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The severity of reaction after food challenges depends on the indication: A prospective multicenter study

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A running title:

Risk of oral food challenges

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<Abstract>

Background: There are expanding indications for oral food challenges (OFCs). Although several studies have examined the risk of OFCs, little has been reported on allergic reactions during OFCs depending on the indication. This study assessed the prevalence, severity and treatment of allergic reactions depending on the indication for OFCs.

Methods: We performed a prospective multicenter study between March 2012 and May 2013. Severity of symptoms elicited by OFCs was classified according to grading of anaphylaxis that ranges from grade 1 (most mild) to grade 5 (most severe).

Results: A total of 5062 cases (median age, 3.8 years; males, 65.2%) were analyzed. Allergic reactions were elicited in 2258 (44.6%) OFCs, of which 991 (43.9%) were classified as grade 1, 736 (32.6%) were classified as grade 2, 340 (15.1%) were classified as grade 3, and 191 (8.5%) were classified as grade 4-5. Epinephrine was administered in 7.1% (n=160) of positive OFCs. Among the top three most common food allergens (hen's egg, cow's milk, and wheat), severity differed significantly depending on the indication for OFC, and adjusted standardized residuals indicated that severity of allergic reactions was higher for the indication to assess threshold level for oral immunotherapy. In addition, the prevalence of epinephrine use was highest for the indication to determine safe intake quantity.

Conclusions: Our study suggested that prevalence, severity, and treatment of allergic reactions differ depending on the indication for OFC. Further studies are needed to determine differences in risks depending on the indication for OFC.

Keywords: *Food allergy; food challenge; indication; children; severity; allergic reaction; epinephrine*

<Original Article>

Introduction

Food allergy affects nearly 8% of children and 5% of adults, and the prevalence and severity of childhood food allergy is greater than previously reported.¹ In Japan, the estimated prevalence is 5–10% among infants, 5% among young children, and 4.5% among schoolchildren. The most frequent causative foods are hen's egg (39.0%), cow's milk (21.8%), and wheat (11.7%).² Recommendations for the management of food allergies consist of strict and careful food avoidance and treatment of accidental exposures with medications.³ Oral food challenges (OFCs) are the gold standard for diagnosis and management of food allergy.⁴ The diagnosis of a food allergy requires consideration of the details of a patient's history and allergy tests such as skin prick test (SPT) and specific IgE level (sIgE).³ When these factors do not clearly confirm or refute food allergy, the clinician may perform a clinician-supervised OFC, which can also be used to determine whether a food allergy has resolved. In addition, OFCs can be undertaken to determine a safe intake quantity or to evaluate the symptom-inducing threshold level for oral immunotherapy (OIT).^{2,5}

Although OFCs may induce allergic reactions with symptoms ranging from mild to severe or potentially life-threatening, they have several benefits. First, positive results can confirm a diagnosis of food allergy. When OFCs prove that a patient can eat a suspected or previously experienced food allergen without eliciting allergic symptoms, the patient's quality of life and nutrition can be improved. Furthermore, knowing the dose that can cause symptoms may provide helpful information to patients and their caregivers. It has been reported that performing OFCs resulted in better caregiving to children with food allergies, regardless of a pass or fail outcome.⁶ In Japan, there are 312 facilities that perform OFC among 514 pediatric training programs offered by the Japanese Society of Pediatrics,⁷ which suggests that OFC has become routine for the diagnosis and

management of food allergy.

