Food allergy and chronic urticaria: the value and limits of in vitro testing for IgE antibodies specific for food allergens

Mohamed Osman Gad El-Rab, M.D. FACAI.

ABSTRACT

Objective: The intent of this study is to evaluate chronic urticaria patients in view of the observation that multiple food allergies could be a causative factor. The CAP Radioallergosorbent (RAST) Fluorimunoassay (FEIA) test will be utilized for measuring specific IgE antibodies. The value, interpretation and limits of the test, being a new sensitive assay, will be evaluated. Design: Patients suffering from chronic urticaria, who gave clinical history suspecting foods as causing their complaints, were selected, for this investigation. Subjects: The study included 112 patients suffering from chronic urticaria. The sex distribution was 61 female and 51 male. Their ages ranged between 19 to 65 years. Serum samples were obtained and tested against the suspected food allergens. These included 16 foods which consisted of egg (white), egg (yolk), milk, fish, meat, peanut, wheat, tomato, strawberry, cacao, chicken meat, shrimp, cheese, yeast, banana and orange. Results: Specific IgE antibodies, to one or more food, were detected in 42 (37.5%) of the patients. These included reactions in all CAP RAST classes, class 1 to class 4. Out of these, only six patients (5.4%) showed multiple food allergies with significant CAP RAST values. These were further evaluated for possible food allergy. Conclusion: Detection of IgE antibodies, specific for food allergens, is worthwhile in chronic urticaria patients who suspect foods as causing their complaints. As the assay is sensitive, results should be interpreted carefully. Because the test is expensive and the yield is low, the panel of food allergens, selected for testing, should be limited to the minimum possible number.


Keywords: Chronic urticaria, food allergens, IgE antibodies, in-vitro assay.

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hronic urticaria (CU) is defined as recurrent episodes of pruritic hives, with or without angioedema, of at least 6 weeks durations.1 The condition is common with a cumulative prevalence of between 15% to 25%.2,3 The cause remains undetermined in 70 - 95% of patients with this disorder.4,5 Although the prevalence of food allergy as the main cause of chronic urticaria is very low, 30 - 40% of patients attribute their symptoms to food intolerance.6 It is known that the skin constitutes the principal target organ in food allergy, being involved in about 75% of food allergy cases.7 The prevalence of food allergy in the general population is estimated to be 1 - 2%/9 and 10% in atopic subjects.10 One study reported food allergy, as the cause of urticaria, in 1.4% of 554 patients.1 In a review by Lehach and Rosenreich 199211 the authors observed that urticaria may result from the ingestion of several different foods at the same time. This makes identification of the causative food difficult for the patient. It also leads the physician to dismiss food as possible provoking factors. The volume of the food consumed and the time of the year are additional variables that the authors observed. Some cases may be due to a hidden or masked food.12

The skin prick test is widely used for evaluation of food allergy. Negative predictive indices are generally very good (greater than 95% accurate) for ruling out IgE - mediated food allergy. However, positive predictive indices show considerable variation (0% to 79%).13 When patients have continuous symptoms, dermogaphism or taking anti-histamines, the alternative is the Radio allergosorbent (RAST) test. A study utilizing the new sensitive Pharmacia CAP System RAST Fluorimunoassay (FEIA), showed encouraging results.14 A similar study by Kaeser, Reveley et al, 1994, using the new sensitive assay, detected specific IgE for food allergens in a significant number of chronic urticaria patients undetected by the usual methods.15,16

The intent of this study is to take advantage of the
new sensitive CAP assay and search for multiple food reactions in patients with chronic urticaria. Patients with strong clinical history suspecting food allergens will be included. The revised cut-off values for the new CAP assay as established by Sampson, 1995, will be utilized for interpretation of the results. These revised values relate the CAP class which is predictive of clinical symptoms to the different food allergens.

**Materials and methods.** One hundred and twelve patients with chronic urticaria attending the allergy clinic at King Khalid University Hospital, Riyadh, were studied. There were 61 female and 51 male, ages 19 to 65 years. They all gave clinical history suspecting foods as causing their symptoms. The disorder was 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. All the patients were considered to have idiopathic urticaria since physical examination and extensive laboratory investigations had failed to detect any probable cause.

The laboratory work-up included complete blood counts, urinalysis, stool examination, antinuclear antibody screening, liver function tests and hepatitis serology.

**Methods.** Blood samples were obtained from the patients and the serum separated and stored at -20°C until assayed.

The samples were tested for the presence of specific IgE antibodies to food allergens in 42 chronic urticaria patients.

**Table 1.** Distribution of specific IgE antibodies to different food allergens in 42 chronic urticaria patients.

<table>
<thead>
<tr>
<th>No. of reactions to Allergens</th>
<th>Patient Serial No. (1)</th>
<th>RAST Score (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One allergen (Total No. = 21) of patients</td>
<td>-3, 5, 6</td>
<td>1</td>
</tr>
<tr>
<td>-8, 11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-13, 21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>-4, 7, 12, 21</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>-2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Two allergens (Total No. = 11) of patients</td>
<td>-24, 25</td>
<td>2</td>
</tr>
<tr>
<td>-29, 32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-22, 26, 28</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Three allergens (Total No. = 7) of patients</td>
<td>-35</td>
<td>3</td>
</tr>
<tr>
<td>-34, 39</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>-36</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>-38</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>-33, 37</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Four allergens (Total No. = 3) of patients</td>
<td>-42</td>
<td>8</td>
</tr>
<tr>
<td>-40, 41</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

(1) Patient serial no.: Patients with positive reactions were given serial numbers from 1 to 42.

