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Role of Patch Test in the Etiological Diagnosis of Chronic Urticaria

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ABSTRACT
Chronic urticaria is one of the enigmas in dermatology and exact etiology is controversial. Chronic urticaria can be ascribed to autoimmunity, reactions to food additives and illness including chronic infection, however approximately 50% of cases still remain unexplained. Even extensive panel of screening investigations added little to the diagnosis of chronic urticaria. Contact sensitization may play a role in the etiopathogenesis of chronic urticaria. Interestingly, many patients of chronic urticaria do not exhibit the physical signs for contact allergy. Patch test for contact sensitization can be helpful in the management of chronic urticaria. The present study evaluated the role of patch testing for the etiological diagnosis of chronic urticaria.
Material and Methods: *This study recruited 100 patients with the clinical diagnosis of chronic urticaria, attending the outdoor patient department, with exclusion of children, pregnant and lactating mothers, patients of acute urticaria, urticarial vasculitis, SLE, and on immunosuppressive drugs. Patients were patch tested with Indian Standard Series allergens approved by Contact and Occupational Dermatitis Forum of India.*
Results: *We observed positive patch test reactions for various allergens in 32% of chronic urticaria patients. There was female preponderance with 55% of the patients. Majority of the patients (34%) were in the age group of 41-50 years. There was a wide range of duration of urticaria from 1.5 months to 360 months (30 years). Most of the patients (29%) presented to us within 7 months to 1 year duration. Nickel was the most common allergen (24%), followed by fragrance mix (12%). Contact sensitivity to Paraphenylenediamine (PPD) and myroxylon pereire resin were found in 2% patients each and epoxy resin; neomycin, cobalt, nitrofurazone, 2-mercaptobenzothiazole, benzocaine and thiuram mix in 1% each. Eighteen patients (18%) had positive reactions to a single allergen, 12% patient revealed sensitivity to two allergens and 2% patients had positive reactions to three allergens.*
Conclusion: *Patch test, which is originally used for the etiological diagnosis of contact dermatitis, can be employed to know the cause of chronic urticaria, being safe, simple, inexpensive and reasonably sensitive.*
Keywords: *chronic urticaria, angioedema, patch test, sensitizers, contact dermatitis.*

Introduction

Urticaria is a spectrum of manifestations ranging from superficial pink, itchy weals in the upper dermis merging with angioedema of the subcutaneous and submucosal tissues. In 1769, William Cullen introduced the word "urticaria". It affects 15-25% of people at least once in their life time[1] . Although it may occur at any age, it is most frequent in the age group of 20-40 years [2].

Clinically urticaria is characterized by pruritic, pink-to-red oedematous lesions (wheals) that often have pale centre with variable size and shape ranging from a few millimetres to several centimetres and may be round, or form rings, a map-like pattern or giant patches. They are characterized by fleeting nature and usually last from 1-24 hours. Approximately 40% of patients with urticaria also experience angioedema.

Urticaria is a type-1 hypersensitivity state (Coombs and Gell) triggered by a polyvalent antigen bridging two specific IgE molecules that are bound to mast cells or basophils, leading to release of histamine and other mediators like bradykinin, prostaglandin E1 and E2 [3]. Mast cells the primary effector cells in urticaria are widely distributed in the skin, mucosa and other areas of the body and have high-affinity immunoglobulin E (IgE) receptors. Mast cell degranulation leads to the rapid release of various inflammatory mediators, such as histamine, leukotrienes and prostaglandins, which, in turn, cause vasodilatation and leakage of plasma in the skin. There is also a more delayed (4–8 hour) secretion of inflammatory cytokines e.g. tumor necrosis factor (TNF), interleukin (IL) 4 and 5, which potentially lead to further inflammatory responses and longer-lasting lesions [4,5].

Any pattern of recurrent urticaria occurring at least twice a week for at least 6 weeks is called chronic urticaria [6]. Allergenic triggers can be identified in up to 60-80% of acute urticaria cases, [2] while in chronic urticaria the cause may not be found in more than three-fourth of the cases [3].

