Increasing specific immunoglobulin E levels correlate with the risk of anaphylaxis during an oral food challenge

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Abstract
Background: Oral food challenges (OFCs) are necessary to diagnose food allergies; however, these tests can cause anaphylaxis. Higher specific immunoglobulin E (sIgE) levels to causative food have been associated with a positive OFC. To date, no data have been found to indicate the factors associated with severe symptoms or anaphylaxis among challenge-positive patients. This study aimed to clarify the association of sIgE with causative foods and anaphylaxis during OFC among the whole study population and challenge-positive patients.

Methods: This cross-sectional study collected symptom and severity data between June 2012 and December 2016 during an open OFC to diagnose food allergy or confirm tolerance acquisition. We analyzed the risk factors for anaphylaxis during OFC.

Results: A total of 2272 cases were analyzed (median age: 3.5 years; egg: 1166 cases; milk: 589 cases; wheat: 388 cases; and peanut: 129 cases). Among 979 challenge-positive patients, anaphylactic reactions were observed in 334 cases. A statistically significant association was observed between anaphylaxis during OFC and higher sIgE levels to causative foods (odds ratio: 2.71, 95% confidence interval: 1.94-3.78, for the third compared to the first tertile, P-value for trend <.001). Only gastrointestinal, respiratory, cardiovascular, and neurological symptoms were also statistically significantly associated with higher sIgE levels to causative foods.

Conclusions: The risk of all symptoms, except skin symptoms, during OFCs increased with increasing sIgE levels, and this consequently increased anaphylaxis during OFCs. The mechanism of how sIgE affects the prevalence of gastrointestinal, respiratory, cardiovascular, and neurological symptoms or anaphylaxis is unknown; thus, further study is required.

Keywords
anaphylaxis, children, food hypersensitivity, oral food challenge, pediatric
INTRODUCTION

The oral food challenge (OFC) test is a standard and accurate method for diagnosing food allergies; however, anaphylaxis can occur during this test. Information predicting whether a person will experience anaphylaxis before performing an OFC is valuable, as it can be used to decide whether a person should undergo an OFC. A history of anaphylaxis to causative foods, being older, and having an allergy to food other than eggs were reported as risk factors for a severe reaction during a double-blind placebo-controlled food challenge (DBPCFC). In addition, higher specific immunoglobulin E (sIgE) levels to causative foods have been associated with a positive OFC and the severity level of the anaphylactic reaction among all patients who underwent an OFC (OFC-negative and OFC-positive patients). However, as these previous studies evaluated all patients, including challenge-negative patients, the identified risk factors for anaphylaxis may include the risk factors for a positive OFC. To clarify whether a high sIgE level for causative food is associated with anaphylaxis, an evaluation of only OFC-positive patients is needed. However, no data were found to indicate that a high sIgE level for causative food is associated with severe symptoms or anaphylaxis among challenge-positive patients. Therefore, in the present study, we aimed to clarify the association between sIgE and anaphylaxis during OFC among only challenge-positive patients, as well as among all patients.

METHODS

2.1 Study design

A cross-sectional study was performed to assess anaphylaxis induced by an OFC. Data from OFCs were collected prospectively between June 2012 and December 2016 (UMIN Registry Number UMIN0000013025). The ethics committee of Sagamihara National Hospital (January 2014) approved this study. Written informed consent was obtained from all patients and their guardians. Patient anonymity was preserved using methods approved by the ethics committee.

2.2 Study participants

We initially analyzed the study participants who were diagnosed as having, or suspected to have, allergies to hen’s egg, cow’s milk, wheat, or peanuts. Most patients were referred to our hospital from other pediatric clinics for an OFC. Those who had undergone a first challenge test with a low target dose of cow’s milk, wheat, and peanuts, or with a medium target dose of hen’s egg, were included in the analysis. We excluded participants who had been given another form of food, such as egg yolk, in the OFC. We also excluded patients with missing laboratory data (egg white, ovomucoid, milk, wheat, peanut, and Ara h 2 sIgE levels) or missing clinical data during the OFC.

