

Prevalence of IgE antibodies specific for food allergens in patients with chronic urticaria of unexplained etiology

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We investigated whether some cases of chronic urticaria of unexplained cause might be related to food allergy which had remained undetected during routine examination. This investigation was undertaken as the consequence of the availability of a new *in vitro* assay for specific IgE with increased sensitivity. The following three groups of subjects were studied: 1) a control group of 60 nonatopic subjects, 2) 60 patients with allergy to perennial aeroallergens without skin involvement, and 3) 60 patients suffering from chronic urticaria with no evidence of any triggering factor despite careful clinical investigation. Specific IgE against 19 food allergens frequently involved in urticaria were investigated in all subjects with the new CAP System (Pharmacia). Positive results (CAP > 0.70 kU/l) for one or more food allergens were found in none of the nonatopic controls, in six of the subjects with respiratory allergy, and in 16 of the urticaria patients. The use of an *in vitro* test with an increased sensitivity allowed us to detect a significant prevalence of IgE specific for food allergens in patients with chronic urticaria of unknown origin. This suggests that, in several of those patients, chronic urticaria might be triggered by a food allergy undetected by the usual methods.

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The cause of chronic urticaria remains undetermined in 70–95% of patients with this disorder (6, 12), and the various factors eliciting the attacks often escape careful diagnostic procedures. Drugs, food additives, and natural constituents of foods (allergens) frequently trigger acute and chronic urticaria. Mechanisms such as inflammatory diseases, immune complexes, and various local or focal infections seem to be much more rarely involved in the pathogenesis of chronic urticaria.

About 30–40% of patients with chronic urticaria attribute their symptoms to food intolerance (11, 20). It is also known that the skin constitutes the principal target organ in food allergy, being involved in about 75% of food allergy cases. Urticaria, which is present in 65% of cases of food allergy (9), is its most common manifestation. The prevalence of food allergy in the general population is estimated to be 1–2% (1, 4, 17), and 10% in atopic subjects (15).

The role of food components in triggering the acute form of urticaria is generally obvious (12, 14). Since there is no reason to separate the eliciting mechanisms of acute from those of chronic urticaria, the food allergens causing episodes of the former should

also be considered to play a role in the attacks of the latter. Acute and chronic urticaria differ by their chronologic expression, but not by any known etiologic mechanism (7, 12). Thus, food allergens recognized as most frequently causing acute urticaria – such as those of fish, seafood, fruits, and vegetables in Europe (16), or hen's eggs, milk, peanuts, almonds, and seafood in the USA (14, 19) – might also cause bouts of disease in cases of unexplained chronic urticaria. Cereals, tea, and coffee should also be added to the lists. It would also be difficult to maintain that the role of food allergens can be common in the acute form and exceptional in the chronic form of the disease.

It is possible that, in current practice, food allergens are rarely held to cause chronic urticaria (6, 12) merely because the tools available to detect reaction to them are not sensitive enough.

For these reasons, we took advantage of the availability of a new *in vitro* assay that detects specific IgE with increased sensitivity (13), and investigated whether some cases of chronic urticaria of unexplained cause might be related to a food allergy that was not detected by the usual investigations. The

prevalence of specific IgE antibodies against food allergens detected by this new assay in urticaria patients was compared with that of two control groups: nonatopic subjects and allergic patients without urticaria.

Material and methods

Patients

Three groups, each of 60 subjects, were studied.

Group 1. A control group of 60 nonatopic and healthy persons (mean age 37 years, $SD \pm 7$ (22–57); 30 men and 30 women) was selected from among hospital employees. None gave any history of rhinitis, asthma, pollinosis, or skin disease during a personal interview. Skin tests for six allergens (grasses, trees, weeds, cat dander, *Dermatophagoides pteronyssinus*, and *D. farinae*) were negative. Total IgE concentrations were lower than 50 IU/l in all subjects, and no specific IgE was detected by a multiallergen test (Phadiatop, Pharmacia, Uppsala, Sweden).

Group 2. Sixty patients (mean age 38 years, $SD \pm 11$ (18–68); 31 men and 29 women) with asthma or chronic rhinitis caused by the perennial aeroallergens of mites and/or animal danders (cat and horse), but without urticaria or any other skin disorders, were selected from among our outpatients. Reactivity to aeroallergens was confirmed by skin tests and *in vitro* tests (RAST). For exclusion of patients with a possible oral allergy syndrome, none of those with clinical or biologic signs of reactivity to pollens were included in this group.