Several recent studies have shown that contact allergy can play a role in the etiopathogenesis of chronic urticaria [2,7]. In some patients with chronic urticaria, a unique pathway is activated whereby exposure to an allergen stimulates T-cell production of histamine releasing factors (HRFs), which represent a heterogeneous group of cytokines. These HRFs subsequently bind to mast cell or basophil receptors to initiate histamine release, hence explaining the role of contact sensitization in chronic urticaria [8]. Furthermore, it is hypothesized that HRFs are involved in the immunologic pathway by which contact allergens produce a type IV, T cell-mediated urticaria. As with allergic contact dermatitis, allergens absorbed through the skin or systemically are delivered to antigen-presenting cells, with subsequent activation of T cells. Here, however, the pathways of allergic contact dermatitis and allergic contact urticaria diverge. In some patients with chronic urticaria, it is proposed that an alternative pathway is activated whereby exposure to an allergen stimulates T-cell production of HRFs, which subsequently bind to mast cell or basophil receptors to initiate histamine release [9]. The rarity of this phenomenon may be attributed to a high allergen threshold for T-cell-mediated HRFs release. Alternatively, mast cell degranulation may require activation of a high threshold number of HRF receptors. In some patients, the combination of multiple contact and systemic allergens may act synergistically to surpass this threshold, presenting clinically as urticaria [8].

Material and Methods

This study evaluated the patch test in 100 patients, attending the outdoor patient department of Dermatology, Venereology and Leprosy at Indira Gandhi Medical College, Shimla with the clinical diagnosis of chronic urticaria. Adult patients of chronic urticaria were studied, excluding children, pregnant and lactating mothers, patients of acute urticaria, urticarial vasculitis, SLE, and on immunosuppressive drugs. All study group patients were patch tested with Indian Standard Series allergens approved by Contact and Occupational Dermatitis Forum of India.

Clinical details regarding age, gender, age of onset and duration of urticaria, frequency of episodes, and

average duration of remission, systemic manifestations, number and distribution of individual urticarial wheals or presence of angioedema and urticaria activity score were recorded on a pre-designed proforma. Urticaria activity score was calculated as described by Sabroe et al(10), which describes pruritus severity score as no pruritus /absent=0 , present but not disturbing=1 , disturbing but not hampering daytime activity or sleep=2 , hampering daytime activity or sleep=3 .

Wheal score (average no. of weals in 24 hours): Less than 10 wheals=1, 10-50 wheals=2, >50 wheals=3, and if involving almost whole body=4.

Urticaria activity score is calculated by addition of pruritus severity score and wheal score.

A thorough clinical examination and laboratory work up were done to exclude systemic diseases known to cause urticaria, before applying the patch test. The laboratory work up included complete hemogram, erythrocyte sedimentation rate, hepato-renal function tests, fasting blood glucose examination, thyroid hormones and auto antibodies, antinuclear antibodies, urinalysis and stool examination for ova and cysts. Twenty five allergens present in Indian Standard Series (ISS) - 2008 approved by Contact and Occupational Forum of India (CODFI) were employed.

After 48 hours patches were removed and readings were taken by examining for signs of dermatitis and at 72 hours second readings were observed.

Results were recorded on a pre-designed proforma graded according to the International Contact Dermatitis Research Group criteria.

Observations

This study had slight female preponderance comprising 55% women. The age of the patients ranged from 18-75 years. Majority of the patients (34%) were in the age group of 41-50 years. Age of onset of urticaria in patients ranged from 13-69 years with majority in 41-50 years range. There was a wide range of duration of urticaria from 1.5 months to 30 years.

Table 1: Total duration of disease in patients included in the study

Total duration of disease	Number of patients
0 to 6 months	24
7 months to 1 year	29
> 1 year upto 3 years	16
>3 years upto 5 years	9
> 5 years upto 7 years	11
> 7 years upto 9 years	6
> 9 years upto 11 years	1
> 11 years upto 13 years	3
> 13 years	1

Most of the patients (82%) had variety of symptoms along with associated urticaria. Most common amongst these were malaise (36%) and flushing (34%). The individual associated symptoms are summarized in table 2.