Recently, OIT has been explored as a viable treatment option for food allergy,⁸ but to date, a standard protocol for OIT has not been established. Although typical OIT (referred to as the “rush OIT”)^{9,10} is generally performed in hospital settings, some OIT (except for rush OIT) may be performed in clinic settings.^{11,12} Sato et al. reported that OIT was provided by 102 (28%) of 360 training and teaching facilities in the Japan Pediatric Society. Of those 102 facilities, 93 (91%) provided outpatient OIT, which was defined as treatment and follow-up without hospitalization.¹³

Several studies dealing with the risk of OFCs have been published.¹⁴⁻¹⁷ The risks associated with OFCs should be minimized by performing the procedures outlined in various reports and guidelines.⁴ In studies of OFCs and epinephrine use, OFCs performed for entry into food therapeutic trials had a higher overall prevalence of positive reactions that required epinephrine use than did OFCs performed for the assessment of tolerance.¹⁸ Unfortunately, there has been one report of a child who died during OFC.¹⁹ Until now, there has been little information from prospective multicenter studies regarding severe reactions during OFCs and whether the differences in allergic reactions depend on the reason for use of the OFCs. The purpose of the present study was to prospectively examine the prevalence, severity, and treatment of allergic reactions during OFCs in children, and to assess whether the allergic reactions differ depending on the reason for performing the OFC.

METHODS

Subjects

We conducted this prospective multicenter study between March 2012 and May 2013. Among 179 facilities with councilors of the Japanese Society of Pediatric Allergy and Clinical Immunology who either performed OFCs or published about OFCs on the website of the Japanese Society of

Food Allergy, 142 facilities agreed to participate in the study. To minimize any imbalance in the number of OFCs among each facility, the maximum number of OFCs was limited to 100 in each facility during a 6-month period. This study was approved by the Institutional Review Board (IRB) of the University of Toyama and funded by the Japanese Society of Pediatric Allergy and Clinical Immunology.

Oral food challenges

The OFCs were performed by allergy specialists in reference to the Japanese OFC guideline^{2,20} because it was important for patient safety to match clinical situations (e.g., an indication for OFCs or individual patient needs). The indications for OFCs were classified into four categories: to confirm diagnosis, to confirm tolerance, to determine safe intake quantity, or to assess threshold level for OIT. The Japanese guideline does not describe a unified protocol for OFCs, but instead recommends that food challenge should be started at a low dosage that is determined by consideration of the patient's background. Therefore, there was no unified protocol in this study. Challenges were terminated at the discretion of investigators when objective signs or subjective symptoms were observed. Medical treatments (e.g., antihistamines, epinephrine, bronchodilators, intravenous fluids, and oxygen) for a positive reaction were administered as needed for symptoms at the discretion of the practitioner in reference to the Japanese OFC guideline.^{2,20} In cases with a grade 4-5 reaction, further detailed information on the OFC method, elicited symptoms, and treatments was collected prospectively.

Assessment of severity

The severity of symptoms was graded based on organ system involvement using the classification of anaphylaxis modified from the original version proposed by Sampson,²¹ which

was issued in the Japanese Guideline for Food Allergy.²⁰ In this classification, objective symptoms observed during positive challenges are divided into five systems: skin, digestive organ, respiratory organ, circulatory organ, and neurological (Table 1). The severity was classified depending on the organ system most affected.

Statistical analysis

Statistical analysis was performed by using SPSS for Windows (IBM SPSS Statistics 22). We used the nonparametric Mann-Whitney test and Kruskal Wallis test for continuous variables and Pearson's chi-squared test for categorical variables, except when expected cells were found to be less than 5, in which case we used Fisher's exact test. If the overall chi-squared test was significant, standardized adjusted residuals for the cell percentage of each sub-category were examined to determine which cell differences contributed to the chi-squared test results. An adjusted residual score greater than 1.96 for a given sub-category percentage indicated that the sub-category differed significantly from the overall percentage. A *P* value < 0.05 was considered statistically significant.

Results

Baseline characteristics of patients

The study included 5270 patients with OFCs from 119 facilities (112 hospitals and 7 private clinics) across Japan. After excluding patients who were older than 19 years of age, had been administered placebo food, had undergone food-exercise challenges, or had insufficient questionnaire information, 5062 patients (median age, 3.8 years; males, 65.2%) with OFCs were selected for analysis. Among these patients, the most common foods with which they were challenged were hen's egg (2468), cow's milk (1108), and wheat (600). OFCs with food types

such as baked hen's egg or cow's milk were included in the analyses of OFCs with native hen's egg or cow's milk.