2.3 OFC testing method

The challenge foods used in the OFC were prepared in the nutrition management room of Sagamihara National Hospital (Table S1). In Japan, a stepwise OFC starting from a low dose is recommended in the food allergy guidelines, even for patients with high levels of antigen-sIgE antibodies. The challenge foods were heated, and the amount of protein in the milk, wheat, and peanuts was low for all patients, including those with higher antigen-sIgE antibodies. The OFC has been previously described in detail. OFCs were implemented while the patients’ allergic diseases (eg, atopic dermatitis, asthma, and allergic rhinitis) were well controlled. Study participants who exhibited OFC-induced allergic symptoms (ie, had a positive OFC) were treated according to the European Academy of Allergology and Clinical Immunology (EAACI) guidelines. The term “anaphylaxis,” which is used throughout this manuscript, is as defined by the World Allergy Organization. The term “non-anaphylactic reaction” reflects an immediate reaction without anaphylaxis.

2.4 sIgE analysis

We used the Immuno CAP™ (Thermo Fisher Scientific, Uppsala, Sweden) to detect antigen-sIgE antibodies in the serum of those challenged with causative foods (egg white, milk, wheat, and peanuts). We also retrospectively reviewed the sIgE levels within a 6-month period before we performed the OFC. The sIgE levels for ovomucoid, casein, omega-5 gliadin, and Ara h 2 were also evaluated.

2.5 Statistical analysis

The Mann-Whitney U or Fisher exact test was used for intergroup comparisons of data. A P-value <.05 was considered statistically significant. Three-group comparisons were performed using the Mann-Whitney U or Fisher exact test with Bonferroni correction. Univariate and multivariate analyses were performed to determine the significant factors causing anaphylaxis during the OFCs. All analyses were performed using SPSS software (version 24.0; SPSS Inc., Chicago, IL). Probability curves for antigen-sIgE levels were constructed, as previously described.

RESULTS

3.1 Clinical and demographic characteristics of study participants

There were 2397 patients diagnosed as having or suspected of having allergies to hen’s egg, cow’s milk, wheat, or peanuts. Of these, 2272 patients (egg allergy: 1166 cases; milk allergy: 589 cases; wheat allergy: 388 cases; and peanut allergy: 129 cases) were included in our data analysis (Figure 1). We excluded patients for whom laboratory data (114 cases) and clinical data (11 cases) were missing. These 125 patients had a significantly lower age and lower
A total of 2272 OFCs were carried out in 1757 participants (median age: 3.5 years) as 388 participants receive OFCs to two or more antigens. Among the participants, 1532 (67.4%) had a history of an immediate reaction to the food within 2 hours after ingestion and 417 participants (18.4%) had a history of an anaphylactic reaction to the food (Table S3). The remaining patients were those suspected of having a food allergy with a positive sIgE. Of the 2272 participants who were involved in the OFCs, 1293 (56.9%) did not show any symptoms and 979 (43.1%) reacted to the OFC (Table 1). Among the participants with a reaction, 645 (28.4%) had a non-anaphylactic reaction and 334 (14.7%) had an anaphylactic reaction to the food.

### 3.2 | OFC-induced symptoms

The study participants exhibited a range of OFC-induced symptoms. These included skin symptoms (679 participants, 69.4%), respiratory symptoms (646 participants, 66.0%), and gastrointestinal symptoms (566 participants, 57.8%; Table S4). Three hundred and thirty-four participants (34.1%) had an anaphylactic reaction to the OFC. Skin symptoms were the most common in milk OFC (84.4%). Respiratory symptoms were common in milk OFC (81.6%) and wheat OFC (81.8%). Gastrointestinal symptoms were common in egg OFC (81.6%) and peanut OFC (81.8%). Anaphylaxis was the most common in milk OFC (47.9%). Numerous study participants (828 participants, 84.6%) were also treated for OFC-induced symptoms (Table S5). All patients with anaphylactic reaction received treatment. One hundred and fifty-one participants with non-anaphylactic symptoms did not need any treatment, as their symptoms improved rapidly without treatment.

