Original Article

Skin test positivity to aeroallergens in the patients with chronic urticaria without allergic respiratory disease

Z. Caliskaner[1], S. Ozturk[1], M. Turan[2], M. Karaayvaz[1]

Gülhane Military Medical Academy and Medical Faculty,
[1] Department Allergy and [2] Department of Hydroclimatology and Medical Ecology, Ankara, Türkiye
(www.gata.edu.tr/dahilibilimler/allerji/index.htm)

Summary. The etiology of chronic urticaria and angioedema remains uncertain in most of the patients. There are several agents and factors including medications, foods and food additives, infections, contactants, inhalants, physical factors and autoimmunity that implicated in provoking urticaria symptoms. In addition, the possible role of house dust mites has been considered in a few reports. We investigated skin test positivity to house dust mites and other inhalants in 259 patients with chronic idiopathic urticaria and angioedema but without allergic rhinitis and/or asthma. Results were compared with both 300 healthy controls and 300 atopic patients. Immediate cutaneous reactivity to one or more allergens was detected in 71 patients in the study group (27.4 %). The most common allergens were house dust mites (24.7 %). Skin prick test sensitivity to other inhalant allergens including pollens, molds and cockroach were 7.7 %, 0.4 % and 0.8 %, respectively. In the healthy control group 7 % of patients were found as atopic with respect to skin prick test results. The most common allergens in healthy controls were pollens (6 %), and house dust mites (4.7 %). In atopic control group, pollens and mites are also the most common allergens detected in skin prick test (62 % and 50.3 %, respectively). The difference between study and healthy control group was statistically significant with respect to presence of atopy and mite sensitivity ($p<0.001$). Similar differences were not established in other inhalant allergens. Significant mite sensitivity in the study group is not a coincidence. Because, ratio of skin test positivity to house dust mites in the study group was higher than the healthy controls, but was not as high as atopic patients. Furthermore, the rate of skin reactivity to other aeroallergens was not different from healthy controls. Urticaria as a sole clinical manifestation in mite sensitive patients was unusual.

Keywords: urticaria, dermatophagoides, mites

Introduction

Chronic urticaria and angioedema (CUA) is a common disorder that affects 15-20 % of the general population during their lifetime. CUA negatively affects both work and social life of the patients because of its chronic relapsing course and poor response to therapy. Despite advances in diagnostic immunology, the etiology of CUA remains uncertain in most of the cases. Troubles in determining the etiology makes the treatment difficult. Dietary eliminations, antihistamines and corticosteroids are providing only symptomatic relief, and CUA usually recurs soon after discontinuation of the treatments.

Up to date, there are several agents and factors have

been implicated in provoking CUA including medications, foods and food additives, infections, contactants, inhalants, physical factors and in the most of the cases, autoimmunity [1, 2, 3]. In addition, there are few reports about the relation between dermatophagoides and CUA [4, 5, 6, 7].

In the present study, we investigated skin test positivity to house dust mites and other inhalants in the patients with idiopathic CUA without allergic rhinitis and/or asthma.

Material and methods

Study protocol and patient selection:

Three hundred and twenty-five consecutive patients with CUA without allergic rhinitis and/or asthma, which were evaluated at GATA Allergy Clinic, Turkey, on outpatient basis were included in this prospective study. Diagnosis of CUA was defined as recurrent episodes of hives with or without angioedema of at least 6 weeks duration [8]. Physical urticarias such as dermographism or pressure urticaria were not included. Etiology of CUA was evaluated by medical history, physical examination and laboratory tests. After a throughout physical examination, laboratory investigations were performed to define CUA etiology, including complete blood count (*Coulter STKS Counter, Coulter Electronics, Miami, Florida, USA)*, erythrocyte sedimentation rate (*Westergren Method*), urine and stool microscopy, peripheral blood smear, serum total eosinophil count, BUN, creatinine, AST, ALT, ALP, bilirubins, total protein, albumin (*Technicon Dax 48 autoanalyser, Bayer, Berkeley, California, USA*), complement levels, CRP, RF (*nephelometric assay*), HbsAg, anti HCV, ANA, anti dsDNA, chest and sinus x-rays, free T3, free T4, thyroid stimulating hormone (TSH), antithyroglobuline antibody(anti-TG Ab) and antithyroid peroxidase antibody (anti-TPO Ab) (*chemiluminescence method by using DPC, Diagnostic Products corp., Los Angeles, California, USA*). In addition to these tests, helicobacter pylori infection was investigated in those patients with chronic gastric complaints.

