹⁸; however, there has been little investigation (limited to nickel) into the relationship between contact allergens and CU,^{19,20} and the underlying mechanisms of the disease are unknown. It has been hypothesized that small amounts of the substances are absorbed through the skin or the digestive tract into the bloodstream over the long-term and are delivered to antigen-presenting cells in the skin, which provide the necessary signals for mast cell activation. Nonetheless, the reasons for a selectively cutaneous localization of the reaction remain largely unclear.

Management of CU is debated among physicians, and several diagnostic flowcharts have been proposed.^{1,2} In general, patch tests for contact dermatitis are not recommended as a fundamental part of the diagnostic procedure, but Guerra et al¹⁷ suggested that contact allergy often plays a role in CU.

There have been inadequate reports of CU found to be caused by common contact sensitizers.²¹⁻²⁴ Interestingly, no signs of contact allergy were demonstrated in CU patients before urticarial attack.

Our findings supported our patient selection criteria and also confirmed that contact sensitization may be one of the many possible mechanisms involved in the etiology of CU. Urticaria may have a delayed-type hypersensitivity reaction element, and patients with CU without an obvious causal factor can have positive patch test results.

The role of contact sensitization in CU has not yet been established, as another study showed no relationship between avoidance of contact allergens and the course of CIU.²⁵ In that study, patients with severe CIU who previously had been patch tested were retrospectively studied. Three groups were studied: CIU patients with positive patch tests; CIU patients with negative patch tests; and a control group, which included patients with CIU who had not been patch tested. The groups were followed monthly to assess changes in CUSS after allergen avoidance.

Forty-three patients with severe CIU were patch tested. Nickel sulfate testing was positive in 4 cases (9.3%); potassium dichromate testing was positive in 2 cases (4.7%); and cobalt, balsam of Peru, paraphenylenediamine, fragrance mix, and epoxy resin testing were positive in 1 case (2.3%) each. The mean (SD) baseline CUSS score (5.4 [0.5]) significantly improved after 1 month of allergen avoidance (3.2 [1.1]; $P < .001$); however, similar improvement in CUSS was observed in 34 patients with CIU with negative patch test results (5.3 [0.5] to 3.2 [1.3]; $P < .001$) and in 49 patients with CIU in the control group after 1 month (5.2 [0.4] to 3.4 [1.3]; $P < .001$).²⁵

The main findings of our study were that 53.4% of patients with CIU had positive patch test results and that avoidance of the sensitizing substance was effective in 5 of 8 patients who completed an avoidance program. Almost all of the patients showed notable remission of symptoms after limiting their exposure to the offending allergens. This study clearly showed that a cause or pathogenesis for CIU could be identified, thus showing that CIU occurs less frequently than is usually assumed.

Our study had limitations. The first is our lack of a controlled challenge test, which is important to confirm an allergen as a cause of CIU.²⁶ Nonetheless, avoidance of the revealed contact allergen was associated with comparable improvement of CIU severity after 1 month in 5 of 8 patients, though such measures were not tested in all 31 of 58 CIU patients who had positive patch test results.

Conclusion

We propose that patch tests should be performed while investigating CU because they give effective diagnostic and therapeutic results in a substantial number of patients. Urticaria, or at least a subgroup of the disease, may have a delayed-type reaction element, which may explain the disease etiology for many CIU patients. Patients with CU without a detectable underlying etiologic factor can have positive patch test results.

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