(2) RAST Score: RAST class reactions added up for each patient.

specific IgE antibodies to food allergens. These were selected from those most frequently suspected, by the patients, as causing their complaints. They consisted of egg (white), egg (yolk), milk, fish, meat, peanut, wheat, tomato, strawberry, cacao, chicken meat, shrimp, cheese, yeast, banana and orange.

Specific IgE was measured by the new Pharmacia CAP system (Uppsala, Sweden), which has already been shown to be very sensitive. The patients’ serum is added to the allergen of interest which is covalently coupled to immunoCAP. After washing away non-specific IgE, enzyme labelled antibodies against IgE are added to form a complex. After incubation, unbound enzyme anti-IgE is washed away and the bound complex is then incubated with a developing agent. After stopping the reaction, the fluorescence of the eluate is measured in fluorocount 96. The higher the fluorescence value, the more specific IgE is present in the specimen. 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 borderline (class 1) and those above 0.70 to be positive. Values between 0.70 and 3.5 ku/L are attributed to class 2, 3.5 ku/L to 17.5 ku/L to class 3, 17.5 to 50 ku/L to class 4 and 50 to 100 ku/L to class 5.

**Analysis of the results.** The revised cut-off values of the CAP RAST, for food hypersensitivity, as established by Sampson were used for interpretation of the results.

This system relates the CAP class, which is predictive of clinical sensitivity, for each food. Accordingly, at least class 2 values appear to be predictive for symptomatic food allergy to egg; while a class 3 value, and above, appear to be predictive for sensitivity to fish, peanut and milk. For wheat, the CAP RAST have little predictive value. Cut-off value for other foods have not yet been established. In order to have a numerical value for interpretation, the patient’s reactions (class 1 - 4) to different allergens were added together. The range for this aggregated score was 1-9. Patients with scores of 7 or more are considered to have multiple food reaction with significant CAP class values.

**Results.** Specific IgE was found to be positive (>0.70 ku/L) for one or more food allergens in 42 (37.5%) of the patients with chronic urticaria. The distribution of the patients and their corresponding RAST scores appear in Table 1. Twenty one (18.8%) patients reached to one allergen, 11 (9.8%) to two allergens, 7 (6.3%) to three allergens and 3 (2.7%) to four allergens. Only six patients (5.4%) (nos. 33, 37, 38, 40, 41 and 42) had a score of 7 or more indicating multiple reactions with significant CAP classes.
Specific IgE was more frequently encountered for some of the food allergens tested than for others. Table 2 shows the unhomogenous distribution of the specificities. Positive reactions were more frequently encountered to egg (white), peanut, milk, fish meat and tomato. No reactions were observed against banana and orange allergens. Most reactions fall within class 1 with less reactions in class 2 and 3 respectively. Only two class 4 reactions were observed to fish and wheat.

**Discussion.** By searching for multiple food reactions, using the CAP assay, it appears from the present study that six patients (5.4%) were worth further evaluation for possible food allergy. These are patients who reacted with at least a CAP class 2, and above, to more than two food allergens. They include patients with the serial numbers 33, 37, 38, 40, 41 and 42 with scores of 7 or more, Table 2. The observed reactions were more frequently encountered to egg (white), peanut, milk and fish. Lesser reactions were noted to meat, tomato and egg (yolk). This pattern is similar to that reported from U.S.A. where egg, milk, peanuts, almonds and seafood frequently cause urticaria. In Europe, the pattern is a little different where fish, seafoods, fruits and vegetables were more frequently observed. It is noticeable that the yield of the test is low. This could partly be due to interpretation of the results according to the revised cut-off values. This revised system excludes almost all class I values as having no clinical significant (between 0.35 - 0.70 ku/L). It is worthy of note that if borderline results (class I) were also included, the prevalence of food-specific IgE in this study would be 37.5%. A similar investigation reported a prevalence of 27%. It should be borne in mind that because of the high sensitivity of the test, the clinical interpretation of a positive result is difficult. Most of the low borderline values could result from cross-reactions, past sensitivity or possibly, false-positive reactions. It need not be emphasized that detection of specific IgE should be considered only as an addendum to the clinical work-up in patients with suspected food allergy. The only conclusive evidence for confirming food allergy is by double-blind placebo-controlled food challenge (DBPCFC). However, this procedure is time-consuming, expensive and its interpretation, with multiple food allergies, is not straightforward. A simple and practical alternative is by elimination of the food followed by provocation. Patients are first asked to keep a daily record of their symptoms, for 2 weeks, while taking their regular diet. The corresponding food is then eliminated for another 2 weeks. If there is no clear improvement within 2 weeks, then it is unlikely that food allergy is the cause of the patients' complaints. With improvement, the diet period is followed by an open challenge for confirmation. This procedure is very essential in order to give sound counselling regarding elimination of certain foods. Most patients restrict their diet without justification and this have been reported to cause serious nutritional deficiencies and disease. In conclusion, one may add that since chronic urticaria patients are very upset by the unpredictable nature of the disease, and the fact that the symptoms may continue indefinitely, efforts should be made to identify the cause. Furthermore, since the yield of the test is low, it may be advisable to limit the number of tests to the minimum possible. This is hoped to reduce laboratory cost and time.

**References**