At the end of these investigations 66 patients who were positive for any etiological factor that may cause CUA were excluded from the study. The remaining 259 patients with chronic idiopathic urticaria and angioedema were further studied for inhalant allergen sensitivity and served as study group. As previously described, none of the patients in study group has either history or symptoms of allergic rhinitis and/or asthma.

The patients in study and control groups underwent allergy skin prick test (SPT). SPTs was performed when the patients were asymptomatic and at least 7 days antihistamine-free period after the last dose of antihistamines. Fifty-six common aeroallergens (pollens found in Turkey's atmosphere, molds, house dust mites and animal dander) were used (*1/20 w/v for pollens and molds, 10.000 AU/ml for mites and dander, Greer Lab, Lenoir, USA*). SPT was performed using disposable lancets and the reactions were recorded 15 minutes after the test. Reactions with a wheal diameter greater than 3 mm with surrounding erythema were considered as positive, if the positive control histamine was positive and negative control was negative. The wheal without erythema was accepted as irritant reaction and was excluded. In addition, to differentiate dermographic and irritant reactions, test with negative control solution (diluent with 0.9% saline and 0.4% phenol) was particularly performed to all patients.

Control groups

Two control groups were formed:

Control group I: Healthy control group consisted of 300 individuals (150 male and 150 female) who have not history of atopy, allergic rhinitis and/or asthma. These controls were used to establish asymptomatic skin test positivity to aeroallergens in normal population.

Control group II: Atopic control group consisted of 300 patients (165 male and 135 female) with allergic rhinitis and/or asthma who previously underwent SPT with the same procedure.

Statistical analysis

Statistical analyses were performed by microprocessor using a statistical software package (SPSS for windows, SPSS Inc., USA). Differences between the groups were investigated using chi-square test and Mann-Whitney U test. Fisher's Exact Test was applied as appropriate. Data were expressed as mean ± standard deviation in the text. The alpha was set to 0.05 in all calculations.

Results

The mean age was 27.96 ± 9.82 years in the study group, 25.51 ± 12.72 years in the atopic control group and 25.76 ± 11.30 years in the healthy control group.

Immediate cutaneous reactivity to one or more allergens was detected in 71 patients in the study group (27.4 %). The most common allergens were house dust mites (24.7 %). SPT sensitivity to other inhalant allergens including pollens, molds and cockroach were 7.7 %, 0.4 % and 0.8 %, respectively.

In the healthy control group 7 % of patients found as atopic with respect to SPT results. This ratio was similar to a previously reported study from our country [9]. The most common allergens in this group were pollens (6 %), and house dust mites (4.7 %). Other allergens including molds, animal dander and cockroach were detected in only 2, 1 and 1 patients, respectively.

Pollens and mites are also the most common allergens

detected in SPT in our atopic controls (62 % and 50.3 %). Mold sensitivity was 4.3 %, animal dander sensitivity was 4.7 % and cockroach sensitivity was 3.3 % in the atopic control group.

The difference between study and healthy control group was statistically significant with respect to presence of atopy ($p<0.001$). In addition, the significant immediate cutaneous reactivity to one or more mites in patients with chronic urticaria was exposed. The difference between the mite positivity of the study group and healthy control group was statistically significant ($p<0.001$). Similar differences were not established in other inhalant allergens.

House dust mites, pollens, molds, dander and cockroach sensitivity in the study group was not as high as in atopic patients. However, there is a clear association between mite sensitivity and chronic urticaria.

Skin test results obtained from each group and comparison of the results were summarized in Table 1 and Table 2.