### 3.3 | Antigen-sIgE levels and reactions to the OFC among whole study population

Depending on their reaction to the OFC (no reaction, non-anaphylactic reaction, or anaphylactic reaction), significant differences in the sIgE levels were observed among the participants. The median sIgE levels (kU A/L) according to OFC reaction were as follows: egg: 7.0, 17.1, and 27.0; milk: 10.9, 29.1, and 53.0; wheat: 11.2, 32.4, and 67.2; and peanut: 9.9, 19.1, and 76.1, respectively (Figure 2). Significant differences were also observed in sIgE levels for ovomucoid (1.8, 10.4, and 14.8), casein (7.9, 23.5, and 52.8), omega-5 gliadin (1.1, 4.3, and 15.1), and Ara h 2 (0.7, 13.1, and 46.0; Figure 3). The probability curves for egg, milk, wheat, and peanut-specific levels of sIgE indicated that a high sIgE level was associated with a high rate of positive OFC and a high occurrence rate of anaphylactic reaction (Figure 4). Data from 2027 participants challenged with ovomucoid, casein, omega-5 gliadin, and Ara h 2 also revealed associations among a high sIgE level, positive OFC result, and anaphylactic reaction (Figure S1).

### 3.4 | Antigen-sIgE levels and reactions to the OFC among challenge-positive patients

We examined the relationship between sIgE levels for causative foods and an anaphylactic reaction during the OFC in 979 challenge-positive patients. We divided participants into three groups according to sIgE level tertiles for the causative foods: T1 (low sIgE) (n = 324), T2 (medium sIgE) (n = 328), and T3 (high sIgE) (n = 327) (Table S6). Among the participants who had a positive OFC, the high incidence of anaphylaxis was related to a higher sIgE level (Table S7). A statistically significant association was observed between anaphylaxis during the OFC and the sIgE level for the causative foods (odds ratio: 2.71, 95% confidence interval: 1.94-3.78, for
### TABLE 1  Clinical and demographic characteristics of participants with a positive oral food challenge result

| Challenge food | Egg (n = 448) | Milk (n = 326) | Wheat (n = 143) | Peanut (n = 62) | Total (n = 979) |
|----------------|---------------|---------------|-----------------|----------------|-----------------|
| Sex (male)     | 305 (68.1%)   | 212 (65.0%)   | 100 (69.9%)     | 41 (66.1%)     | 659 (67.2%)     |
| Age (y)        | 5.3 (2.8-7.6) | 5.0 (3.2-6.9) | 4.4 (2.5-5.7)   | 6.9 (5.8-9.1)  | 5.2 (3.2-7.1)   |
| History of immediate reaction to causative food | 328 (73.2%) | 265 (81.3%) | 129 (90.2%) | 50 (80.6%) | 772 (78.9%) |
| History of anaphylaxis to causative food | 69 (15.4%) | 121 (37.1%) | 59 (41.3%) | 23 (37.1%) | 272 (27.8%) |
| Atopic dermatitis, current | 244 (54.5%) | 201 (61.7%) | 76 (53.1%) | 22 (35.5%) | 543 (55.5%) |
| Bronchial asthma, current | 69 (15.4%) | 81 (24.8%) | 30 (21.0%) | 13 (21.0%) | 193 (19.7%) |
| Allergic rhinitis, current | 85 (19.0%) | 49 (15.0%) | 14 (9.8%) | 11 (17.7%) | 159 (16.2%) |
| Total IgE (IU/mL) | 595 (235-1280) | 654 (260-1615) | 444 (204-1186) | 478 (276-1160) | 588 (234-1360) |
| Antigen-sIgE (kU/L) | | | | | |
| Egg white | 20.6 (7.9-44.8) | | | | |
| Milk | 40.0 (14.9-92.3) | | | | |
| Wheat | 50.1 (15.5-172) | | | | |
| Peanut | 33.3 (8.8-74.0) | | | | |
| Component-sIgE (kU/L) | | | | | |
| Ovomucoid | 11.2 (4.4-28.0) | | | | |
| Casein | 39.9 (12.7-92.6) | | | | |
| Omega-5 gliadin | 5.8 (1.7-17.4) | | | | |
| Ara h 2 | 20.6 (6.7-46.3) | | | | |

IgE, immunoglobulin E; sIgE, specific immunoglobulin E.

