Food Allergy in Korean Patients with Chronic Urticaria

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Background: The etiology of chronic urticaria (CU) remains unknown in most patients. Possible causes in some cases include food, but the role of allergy to food antigens in patients with CU remains controversial. Objective: The aim of this study was to evaluate the association between food allergy and CU. Methods: Korean patients with CU were assessed for a previous history of food allergy that caused symptoms of CU. Blood samples were taken from 350 patients to measure food allergen-specific IgE. Based on history and laboratory results, open oral food challenge (OFC) tests were performed. Results: Of 350 participants, 46 (13.1%) claimed to have experienced previous food hypersensitivity. Pork (n=16) was the main food mentioned, followed by beef (n=7), shrimp (n=6), and mackerel (n=6). We found that 73 participants (20.9%) had elevated levels of food-specific IgE, with pork (n=30), wheat (n=25), and beef (n=23) being the most common. However, when the open OFC tests were conducted in 102 participants with self-reported food hypersensitivity or raised levels of food-specific IgE, only four participants showed a positive reaction to pork (n=3) or crab (n=1). Conclusion: Although some participants claimed to have a history of CU related to food intake, when an open OFC test was conducted, few of them had positive results. We therefore conclude that food allergy is an uncommon cause of chronic CU. (Ann Dermatol 28(5) 562 ∼ 568, 2016)

Keywords:
Food allergy, Prevalence, Urticaria

INTRODUCTION

Chronic urticaria (CU) is defined as spontaneous urticaria that lasts over six weeks without improvement. It is a heterogeneous disease in which allergy may be involved. A food allergy is defined as an adverse effect arising from a specific immune response, which occurs reproducibly on exposure to a given food. The skin diseases that are related to food allergy include urticaria, oral allergy syndrome, and atopic dermatitis.

In CU, food allergy is known to be a rare cause. It is known that in less than 2% of cases is food itself, or food additives, the reason for CU. However, many people think that foods are the reason, or an aggregating factor, in urticaria and undergo inappropriate food restriction. Some who do this, suffer nutritional imbalance and decline in quality of life. Although physicians in clinical practice educate their patients with CU that there is a low probability that the suspected food is the cause of urticaria, many patients constantly try to associate the presence of their symptoms with specific foods.

There have been several studies on the correlation between CU and the prevalence of food allergy, but few large-scale studies have been reported. Moreover, many of these studies have been based only on patients’ self-perception of food reactions. Specifically, there have been a few studies about the prevalence of food allergy in CU patients in Korea, involving the use of medical history, questionnaires, food specific IgE test, and skin prick test. However, there was only one study about food allergy using oral food challenge (OFC) test in small number of patients with CU. For these reasons, the relation between food and CU needs to be determined. Therefore, we carried out an investigation about the prevalence of food al-
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MATERIALS AND METHODS

Patients

This study included 350 Korean patients with CU who attended the Department of Dermatology, Hallym University Kangnam Sacred Heart Hospital between October 2011 and August 2014. There were 143 men (40.9%) and 207 women (59.1%). The average age was 39.66 ± 17.20 years (range, 2–79 years). Prevalence period of disease was 23.89 ± 46.59 months (range, 2–240 months). All patients had been medicated with one or several antihistamines (fexofenadine, levocetirizine, or other) before the food challenge. Of the 350 patients, 49 (14.0%) were on immunosuppressant therapy (cyclosporine and/or methylprednisolone). There were no significant differences between the patient group with and without past history of food allergy (n=9, 19.6% vs. n=40, 13.2%, p=0.243). The patient demographics are described in Table 1. CU was defined as urticaria that has been continuously or intermittently present for at least six weeks. Each patient studied, had active urticaria at the time of challenge. For those with persistent urticaria, despite the use of antihistamines and/or immunosuppressants at the time of enrollment, no changes were made in medications. For patients whose hives were completely suppressed by their current medication, their antihistamines and/or immunosuppressants doses were reduced until hives returned at a tolerable level. This was defined as the minimum effective dose, which was individualized for each patient12. Exclusion criteria included pure physical urticaria, infectious disease, vasculitis, thyroid disease, systemic lupus erythematosus and malignancy. The protocol was approved by the Institutional Review Board of Hallym University Kangnam Sacred Heart Hospital (IRB no. 2015-05-61). Informed consent was obtained from each participant and from their parents, if they were 18 years old or less.