Mite positive patients in the study group were similar to mite negative patients with respect to age and gender. The mean age was 26.52 ± 8.35 years in the mite sensitive patients and 28.44 ± 10.23 years in mite insensitive patients. There is a slight gender difference between them. The male dominance was observed in the mite positive patients while female dominance in mite negative patients. These differences were statistically insignificant (Table 3).

Table 1. The comparison of skin test results between study and healthy control group

	Study group		**Healthy control group**			**p**
Number of patients	259		300			
Female	147	56.8 %	150	50 %	2.548	0.110
Male	112	43.2 %	150	50 %		
Presence of atopy	71	27.4 %	21	7 %	42.126	< **0.001**
Mites	64	24.7 %	14	4.7 %	46.511	< **0.001**
Pollens	20	7.7 %	18	6 %	0.651	0.421
Molds	1	0.4 %	2	0.7 %	0.205	1 (*)
Animal dander	0	0 %	1	0.3 %	NA	
Cockroach	2	0.8 %	1	0.3 %	0.502	0.599n(*)

NA: Not applicable, (*) Fisher's Exact Test

Table 2. The comparison of skin test results between study and atopic control group

	Study group		**Atopic control group**			**p**
Number of patients	259		300			
Female	147	56.8 %	135	45 %	7.686	0.006
Male	112	43.2 %	165	55 %		
Presence of atopy	71	27.4 %	300	100 %	NA	
Mites	64	24.7 %	151	50.3 %	38.556	< **0.001**
Pollens	20	7.7 %	186	62 %	175.970	< **0.001**
Molds	1	0.4 %	13	4.3 %	8.869	0.003(*)
Animal dander	0	0 %	14	4.7 %	NA	
Cockroach	2	0.8 %	10	3.3 %	4.340	0.037(*)

NA: Not applicable, (*) Fisher's Exact Test

Table 3. Demographic features of mite positive and negative patients in the study group

	CUA patients wit mite sensitivity		**CUA patients without mite sensitivity**			**p**
Number of patients	64	24.7 %	195	75.3 %		
Mean age	26.52 ± 8.35 years		28.44 ± 10.23 years		z = -1.409	0.159
Gender						
Male	33	51.6 %	79	40.5 %	2.397	0.122
Female	31	48.4 %	116	59.5 %		

Discussion

CUA is a common dermatologic symptom and impair quality of life in many of patients. Albeit advances in understanding of pathophysiological mechanisms that led to significant improvements in diagnosis and treatment, the etiology still remains as a dilemma in many patients with CUA. In the present study we aimed to call physician's attention to a possible cause of CUA.

The sensitivity to mites in patients with CUA is frequently encountered in our clinical practice. Depending on this observation, we performed SPT with inhalant allergens to all CUA patients to reveal frequency of aeroallergen sensitivity. Our results exposed that approximately one fourth of CUA patient sensitive to house dust mites.

The house dust mites are the most common environmental allergens. Mites sensitize and induce allergic disorders such as perennial rhinitis and asthma in predisposed individuals. In addition, house dust mites are important deteriorating factors in patients with atopic dermatitis [10]. Although there is no clear published data indicating that mite sensitivity leads to urticaria, our results proposed that mite allergens may cause urticaria in some mite sensitive patients.

Mite allergens enter to body mainly by inhalation. There are some additional entering routes for mite allergens: by ingestion and directly through the epidermis [11]. Anaphylaxis induced by mite-contaminated foods has been reported for several times. Mite allergens are resistant to high degree temperatures and positive results in skin tests may be obtained even mite-contaminated foods heated at 100 degrees. The most commonly contaminated food is wheat flour with respect to previously reported data [12, 13, 14, 15, 16]. Bread is the main consumption way of flour and also an important dietary element in many of countries, as in our country. For this reason we hypothesize that, breads "produced by mite-contaminated flour" may be an entering route and triggering way for mite allergens. So, we recommended to our mite-sensitive CUA patients to absolute elimination of bread and other flour-containing foods. Only three patients carried out this recommendation and found it useful at various degrees. Since number of patients was so small that underwent this elimination, obtained results were not convincing. However, trying to strict dietary elimination in a large group of patients may provide more persuading evidences.