Values are expressed as n (%) or median (interquartile range).

![FIGURE 2](image-url)  
**FIGURE 2** sIgE levels for egg white, milk, wheat, and peanuts according to the OFC reaction.  
A. Differences in the egg white sIgE level among egg OFC outcomes.  
B. Differences in the milk sIgE level among milk OFC outcomes.  
C. Differences in the wheat sIgE level among wheat OFC outcomes.  
D. Differences in the peanut sIgE level among peanut OFC outcomes. sIgE, specific immunoglobulin E; OFC, oral food challenge. The P-value was calculated using the Mann-Whitney U test with Bonferroni correction. A horizontal line represents the median and interquartile range.
the third compared to the first tertile, \( P \)-value for the trend <.001). Gastrointestinal (\( P < .001 \)), respiratory (\( P = .004 \)), cardiovascular (\( P < .001 \)), and neurological symptoms (\( P < .001 \)), but not skin symptoms, were statistically significantly associated with the sIgE level for the causative foods.

### 3.5 | Risk factors for anaphylaxis during OFC for each food

The following factors significantly differed between participants with and without anaphylaxis during the OFC: a history of anaphylaxis to the causative food (\( P < .001 \)) and current allergic rhinitis (\( P = .036 \); Table S8). Anaphylaxis during the milk OFC (47.9%) was more common than that during the egg OFC (26.1%, \( P < .001 \)), wheat OFC (30.1%, \( P = .002 \)), and peanut OFC (29.0%, \( P = .048 \)), after Bonferroni correction (Table S4).

We examined the risk factors for an anaphylactic reaction during the OFC in 979 challenge-positive patients for each food. The sIgE levels for the causative foods and their components (ovomucoid, casein, omega-5 gliadin, and Ara h 2) were also considered a risk factor for anaphylaxis during the OFC for all antigens—egg, milk, wheat, and peanut (Table 2). In addition, a previous history of anaphylaxis to the causative food was a risk factor in the milk and peanut OFC.

### 4 | DISCUSSION

The present study is the first to determine that a higher sIgE level produced in response to causative foods is a risk factor for an anaphylactic reaction during an OFC among OFC-positive patients. The present study also confirmed that a higher sIgE level produced in response to causative foods is a risk factor for an anaphylactic reaction...
Among all patients who undergo an OFC, consistent with previous studies. Several studies have shown that the severity of symptoms during an OFC is associated with higher sIgE levels for the causative foods. However, in these studies, OFC-negative patients and OFC-positive patients were compared and severe OFC-induced symptoms were rare. In other words, no study has adequately evaluated challenge-positive patients. Moreover, the study populations were small in these previous studies. Thus, comparisons between challenge-positive patients with non-anaphylactic symptoms and those with anaphylactic symptoms could be performed.

During DBPCFC, a history of anaphylaxis to the causative food and being older were reported as risk factors for having a severe reaction. Results from our open OFC study also confirmed that a previous history of anaphylaxis and higher sIgE level for causative foods were risk factors for anaphylaxis. However, older age was not a risk factor for an anaphylactic reaction in the present study. This result may be attributed to the characteristics of our study population. The participants in the present study (median age, 5.2 years) were younger than those in the previous study (median age, 8.3 years). The present study also included more participants from the general population compared with that in the previous study. In another study, Wainstein et al reported that a previous history of anaphylaxis is not a risk factor for peanut OFC-induced anaphylaxis among patients without symptoms (n = 28), non-anaphylactic symptoms (n = 6), and anaphylaxis (n = 21). In contrast, a previous history of anaphylaxis was a risk factor for peanut OFC-induced anaphylaxis in the present study. Of the 129 participants who underwent a peanut OFC in the present study, 62 were peanut-reactive. This larger sample size may therefore have led to a statistically significant difference.