Patient history of food allergy

We gathered a detailed medical history from each patient that contained the duration of urticaria, past history of food allergy, suspected food antigens, duration of symptoms and latency period prior to urticarial reaction (such as pruritus, wheals, flares, or swelling). In terms of food allergy, some people were regarded as negative: those who showed inconsistent reaction to certain foods, whose foods contained many artificial additives, those for whom food reactions were complicated by other factors (e.g., exacerbation by physical exercise after meals), and those who reported no food allergy history. An experienced dermatologist was responsible for interpreting the history of food allergy.

Measurement of serum food-specific immunoglobulin E levels

Blood samples were taken from the patients to measure their allergen-specific IgE using a Korean-food-panel multiple allergosorbent test-chemiluminescent assay (MAST-CLA) allergy system (MAST Immunosystems, Mountain View, CA, USA). This assay can simultaneously measure 35 dif-

Table 1. Patient demographics

| Variable                                  | Chronic urticaria |    |       |    |   | p-value |
|-------------------------------------------|-------------------|----|-------|----|---|---------|
|                                            | The patients with food allergy history (n=46) |    |       |    |   |         |
| Sex                                        | Male              | 22 | (47.8)|    |   | 0.302   |
|                                            | Female            | 24 | (52.2)|    |   |         |
| Age (yr)                                   | 36.37 ± 16.69     |    |       |    |   | 0.164   |
| Age (yr)                                   | Disease duration (mo) | 28.96 ± 58.79 |    |       |    |   | 0.492   |
| Immunosuppressive medication history       | Nonusers          | 37 | (80.4)|    |   | 0.243*  |
|                                            | Users (mg/d)      | 9  | (19.6)|    |   |         |
|                                            | CsA (100)+MPD (4) | 1  | (2.2) |    |   |         |
|                                            | CsA (25)+MPD (4)  | 1  | (2.2) |    |   |         |
|                                            | CsA (100)         | 2  | (4.3) |    |   |         |
|                                            | CsA (25)          | 3  | (6.5) |    |   |         |
|                                            | MPD (4)           | 2  | (4.3) |    |   |         |

Values are presented as number (%) or mean ± standard deviation. CsA: cyclosporine, MPD: methylprednisolone. *There were no significant differences between the patient group on immunosuppressant therapy with and without past history of food allergy.
ferent specific IgE antibodies. Associated allergens consisted of those from food as well as inhalant allergens, including mold and pollen, all of which frequently provoke a positive reaction from Korean people. Based on hospital experience, results from standards, and other data that showed that Class 1 results might be observed in healthy subjects who lacked clinical evidence of allergic disease\(^{13-15}\), a MAST class of ‘2’ or above (Allergen-specific IgE content \(\geq 0.70\) IU/ml) was considered positive.

**Open oral food challenge test**

We selected foods for open OFC testing based on food allergy history and serum food-specific IgE levels. Subjects who were negative for both history and serum food-specific IgE levels did not undergo open OFC testing. Foods that were suspected of food allergy were forbidden for 14 days before the open OFC test\(^{16}\). On the test day, patients ate their regular amount of the suspected foods, which means the amount they usually ate at one meal, in the morning, from a fasting state. If the patient did not show any reaction, he or she was tested again on the following morning. A test was considered positive if urticaria (wheal-and-flare) were noticed with aggravation of pruritus, by an experienced dermatologist during the 6-hour period after the test\(^{17}\), and systemic symptoms such as in the digestive system or respiratory system were studied together. The patients were instructed to continue to check skin at 9 and 18 hours after ingestion at home, and to call the physician the following day if additional skin symptoms arose. If open OFC tests were conducted for other foods on the same patient, this was done within an interval of 1~2 days.