Positive reactions were seen in 2258 (44.6%) patients with the following prevalence by food type: hen's egg, 43.5% (n = 1074); cow's milk, 54.6% (n = 605); and wheat, 55.0% (n = 330) (Figure 1). Of the positive OFCs, skin symptoms were most frequently elicited (n = 1663, 73.6%), followed by digestive symptoms (n = 904, 40.0%), respiratory symptoms (n = 895, 39.6%), circulatory symptoms (n = 97, 4.3%), and neurological symptoms (n = 252, 11.2%) (data not shown). Among the positive reactions, 991 (43.9%) were classified as grade 1, 736 (32.6%) were classified as grade 2, 340 (15.1%) were classified as grade 3, and 191 (8.5%) were classified as grade 4-5. Epinephrine was administered in 7.1% (n=160) of positive OFCs (Figure 2). Multiple doses of epinephrine were administered to 10 patients (6.3% of the patients administered epinephrine) with grade 4-5 reactions (9 patients dosed twice, 1 patient dosed 4 times). No OFC resulted in death or had sequelae.

Results of oral food challenges depending on indication

Of 5062 OFCs, 777 (15.3%) were for confirming diagnosis, 2408 (47.6%) were for confirming tolerance, 1501 (29.7%) were for determining safe intake quantity, and 376 (7.4%) were for assessing threshold level for OIT (Table 2). There was a significant relationship between the results of OFCs and their indications. The adjusted standardized residuals demonstrated that OFCs for the indications to determine safe intake quantity and to assess threshold level for OIT resulted in more positive responses than did the indications to confirm diagnosis and to confirm tolerance.

We analyzed the top three most common food allergens (hen's egg, cow's milk, and wheat) with positive OFCs to assess differences in the prevalence, severity, and treatment of allergic reactions depending on the indication for OFC (Table 3). There was no significant correlation between the

kind of food and the indication for OFC. The severity of allergic reactions differed significantly depending on the type of indication for OFC. Adjusted standardized residuals demonstrated that the prevalence of grade 1 severity was highest for the indications to confirm diagnosis and tolerance, and the prevalence of grade 3 and grade 4-5 severity was highest for assessing threshold level for OIT. In addition, the use of epinephrine was higher for the indication to determine safe intake quantity than for the other indications.

Characteristics of grade 4-5 reactions

Among OFCs to the three most common food allergens that resulted in reactions with severity of grade 4-5, we compared patients treated with and without epinephrine to assess if there were differences in their characteristics, allergic reaction symptoms, and medications for allergic reactions (Table 4). No significant differences were detected in the median age, sex, history of anaphylaxis, or comorbidities of bronchial asthma and atopic dermatitis. There were also no significant differences between these two groups in the interval time of administration, time from final administration through maximum symptom, kinds of food, or the indication for OFC.

There was a high frequency of respiratory symptoms in patients treated with (90.9%) and without (100%) epinephrine (Table 4). Patients who developed circulatory and neurological symptoms were significantly more often treated with epinephrine (48.1% and 59.7%, respectively) compared to patients who were not treated with epinephrine (13.1% and 18.2%, respectively). Furthermore, antihistamines, steroids, intravenous fluids, and oxygen via mask were administered more often to patients treated with epinephrine than to those not treated with epinephrine. However, the frequency of bronchodilator use by patients not treated with epinephrine was higher (95.5%) than that of patients treated with epinephrine (82.7%).