In the present study, an increasing sIgE level for the causative food was a risk factor for anaphylaxis during the OFC among OFC-positive patients. Therefore, we consider the sIgE level for the causative food to be a risk factor for a positive OFC and an anaphylactic reaction during the OFC. Furthermore, a higher component sIgE antigen level (ovomucoid, casein, omega-5 gliadin, and Ara h 2) was also associated with a similar elevated risk of anaphylaxis for all antigens—egg, milk, wheat, and peanut. We confirmed this result in the egg, milk, wheat, and peanut OFCs separately. This phenomenon may apply to almost all foods. An increasing sIgE level is the most important predictor of allergen-related symptoms in allergen-related asthma-rhinitis.

**FIGURE 4** Fitted probability curves for the OFC outcome at a given sIgE level for egg, milk, wheat, and peanut OFCs. The probability curve was subdivided by any reaction and an anaphylactic reaction to the OFC. Dotted lines represent the probability of any reaction to the OFC. Solid lines represent the probability of an anaphylactic reaction to the OFC. sIgE, specific immunoglobulin E; OFC, oral food challenge.
The risk of both ocular nasal and asthma-like symptoms increases with increasing sIgE levels. Increases in sIgE levels related to food may also contribute to gastrointestinal, respiratory, cardiovascular, and neurological symptoms. As specified in the definition of anaphylaxis,13 multiple organ symptoms tend to be involved. Consequently, the higher incidence of all symptoms, except skin symptoms, may have affected the higher incidence of anaphylaxis. The mechanism of how sIgE affects the prevalence of gastrointestinal, respiratory, cardiovascular, and neurological symptoms or anaphylaxis is unknown; thus, further study is required in this area.

The present study had several limitations. First, we used an open OFC and the amount of milk and egg was lower than that recommended by the EAACI. In addition, the OFC was not a DBPCFC. However, this did not affect the results considerably, as we assessed anaphylaxis. The reduced amount of cooked egg may have contributed to the low incidence of anaphylaxis in the egg allergy group. Nevertheless, anaphylaxis is not rare and for safety reasons, we were forced to set the target dose as less than the dose recommended by the EAACI. After passing the low-dose OFC, patients usually underwent a middle-dose OFC. Second, more high-risk patients with a high sIgE level for the causative food and a higher incidence of a previous history of anaphylaxis may have existed in the present study population compared to that in a general setting, as most patients were referred to our hospital from other pediatric clinics. Indeed, the sIgE levels for the causative foods were very high, and the frequency of a history of anaphylaxis was high as a result; thus, the frequency of OFC-induced respiratory symptoms might be relatively high in the present study. Third, variation between patients who received egg, milk, wheat, and peanut OFCs existed. Patients who received a peanut OFC were older than those who received other OFCs. Patients who received a milk or wheat OFC more frequently had a history of anaphylaxis in comparison to patients who received an egg or peanut OFC. This may have resulted in bias toward higher IgE levels and a greater number of high-risk patients in the present single-center study. Therefore, a multicenter study is warranted in the future to confirm our results.

The risk of all symptoms, except skin symptoms, during OFCs increased with increasing sIgE levels and, consequently, increased anaphylaxis during OFCs. The reason why increasing sIgE levels did not increase skin symptoms, but increased gastrointestinal, respiratory, cardiovascular, and neurological symptoms, as well as anaphylaxis, should be further evaluated in a multicenter study.

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**CONFLICTS OF INTEREST**

M. Ebisawa is on the scientific advisory board of DBV Technologies and has received lecture fees from Pfizer and Siemens. The other authors declare that they have no conflict of interests.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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