**Statistical analysis**

The results were expressed as means±standard deviations. The chi-square test for nominal variables and the Student’s t-test for continuous variables were used to determine the significance of differences. Significance levels for all analyses were set at \(p<0.05\). All statistical analyses were conducted using PASW Statistics ver. 18.0 (IBM Co., Armonk, NY, USA).

**RESULTS**

**Patient history of food allergy**

Of the 350 patients, 46 (13.2%) had a self-reported history of food allergy. There was a tendency that the patient group with food allergy past history had longer disease periods, but this was not statistically significant (28.96±58.79 months vs. 23.15±44.61 months). Neither sex nor age appeared statistically significant. The most common suspicious foods reported were pork (n=16, 4.6%), beef (n=7, 2.0%), shrimp and mackerel (n=6, 1.7% for each), crab (n=4, 1.1%), dog meat soup (n=3, 0.9%), egg, chicken, wheat, and peanuts (n=2, 0.6% for each), salmon, buckwheat, beer, coffee, ramen, and fermented soybean paste (Cheonggukjang) (n=1, 0.3% for each) (Table 2).

**Serum food-specific immunoglobulin E levels**

Of the 350 patients, 73 (20.9%) showed elevated serum food-specific IgE levels. Of the 73 patients, 41 were male and 32 were female. The mean age was 33.52±18.16 years (range, 2~70 years), and the mean duration of disease was 26.89±62.92 months (range, 3~240 months). Pork-specific IgE was highest (n=30, 8.6%), followed by wheat (n=25, 7.1%), beef (n=23, 6.6%), garlic (n=20, 5.7%), crab and milk (n=11, 3.1% for each), peach (n=5, 1.4%), egg, cheese, crab, and barley (n=3, 0.9%), shrimp (n=2, 0.6%), salmon, lemon/lime/orange, and peanuts (n=1, 0.3% for each) (Table 3). Seventeen (37.0%) of the 46 patients with a history of food allergy showed elevated serum food-specific IgE levels, while 56 (18.4%) of the 304 patients without a history showed elevated serum food-specific IgE levels (Fig. 1).

![Table 2. Frequency of positive reactions to food allergens in self-reported history](https://example.com/table2.png)

| Variable                          | No. of patients (%) |
|-----------------------------------|--------------------|
| Number of suspicious foods        |                    |
| 2                                 | 10 (2.9)           |
| 1                                 | 36 (10.3)          |
| 0                                 | 304 (86.9)         |
| Total                             | 350 (100.0)        |
| Types of suspicious foods         |                    |
| Pork                              | 16 (4.6)           |
| Beef                              | 7 (2.0)            |
| Shrimp                            | 6 (1.7)            |
| Mackerel                          | 6 (1.7)            |
| Crab                              | 4 (1.1)            |
| Dog meat soup                     | 3 (0.9)            |
| Egg                               | 2 (0.6)            |
| Chicken                           | 2 (0.6)            |
| Wheat                             | 2 (0.6)            |
| Peanut                            | 2 (0.6)            |
| Salmon                            | 1 (0.3)            |
| Buckwheat                         | 1 (0.3)            |
| Beer                              | 1 (0.3)            |
| Coffee                            | 1 (0.3)            |
| Ramen                             | 1 (0.3)            |
| Fermented soybean paste (Cheonggukjang) | 1 (0.3) |
Open oral food challenge test
The open OFC test was performed on 102 patients based on their self-reported history of food hypersensitivity (n = 46), and/or on their increased food-specific IgE (n = 56). Among 102 patients, four showed positive response. The offending food was pork (n = 3), followed by crab (n = 1). Two (4.3%) of the 46 patients with a history of food allergy showed positive response, while two (0.7%) of the 304 patients without a history showed positive response. Two of four patients with positive open OFC test results showed a history of food hypersensitivity and elevated serum food-specific IgE levels; two patients showed only elevated serum food-specific IgE levels without positive history (Fig. 1). After four patients who showed a positive reaction on open OFC did not consume the offending food, their skin symptoms, such as wheals and pruritus, were improved and the stable conditions persisted for four weeks or more without antihistamines.