DISCUSSION

Food allergies seem to have greatly increased in the last few decades,¹ and OFCs are crucial for the diagnosis and management of these reactions. New therapies for food allergy, such as OIT, are increasing in number and may also increase the demand for OFCs. This study demonstrated that the indications to determine safe intake quantity and to assess threshold level for OIT were more positively associated with OFC than the other indications. Furthermore, the severity of the reaction for the indication to assess threshold level for OIT was more severe than that of the other indications. Epinephrine was administered in 7.1% of positive reactions among all OFCs. And the use of epinephrine was higher for the indication to determine safe intake quantity than for the other indications. To our knowledge, this is the first prospective multicenter study to examine the severity of allergic reactions to OFCs depending on the indication in children.

Although several studies have examined the risk associated with OFCs,¹⁴⁻¹⁸ they were retrospective or single-center studies. A recent multicenter review of 6377 OFCs showed that the prevalence of allergic reactions was 14%, the prevalence of anaphylaxis was 2%, and there were no fatal reactions.¹⁷ On the other hand, Noone et al. reported that among 74 positive OFCs performed as a screening test for food allergy therapy trials, 39.2% of patients were treated with epinephrine.¹⁸ To date, age, severity of prior reactions, in vitro test results, and comorbidities (e.g., asthma) have been known as factors that affect results of OFCs.^{4,15,22,23} The present study suggests that the indications are associated with the prevalence and severity of allergic reaction or prevalence of epinephrine use. One major reason for these observed differences could have been the patient selection process. When OFCs were performed to assess threshold level for OIT, patients with persistent food allergy may have developed more severe reactions than patients with transient food allergy.²⁴ Secondly, these differences might be explained by the rigidity of the protocol for OIT in research studies. In effect, the need for objective symptoms to be considered remarkably positive in

order for the OFC to be diagnostic could lead to greater severity of symptoms because the threshold level might be an important criterion for OIT.

Notably, patients with grade 4-5 reactions who were treated with epinephrine in our study more often developed cardiovascular or neurological symptoms compared to patients who were not treated with epinephrine. On the other hand, patients not treated with epinephrine more often developed respiratory symptoms compared to patients treated with epinephrine. A possible reason for this was that patients with respiratory symptoms such as wheezing used inhaled bronchodilators immediately and symptoms disappeared without the use of epinephrine. Therefore, it is critical to monitor not only respiratory symptoms but also early signs of cardiovascular or neurological involvement. Furthermore, grade 4-5 reactions developed later than 1 hour after final administration of food in 28.7% (N=47) of OFCs for the three most common food allergens (hen's egg, cow's milk, and wheat). There were no OFCs in which severe symptoms developed more than 3 hours after the last administration. In addition, there was no significant association between the kind of food and the time lag from final administration through maximum symptoms (data not shown). This suggests that OFCs should be monitored closely and carefully under supervision not only during administration of food but also for more than 1 hour after the final challenge.

A limitation of our study is that it was not performed with a unified protocol. Although there are several weaknesses of real-world data, such as lack of good quality, such data could shed light on the everyday medical practice of OFC use. This study was performed for existing patients according to clinical need rather than following a research protocol. Further studies using a unified protocol are needed to determine whether the prevalence, severity, and treatment of allergic reactions differ depending on the indication for OFC. Another limitation is that not enough data for SPTs and sIgE levels were collected, although previous studies have shown that increased symptom severity during OFCs was related to these factors.^{22,25} Because SPT is not a routine

procedure in Japan, SPTs were performed only in a few cases. The data on sIgE level were collected from 4865 (96.1%) out of 5062 patients, however, levels were measured using different methods such as ImmunoCAP IgE assay and multiple allergosorbent test chemiluminescent assay (MAST CLA). Because each method has its own unique characteristics, the results are not interchangeable.²⁶ Therefore, we could not evaluate the association between sIgE levels and severity of elicited symptoms. Recently, it was reported that levels of sIgE to wheat gluten-derived components correlated well with wheat challenge outcome and severity.²⁷ Further studies will be required to determine the clinical utility of component-resolved diagnostics to define food allergy or predict the severity of allergic reactions.