Group 3. Sixty patients (mean age 41 years, $SD \pm 12.5$ (18–70); 20 men and 40 women) with chronic urticaria were selected from among our outpatients. All were well known to us and had been considered to be “idiopathic” cases at previous examinations because history, physical examination, and extensive laboratory investigation had failed to indicate any probable cause of the urticaria. The blood tests done included erythrocyte sedimentation rate; complete blood counts; total and specific IgE (RAST); and IgG, IgA, IgM, C3, C4, antinuclear antibodies, and creatinine levels, as well as hepatitis serology and liver function tests. The disorders were diagnosed as chronic, because of the persistence for more than 6 weeks of typical relapsing urticarial rashes, each of a duration of more than 24 h. No patient had any associated allergic respiratory manifestation.

Methods

One serum sample from each of the 180 subjects was investigated for the presence of specific IgE against

19 food allergens, selected from among those most frequently involved in urticaria (16, 19). They consisted of six vegetables (potato, carrot, peas, celery, tomato, and soybean), four fruits (apple, orange, banana, and peach), and three meats (pork, beef, and chicken), as well as egg white, cow's milk, rye, and one mixture of nuts (peanut, hazelnut, walnut, almond, and coconut) and one mixture of cereals (wheat, oats, maize, sesame and buckwheat).

Specific IgE was measured quantitatively with the new CAP system of Pharmacia (Uppsala, Sweden), which has already been shown to be very sensitive (8, 13). The technical characteristics of the assay have been described elsewhere (3). The sensitivity of this new immunoassay was increased over conventional RAST by using a new type of solid phase consisting of a CN-Br-activated, flexible, hydrophilic carrier polymer, encased in a capsule (CAP). Sensitivity was also increased by using a mixed conjugate consisting of polyclonal and monoclonal antibodies against the Fc portion of IgE. The assay is calibrated against the World Health Organization (WHO) standard for IgE, and values are expressed as kU/l. Values under 0.35 kU/l are considered to be negative, those between 0.36 and 0.70 to be slightly positive or borderline (class 1), and those above 0.70 to be positive. Values between 0.70 and 3.5 kU/l were attributed to class 2, the subsequent positive values, from 3.5 to >100 kU/l, being attributed to classes 3–6.

Total IgE concentration was measured by the fluoroimmunoassay Pharmacia CAP Sytem FEIA.

The chi-square test was used for statistical analysis.

Results

Specific IgE was found to be positive (>0.70 kU/l) for one or more food allergens in none of the subjects of the nonatopic control group (group 1), in six (10%) of the patients with respiratory allergy without urticaria (group 2), and in 16 (27%) of the patients with chronic urticaria (group 3) (Table 1). The difference was significant between groups 1 and 3, as well as between groups 2 and 3. If borderline results (between 0.35 and 0.70 kU/l) were also considered to be positive, the difference between groups 2 and 3 was less marked and no more significant; however, the difference remained significant between groups 1 and 3. Highly positive results (>3.5 kU/l) were found in no subjects of groups 1 and 2, but in five (8%) of the patients with urticaria (group 3) (Table 1).

The total IgE concentration was 35 IU/l ($SD \pm 38$; 0–97) in group 1, 260 ($SD \pm 263$; 12–867) in group 2, and 204 ($SD \pm 199$; 5–855) in group 3. The difference between the values in groups 2 and 3 was not

Table 1. Number of subjects with positive CAP results

Specific IgE kU/l	No. of subjects		
	Group 1 (nonatopic subjects; n=60)	Group 2 (allergic subjects without urticaria; n=60)	Group 3 (chronic urticaria; n=60)
0.70–100 (class 2 or more)	0	6 (10%)	16 (27%)
0.34–100 (including borderline results, class 1)	0	13 (22%)	20 (33%)
3.50–100 (higher results only, classes 3–6)	0	0	5 (8%)

> 0.70 group 3 vs group 2: $P < 0.05$; group 3 vs group 1: $P < 0.0001$.
 > 0.34 group 3 vs group 2: $P < 0.3$; group 3 vs group 1: $P < 0.000005$.
 > 3.50 group 3 vs group 2: $P < 0.1$.

significant. The total IgE values in subjects with and without specific IgE against food allergens were, respectively, 256 ($SD \pm 240$) and 268 ($SD \pm 259$) in group 2, and of 213 ($SD \pm 185$) and 197 ($SD \pm 155$) in group 3.