Thus, the overall prevalence of true food allergy in the study patients was 1.1% (4/350). Detailed information for each patient is described in Table 4.

DISCUSSION
The prevalence of patients’ self-reported history of food allergy differs by study. Bock found 28% of the children reported adverse reactions to foods. In the study by Young et al., 20% of 15,000 households perceived adverse reactions to food. The new US guidelines summarized a self-report rate of 12% to 13%. Targeting only patients with urticaria, 30%–40% of patients with CU thought their symptoms were related to food. In research in Korea, patients with CU responded that 50.6% of them experienced that CU got worse in relation to food. In our previous research, 35% of patients with urticaria had a
Table 4. Patients with chronic urticaria and positive reactions to oral food challenge tests

| No. | Age (yr) | Sex | Duration (mo) | History of hypersensitivity | Food-specific IgE (Class) | Oral food challenge | Challenge results | Other symptoms |
|-----|----------|-----|---------------|-----------------------------|--------------------------|---------------------|------------------|---------------|
| 1   | 15       | Male| 12            | None                        | Pork (2)                 | Pork                | Wheals, pruritus (20 minutes later) | None          |
| 2   | 44       | Male| 2             | None                        | Pork (2)                 | Pork                | Wheals, pruritus (immediate)    | None          |
| 3   | 26       | Female| 12           | None                        | Pork (2)                 | Pork                | Wheals, pruritus (2 hours later) | None          |
| 4   | 28       | Male| 36            | Crab                        | Crab (3), rice (3), garlic (6), onion (2) | Crab, rice, garlic, onion | Crab-wheals, pruritus (immediate) | None          |

medical history of food allergy. Putting the results of previous research together, patients with urticaria showed a higher self-reported history of food allergy than did the normal population. However, in our study, 13.1% of patients with CU reported a history of food allergy, a rate similar to that of the normal population in other research.

Since people tend to overestimate food as a reason for allergy, to diagnose food allergy, skin prick tests and allergen-specific IgE tests are necessary. The skin prick test is being widely used for determining specific antigens and is considered the gold standard. However, this test has several limitations, including a high percentage of false positive reactions, interference by medications such as antihistamines, and invasiveness. Hence, various in vitro tests measuring serum allergen-specific IgE antibody levels have been introduced. The radioallergosorbent test (RAST), a typical in vitro test using patient sera, has been extensively used for examination of allergens. However, this test has an important handicap in that the examiner is at risk for radiation exposure. Since the evolution and development of fluorescent enzyme immunoassay, the ImmunoCAP system has been widely accepted as a reference method of allergen-specific IgE measurement because of its reliability, reproducibility, and good accordance with skin test results. However, each individual ImmunoCAP test can only detect IgE against a single allergen, making it quite expensive to use in a clinical setting. Accordingly, several multiple allergosorbent test-chemiluminescent assay (MAST) were developed. The MAST-CLA has the advantage that it can test for 35 common allergens simultaneously at a relatively low cost, and thus is suitable as a screening test. Employing a very sensitive chemoluminescence technique, MAST-CLA is safer than other methods that use a radioactive isotope. In addition, MAST-CLA is highly sensitive and specific, and has evidenced good agreement rates of results with the skin prick test or immunoCAP. Thus, we used MAST-CLA as a screening tool for detection of food allergens.