In conclusion, our study results indicated that OFCs may cause severe reactions, especially when used for indications to assess safe threshold level and to assess threshold level for OIT. The range of indications for OFCs is capable of being expanded for the management of food allergy. Therefore, OFCs should be performed only under the care of a trained physician who fully understands the risks of OFC.

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(1)

Table 1. Classification of anaphylaxis

Grade	Skin	Digestive organ	Respiratory organ	Circulatory organ	Neurological
1	<Localized> •pruritus, erythema, urticaria, angioedema	•Oral itch and/or discomfort •Swelling of lips	•Pharyngeal pruritus and/or discomfort	-	-
2	<Generalized> •pruritus, erythema, urticaria, angioedema	•Nausea •1-2 occurrences of vomiting and/or diarrhea •Transient abdominal pain	•Slight nasal congestion, and/or rhinorrhea •Sneezing once or twice •Sporadic cough	-	•Decrease in activity level
3	Above symptoms	•Repeated vomiting and/or diarrhea •Persistent abdominal pain	•Marked nasal congestion and/or rhinorrhea •Repeated sneezing •Persistent cough •Laryngeal pruritus	•Tachycardia (increased ≥ 15 beats/minute)	•Sense of unease
4	Above symptoms	Above symptoms	•Laryngeal tightness •Hoarseness •Barking cough •Dysphagia •Wheezing •Dyspnea •Cyanosis	•Arrhythmia •Decrease in blood pressure	•Unrest •Fear of death

5	Above symptoms	Above symptoms	• Respiratory arrest	• Severe bradycardia • Marked decrease in blood pressure • Cardiac arrest	• Unconsciousness
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Not all symptoms are essential. The symptom grade will be determined according to the organ symptoms of the highest grade.

Grade 1 will not be regarded as anaphylaxis.

Table 2. Results of oral food challenges depending on indication

	All challenges	Positive challenges	Negative challenges	<i>P</i>
	N=5062	N=2258	N=2804	
Age, years, median (25-75%)	3.8 (1.9-6.2)	4.3 (2.3-6.5)	3.3 (1.8-6.0)	< 0.0001
Male gender, N (%)	3302 (65.2)	1481 (65.6)	1821 (64.9)	0.631
History of anaphylaxis, N (%)	1406 (28.6)	795 (35.9)	611 (22.6)	< 0.0001
Data not available, N (%)	141 (2.8)	43 (1.9)	98 (3.5)	
Aims of OFC				< 0.0001
To confirm diagnosis, N (%)	777 (15.3)	247 (31.8)	530 (68.2)	
To confirm tolerance, N (%)	2408 (47.6)	976 (40.5)	1432 (59.5)	
To determine safe intake quantity, N (%)	1501 (29.7)	781 (52.0)	720 (48.0)	
To assess threshold level for OIT, N (%)	376 (7.4)	254 (67.6)	122 (32.4)	

Bold cells show significant adjusted standardized residuals.

OFC, oral food challenge; OIT, oral immunotherapy

Table 3. Clinical characteristics depending on indication for OFC to top three most common food allergens

	To confirm diagnosis N=175	To confirm tolerance N=872	To determine safe intake quantity N=718	To assess threshold level for OIT N=244	<i>P</i>
Age, years, median (25-75%)	2.1 (1.3-3.9)	3.7 (2.0-5.8)	4.1 (2.3-6.4)	5.8 (4.3-8.7)	< 0.0001
Male gender, N (%)	118 (67.4)	575 (65.9)	457 (63.6)	167 (68.4)	0.496
History of anaphylaxis, N (%)	30 (17.2)	268 (31.6)	296 (41.6)	133 (55.0)	< 0.0001
Data not available	1	25	7	2	
Food, N (%)					0.08
Hen's egg (N=1074)	91 (52.0)	482 (55.3)	380 (52.9)	121 (49.6)	
Cow's milk (N=605)	47 (26.9)	241 (27.6)	229 (31.9)	88 (36.1)	
Wheat (N=330)	37 (21.1)	149 (17.1)	109 (15.2)	35 (14.3)	
Severity, N (%)					< 0.0001
Grade 1 (N=853)	95 (54.3)	412 (47.2)	287 (40.0)	59 (24.2)	
Grade 2 (N=672)	46 (26.3)	289 (33.1)	242 (33.7)	95 (38.9)	
Grade 3 (N=308)	19 (10.9)	113 (13.0)	116 (16.2)	60 (24.6)	
Grade 4-5 (N=176)	15 (8.6)	58 (6.7)	73 (10.2)	30 (12.3)	
Epinephrine, N (%)	11 (6.3)	46 (5.3)	63 (8.8)	23 (9.4)	0.022