Just under half of the patients (48%) had episodes of angioedema. Majority of the patients who experienced angioedema, used to have a single episode per week (33%). While there were 5% of the patients who experienced recurrent distressing angioedema even 7 or more episodes per week. Face was the most commonly affected site by angioedema in 34 % patient. The description of individual sites involved in angioedema is summarized in Table 3.

Table 2: The individual associated symptoms

Associated symptoms	Number of patients
Gastrointestinal	
Nausea/vomiting	10
Abdominal pain	15
Diarrhoea	7
Indigestion	5
Cardio-respiratory	
Syncope	15
Flushing	34
Breathlessness	22
Palpitations	10
Joint symptoms	
Joint swelling	6
Joint pain	26
General symptoms	
Malaise	36
Headache	28
Fever	7
Feeling of hot or cold	17

Table 3: The sites involved in angioedema

Site	Number of patients
Face*	48
Mouth **	8
Throat	10
Genitals	1

*included lips or lids **included buccal mucosa or tongue.

Whereas urticarial wheals were present over 3 or 4 body sites in most of patients. Limbs were involved by urticarial wheals in almost every patient (95%) followed by trunk in 93% of patients. One fourth (24%) of the patients had the Urticaria Activity Score (UAS) of 6 (mean UAS 4.8+1.67).

The urticaria activity score of 100 patients of chronic urticaria is summarized in table 4.

Table 4: Urticaria activity score.

Urticaria activity score (UAS)	Number of patients
2	14
3	12
4	17
5	14
6	24
7	19

Patch test results

Thirty two percent of the patients demonstrated patch test positivity to one or more allergens. Nickel was the most common allergen in 24% of the patients, followed by fragrance mix in 12% of the patients. The patch test positivity of individual allergens is summarized in table 5.

Table 5: The positivity of individual allergens in the patients included in the present study

Positive patch test allergen	Number of patients
Nickel	24
Fragrance mix	12
Paraphenylene diamine (PPD)	2
Myroxylon pereirae resin	2
Epoxy resin	1
Neomycin	1
Clioquinol	1
Cobalt	1
Nitrofurazone	1
2-Mercaptobenzothiazole	1
Benzocaine	1
Thiuram mix	1

Discussion

Chronic urticaria is associated with a significant impairment in quality of life as revealed by the response of 142 patients of chronic urticaria to a disease-specific questionnaire and Nottingham health profile, between 49% and 71% of patients experienced problems with the home management. About 71% patients limited their choice of clothing or footwear because of provocation by tight clothes or shoes. Fifty four percent of patients restricted their diet in an effort to improve their symptoms. In 73% patients, urticaria interfered with the sexual relationships. Thirty-eight percent patients had reported marked sleep disturbances and other 54% patients had some sleep interference. Besides these, mobility, exercise, social life, interests and hobbies, holidays were also affected in a significant number of patients [(11)].

Diagnosis of allergic contact dermatitis is regularly done with patch test. Although patch test is not routinely performed in the evaluation of chronic urticaria, studies have found positive patch test results in some patients of chronic urticaria [(8)].

Studies have described patients who had both type I and type IV hypersensitivity to nickel, as well as a positive oral challenge test, whose urticaria resolved with a nickel-free diet [(8,12)].

In a study by Warin et al.[(14)] (1982), 56 patients with chronic urticaria were patch tested with particular reference to the immediate wheal response to nickel, potassium dichromate, balsam of peru, parabens, ethylenediamine, cinnamon oil, cloves, oil of peppermint, sodium metabisulphite and tartrazine; and this was followed by challenge tests to most of the same substances.

In a study by Guerra et al [(7)] (2007), 121 patients with chronic urticaria, 50 (41%) tested positive to contact allergens. Metals were the most common sensitizing agents in 16.5% of patients, with nickel being frequently involved 15.7%, followed by cobalt in 5.8% patients. Parabens and balsam of peru, positive in 5% of patients each were the other significant findings. In a study by Sharma AD (2) (2008), a total of 57 cases with chronic urticaria were patch tested, 11 patients (19.2%) showed

positive reactions to one or more patch test allergens. Nine patients (81.8%) showed complete disappearance of chronic urticaria by 2-3 weeks on avoidance of the allergen and this improvement continued till the end of six weeks. Two cases (11.2%) showed partial recovery from chronic urticaria.