For definite diagnosis, food elimination and food challenge tests are also needed. Food challenge ultimately confirms specific foods as the cause of clinical disease. The double blind placebo-controlled food challenge (DBPCFC) is the gold standard method by which food allergy is determined. However, the DBPCFC is time-consuming and complicated, requiring 6~8 hours of physician-observed time for a full challenge. For these reasons, the DBPCFC is unsuitable for use with outpatients. Open OFC tests are much easier to perform than DBPCFC, and are widely used for office diagnosis. Previous studies demonstrated that open OFC is a useful method for identifying or confirming food allergy, and that it is nearly as efficient as DBPCFC. Therefore, OFC was chosen for this study. It is difficult to perform food challenges and interpret the results of food challenge tests for patients with CU because most patients with CU take antihistamines or immunosuppressants consistently to control erythema and wheal with pruritus. Moreover, CU often tends to wax and wane naturally. Many prior studies have been performed after withholding antihistamines. If antihistamines are withheld before a challenge, then coincidental increase in skin symptoms may occur, although unrelated to the challenge. Therefore, it may be advantageous to continue use of antihistamines during challenge. Another concern is the continuation of antihistamines through other studies, which may have led to false-negative results. To circumvent both of these issues in this study, antihistamines and/or immunosuppressants were reduced to their minimum effective dose.

Although the prevalence rate of food allergy as demonstrated by OFC is not accurately known, in young children (<4 years) it is reported to be 6%~8%, with the rate going down with increasing age. The food allergy frequency of adults is estimated to be about 1.4%~2.0%. The proportion of food allergy as demonstrated by OFC among urticaria patients differs from researcher to re-
In our study, for patients who had a history of food allergy, the probability of elevated serum food-specific IgE levels was high and statistically significant. Such patients also had a higher probability of being positive for OFC tests, compared to those without such histories, though this was not statistically significant. Although 102 patients out of 350, had a history of food allergy or elevated food-specific IgE levels, only 4 (1.1%) received a definite diagnosis of food allergy by OFC. Two of these four patients showed corresponding results from their food allergy history, MAST-CLA, and OFC; the other two patients showed positive reaction to MAST-CLA and OFC, without histories of food allergy. Although many patients with CU do not know exactly which food was the cause, they think their symptoms are related to what they ate. As pointed out in recent large reviews, guidelines, and meta-analyses, self-reported adverse reaction rates exceed rates based on OFC tests. Because of the difficulty of formal examination, suspected foods are usually restricted without food challenge tests. Avoiding suspected foods is not always the best option, because inappropriate dietary restrictions may cause imbalanced nutrition. Therefore, open OFC testing is necessary to diagnose food allergy in patients with CU, who have suspicious food allergy histories.

In our study, the most common food considered allergenic by Korean patients with CU was pork (4.6%). The food most commonly showing a positive result with the serum food-specific IgE test was pork (8.6%). In our OFC test, pork was also the most common food allergen in Korean patients with CU and this result is worthy of notice. However, pork allergy has rarely been reported in the medical literature. It may manifest in a variety of ways: urticaria, oral allergy syndrome, and exacerbation of atopic dermatitis. Over the last 30 years, per capita meat consumption in Korea has increased dramatically due to economic growth and westernized eating habits. In late 2003, with the occurrence of mad cow disease in the US, the demand for pork sharply increased. Currently, pork accounts for half of all meat consumed in Korea. This increased consumption of pork might be accompanied by more frequent reports of adverse reactions to pork.

Adverse reactions to food can occur through the many heterogeneous mechanisms. These include not only immunological IgE-mediated food allergy and non-immunological reactions like pseudoallergy. Pseudoallergic reactions are defined as clinical reactions whose symptoms resemble allergic reactions without identifiable immunologic sensitization. CU may have also been associated with pseudoallergic reactions to food ingredients. In our study, 29 patients showed negative serum food-specific IgE and OFC tests. However they complained to have adverse reaction to certain foods. Further study will be needed to rule out pseudoallergy for these patients by a pseudoallergen-free diet.

This study was conducted to determine the correlation of food allergy and CU in 350 Korean patients. Because only 4/350 (1.1%) patients had a positive response to OFC tests, our study suggests that CU in Koreans is not significantly related to food. Based on our study results, we advised our patients worrying about food allergy not to limit their diets indiscriminately, without diagnosis confirmed by OFC tests.

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