Bold cells show significant adjusted standardized residuals.

OFC, oral food challenge; OIT, oral immunotherapy

Table 4. Demographic characteristics of patients with grade 4-5 reactions who were or were not treated with epinephrine

	Epinephrine N=77	No epinephrine N=99	<i>P</i>
Age, years, median (25-75%)	4.7 (3.2-6.0)	4.3 (2.5-6.5)	0.521
Male gender, N (%)	53 (68.8)	70 (70.7)	0.788
History of anaphylaxis, N (%)	38 (50.7)	53 (53.5)	0.708
Data not available, N	2	0	
Co-morbidities			
Bronchial asthma, N (%)	34 (44.7)	41 (46.1)	0.864
Not available, N	1	10	
Atopic dermatitis, N (%)	49 (64.5)	61 (68.5)	0.581
Not available, N	1	10	
Interval time (min) of administration, median (25-75%)	20 (15-30)	20 (15-30)	0.191
Reaction to initial dose, N (%)	14 (18.2)	23 (23.2)	
Data not available, N	0	1	
The time from final administration through maximum symptom			0.069
0-29 min, N (%)	37 (49.3)	41 (46.1)	
30-59 min, N (%)	12 (16.0)	27 (30.3)	
1 -3 hours, N (%)	26 (34.7)	21 (23.6)	
Not available, N	2	10	
Food			0.787
Hen's egg, N (%)	28 (36.4)	39 (39.4)	

Cow's milk, N (%)	31 (40.3)	41 (41.4)	
Wheat, N (%)	18 (23.4)	19 (19.2)	
Purpose			0.096
To confirm diagnosis, N (%)	6 (40.0)	9 (60.0)	
To confirm tolerance, N (%)	20 (34.5)	38 (65.5)	
To determine safe intake quantity, N (%)	40 (54.8)	33 (45.2)	
To assess threshold level for OIT, N (%)	11 (36.7)	19 (63.3)	
Organ with positive reactions			
Skin, N (%)	73 (94.8)	74 (74.7)	< 0.0001
Digestive, N (%)	41 (53.2)	44 (44.4)	0.246
Respiratory, N (%)	70 (90.9)	99 (100.0)	0.003
Circulatory, N (%)	37 (48.1)	13 (13.1)	< 0.0001
Neurological, N (%)	46 (59.7)	18 (18.2)	< 0.0001
Treatment			
Antihistamines, N (%)	71 (93.4)	68 (78.2)	0.006
Not available, N	1	12	
Bronchodilators, N (%)	62 (82.7)	84 (95.5)	0.008
Not available, N	2	11	
Steroids, N (%)	62 (82.7)	37 (43.0)	< 0.0001
Not available, N	2	13	
Intravenous fluids, N (%)	40 (53.3)	13 (15.3)	< 0.0001
Not available, N	2	14	
Oxygen via mask, N (%)	24 (32.4)	13 (15.3)	0.011
Not available, N	3	14	

Figure legends

Figure 1. Number and rate of positive reactions by food allergens.

Figure 2. Severity of allergic reactions and rate of epinephrine use.