The other possible entrance for mite allergens is direct contact. The immunologic contact urticaria described as a wheal and flare reaction occurring after skin and mucosal contact with allergens. Its prevalence is indefinite, but it may be relatively common and underrecognized clinical entity. There are many agents that may cause contact urticaria including natural rubber latex, animal products and foodstuffs [17]. We have no clear evidences about mite allergens as cause of contact urticaria and how the dermatophagoides can cross the intact skin. However, contact urticaria with mites may be theoretically possible, because the mite allergens are capable of causing this kind of an immunologic reaction. Indeed, in a recently published study about mite allergens and atopic dermatitis, Shah et al. reported that a subgroup of their patients (7 of 20) developed transient but pronounced contact urticaria at sites of mite application [18] .

In our opinion, significant mite sensitivity obtained in patients with CUA is not a coincidence. Because, ratio of skin test positivity to house dust mites in the study group was higher than the healthy controls, but was not as high as atopic patients. Furthermore, the rate of skin reactivity to other aeroallergens was not different from healthy controls. Urticaria as a sole clinical manifestation in mite sensitive patients was unusual.

It is possible to consider the presence of some factors as inappropriate skin test technique or faulty interpretation that may cause unexpected mite sensitivity. As previously noted, this study was designed depending on an unusual observation. We have also some doubts about this association. To eliminate confusing factors, prick test procedure was performed under strict rules and careful attention. First, all tests were performed by the same experienced clinician. Second, deep skin penetration that may cause bleeding and lead to false-positive result was avoided. Third, skin responses with only edema but without erythema were not accepted as positive. In addition to these precautions, we did not perform intradermal tests. Because false positive irritant reactions or faulty interpretations are frequent when using intradermal route for potent allergens such as mites.

Another potential problem of skin test with mite allergens is questionable positive results arising from the proteolytic irritancy of dermatophagoides pteronyssinus (DP). Antigenic determinants of DP exhibit a proteolytic enzyme activity similar to papain and serin proteases. This characteristic may cause irritant reactions with DP in addition to its true allergic responses. From this point of view, the ratio of DP positivity and probable irritant responses in our study group may be questioned. In the study group 64 of 259 patients were sensitive to DP (24.7%) and 53 of them were sensitive to dermatophagoides farinae (DF) (20.5 %). That means 82.8 % of DP positive patients did also show positive skin test response to DF. Even we excluded the 11 patients with only DP positivity, remaining 53 patients with positive skin response to DP and DF together, provide meaningful results.

Clinical relevance of mite sensitivity for etiology and treatment of CUA is unknown. In perennial allergic rhinitis and asthma, avoidance of mite allergens can effectively reduce symptoms. There are no data about whether mite elimination is useful for these patients. However, various chemical and physical methods of reducing mite allergens may be recommended to the patients with CUA and skin test sensitivity to mites, as a general rule.

Allergen immunotherapy with mite allergens provides significant improvement in symptoms and marked reduction in drug intake in mite sensitive patients with allergic respiratory diseases [19, 20]. However, clinical benefit of immunotherapy in CUA patients with mite sensitivity is unclear. One of the limited studies about the treatment of these patients is especially interesting. Lodi et al. described 27 CUA patients with mite sensitivity that treated with mite allergen immunotherapy. They reported complete recovery in 6 patients and partial response in 20 patients (2). It is well known that chronic urticaria is not included in the allergen immunotherapy indications. How these patients benefited from this treatment is obscure.

In conclusion, our results indicate a clear association between house dust mites and chronic urticaria. Nevertheless, the clinical importance of this relationship is still questionable. Whether these patients may profit from mite elimination methods or allergen immunotherapy is not known. Further studies aimed to prove the probable role of mite allergens in urticaria pathogenesis may give an answer to these questions.

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Dr. Zafer Caliskaner

GATA Allerjik Hastaliklar BD,
Ankara, TR-06018
TÜRKIYE
Fax: +90-312-304 4139
E-mail: caliskaner@yahoo.com