In a study by Hession et al [8] (2012), 23 patients with chronic urticaria were patch tested to a Modified North American Contact Dermatitis Group standard, fragrance and cosmetic series. Twenty two patients (96%) had positive patch tests. The most common allergens were potassium dichromate (40.9%), nickel sulfate (31.8%), Myroxylon pereirae (27.2%), cobalt chloride, neomycin and p-phenylenediamine (22.7% each); fragrance mix I, fragrance mix II (18.1% each); cinnamic aldehyde (13.6%); and formaldehyde (9%). Eight (35%) patients experienced improvement of their symptoms with allergen avoidance. Four (17%) patients experienced a complete remission and 4 (17%) patients experienced partial improvement. In present study 32% patients had at least 1 positive patch test reaction of 2+ or stronger. In a study by Sharma AD [2] positive patch test reactions were seen in 19.2%. A higher incidence of patch test reactions in our study can be attributed to the fact that we had employed certain laboratory investigations to rule out the systemic causes of chronic urticaria (like stool for ova and cysts, thyroid profile and anti-TPO antibodies, ANA), whereas in the study by Sharma AD, these preliminary tests were not included.

In the study by Hession et al (8) 96% of the patients had positive reactions of 1+ or stronger. However, when considering the reactions of ++ or stronger significant, they found 39% of the patients having positive results. This result becomes comparable to the result of our study.

In our study, nickel was the most common allergen in 24% patients. This is in accordance with the studies by Guerra et al. (15.7%) and Sharma AD (8.77%) [2,11]. Hession et al [12] too found nickel in a substantial proportion of patients as implicated allergen too. The second most common allergen in our study was fragrance mix I (12%). Positive reaction to fragrance mix have also been reported in the studies by Hession et al. (8.69% patients with ++ or stronger reaction), Sharma AD (1.75%) and Guerra et al (0.83%) [2,7,8].

We also found positive reactions to PPD (2%), which is in conformity to the study by Sharma AD(2). Positive reaction to PPD was found in 8.69% patients in the study by Hession et al [8].

Other allergens found positive in our study were myroxylon pereire resin found in 2% of the patients. Positive reactions were also seen with epoxy resin, neomycin, cobalt, nitrofurazone, 2-Mercaptobenzothiazole, benzocaine and thiuram mix (1% each).

Chen H, et al [16] in their study observed 42.9% (233/543) of subjects with CU had positive reactions to one or more contact allergen(s). Potassium dichromate, benzene mix and carba mix were more common in male patients, while nickel sulfate was more frequent in females.

Magen E et al [15] found no relationship between avoidance of contact allergens and the course of CIU. Nickel sulphate 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. In 43 subjects with severe CIU which were patch tested. 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.

Li LF, Wang J [16] investigated the significance of contact allergen and aeroallergen sensitization in suspected allergic contact dermatitis (ACD), unclassified endogenous eczema (UEE) and non-atopic chronic urticaria (NACU). In 85.7% of the suspected ACD patients, 57.9% of the suspected UEE patients and 52.4% of the suspected NACU patients were positive on patch testing, and the results in 81.0% of the suspected ACD patients and 23.6% of the suspected UEE patients were considered relevant. High positive rates on

aeroallergen intradermal testing were also found in suspected NACU (69.0%), UEE (49.0%) and ACD (59.1%) patients.

Chronic urticaria was considered as a mysterious disease possibly caused by anxiety and intolerance to foods, food dyes, or food additives. Many patients were advised restrictive diets for the treatment of urticaria. Similar views are expressed by Asero et al [17].

Conclusion

The present study can conclude that contact allergy does have a role to play in the pathogenesis of chronic urticaria. Patch test, which is originally used for the etiological diagnosis of contact dermatitis, can be employed for a clue etiological diagnosis of chronic urticaria, being safe, simple, inexpensive and reasonably sensitive. Avoiding the sensitive agents has role in remission of chronic urticaria.

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