Specific IgE was more frequently encountered for some of the food allergens tested than for others. Table 2 shows the unhomogeneous distribution of the specificities. Positive reactions were more frequently directed against common foods, such as cereals, potato, and tomato, or against hidden foods such as soybean. Most positive reactions were found between 0.70 and 3.5 kU/l (class 2); five of the 20

patients of group 3 had reactions between 3.5 and 17.5 kU/l (class 3), and one had reactions between 17.5 and 50 kU/l (against nine allergens). No subject had reactions higher than 50 kU/l.

Discussion

An *in vitro* test more sensitive than those currently used for detecting specific IgE allowed us to detect a high frequency of specific IgE against food allergens in patients with supposedly idiopathic chronic urticaria. Such a high prevalence was not found in a control group of allergic subjects with known hypersensitivity to respiratory allergens, but without chronic urticaria.

The results could not be explained by a nonspecific influence of high IgE levels. Indeed, in the respiratory allergy group, total IgE levels were even slightly higher (although not significantly so) than in the urticaria group. Moreover, in the urticaria group, total IgE levels were not higher in patients with than in patients without specific food IgE. It is thus possible that, in several of our cases of chronic urticaria, the disease was triggered by a food allergy that had escaped the previous investigation.

The role of food allergens is difficult to determine in the so-called chronic form of urticaria, for the following reasons. 1) Patient history is often unreliable because the responsible factor is either hidden (celery, soybean) or its intake is continual (tea, coffee, cereals). 2) Results of elimination diets are often contradictory, because the multifactorial origin of chronic urticaria is not taken into account, or because the lower level of additives in such diets may suppress a necessary cofactor. 3) Skin tests with food allergens are sometimes not reliable because their positive predictive value is poor (2, 5) (despite the fact that the negative predictive value was found to be excellent (18)). False positive results can also be due to dermographic reactions occurring in chronic urticaria patients. 4) The double-blind, placebo-controlled oral food challenge, although constituting the best proof of food allergy (4), is still difficult to interpret, as, for instance, in cases where no single food factor can trigger the symptoms, but where associations of different foods, or of foods and additives, or of foods and physical factors are necessary.

In this context, a test for specific IgE against food allergen that allows one to screen simultaneously for a battery of food allergens is helpful, provided it is highly sensitive. The present study showed that a new assay more sensitive than RAST revealed, in chronic urticaria, a higher prevalence of IgE against food allergens. This assay, in spite of being more sensitive than RAST with the allergens used here, was also found to be very specific, since neither posi-

Table 2. Specificity of IgE reactions (CAP classes 1–6) in 20 of the 60 patients of group 3 showing at least one positive result

	No. of patients in each CAP class							Total positive classes 1–6
	0	1	2	3	4	5	6	
Beef	20	–	–	–	–	–	–	0
Pork	19	1	–	–	–	–	–	1
Chicken	18	1	1	–	–	–	–	2
Egg white	17	1	2	–	–	–	–	3
Lobster	17	1	2	–	–	–	–	3
Cow's milk	16	3	1	–	–	–	–	4
Celery	14	1	4	1	–	–	–	6
Banana	13	3	3	1	–	–	–	7
Peach	13	1	4	–	1	–	–	7
Carrot	13	1	4	0	1	–	–	7
Peas	13	2	3	2	–	–	–	7
Rye	13	–	5	1	1	–	–	7
Potato	12	1	6	–	1	–	–	8
Tomato	12	–	5	2	1	–	–	8
Apple	11	3	5	1	–	–	–	9
Orange	11	2	5	1	1	–	–	9
Soybean	10	4	4	1	1	–	–	10
Mixture of nuts	10	2	6	1	1	–	–	10
Mixture of cereals	8	1	9	1	1	–	–	12

tive nor borderline results were found in a control group of strictly nonatopic persons. The highest values (> 3.5 kU/l) were found only among urticaria patients. The prevalence of 10% found in the group of allergic subjects without urticaria agrees with findings in the literature (15).

It is clear that the exact significance of specific IgE against food allergens cannot be definitely known for each of the cases of chronic urticaria, without additional measures such as avoidance of suspected food allergens, or oral provocation tests. One should also bear in mind that the higher the sensitivity of a test, the more difficult the clinical interpretation of a positive result (10).

We conclude that the detection of a prevalence of 27% of food-specific IgE in chronic urticaria cases labeled idiopathic, when no such IgE was found in the controls, suggests that some of these cases might be triggered, at least in part, by food factors. This finding contributes to a better knowledge of the nature of idiopathic chronic urticaria. It is possible that some among the cases without detected IgE – i.e., the remaining 73% – might have a food hypersensitivity too low to be detected by the present test. Finally, the finding indicates that such cases should be thoroughly investigated for food IgE by the most sensitive technique available, and that each positive patient should try elimination of the corresponding food.

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