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Food allergy treatment guidance based on oral food challenge tests

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Abstract

Japanese Guideline for Food Allergy 2014 states that definitive diagnosis of food allergy should be based on the results of an oral food challenge test (OFC). At the Department of Pediatrics, Nara Hospital, Kinki University Faculty of Medicine, OFCs were not conducted in a uniform manner until a standardized protocol was implemented in 2013. We retrospectively examined protocol-based OFCs by reviewing medical records. The number of OFCs increased during 2013, so did the number of patients for whom an elimination diet was discontinued. On the other hand, the number of patients with symptoms induced during the test also increased; some of these children developed anaphylaxis. Overall, food allergy treatment guided by OFCs may improve nutrition, contributing positively to children's and their families' quality of life.

Key words: food allergy, oral food challenge test (OFC), anaphylaxis (An)

Introduction

Japanese Guideline for Food Allergy 2014 issued by Committee for Japanese Pediatric Guideline for Food Allergy states that definitive diagnosis of immediate-type food allergy should be based on the development of immediate-type symptoms during an oral food challenge test (OFC).[1] However, many patients are still diagnosed with food allergy based on the allergen-specific serum immunoglobulin (Ig) E concentration alone, resulting in the elimination of the suspected food. At the Department of Pediatrics, Nara Hospital, Kinki University Faculty of Medicine, OFCs conducted before 2013 followed the preferences of individual attending physicians because there was no unified protocol. An OFC is a test performed to confirm that symptoms are induced by the ingestion of a food suspected to be an allergen.[1] More specifically, the test can serve for 3 purposes: The first is to identify a suspected allergen as an etiologic factor when there is a suspicion that the patient had exhibited induced condition by eating the food which has never been eaten or when other allergy tests have demonstrated allergen sensitization. The second is to evaluate the possible acquisition of tolerance, since allergies to eggs, milk, and wheat that manifest immediate-type symptoms during early childhood are most likely to subside spontaneously before the child enters a school.[1] The third purpose is to establish safe conditions of intake. Restriction of the ingested amount may help avoiding allergic symptoms, even though the ingestion of a large amount may precipitate them. Further, food preparation, eg. cooking eggs, may reduce allergenicity, In this study, we retrospectively evaluated the usefulness of an OFC protocol that was introduced for the diagnosis of food allergy

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in 2013.

Subjects and Methods

Subjects

Subjects were children brought to Nara Hospital, Kinki University Faculty of Medicine for the management of food allergy in 2012 and 2013. The purposes of OFCs included the identification of an allergen for 75 cases, judgement of the possible tolerance for 5 cases, and determination of a safe dose for 2 cases.

Oral food challenge test (OFC)

The protocol introduced in this study involved an open design; both examiners and subjects could recognize the challenge foods. Food was ingested in 3 gradually increasing volumes at 30-minute intervals. Challenge food included boiled eggs, milk, wheat noodles, and soybean curd. Other food used for challenge were prepared in a standard volume typical for 1 meal. The challenge volume was increased in 4 steps (Table 1), and a subject was assigned to a step on the basis of risk assessment using pre-OFC allergy tests (allergen-specific IgE antibody, skin-prick test). Symptoms were evaluated using Sampson's classification.[2] Subjects experiencing markedly induced symptoms were considered to show positive reactions ; those free of symptoms for up to 2 hours after the final ingestion were considered to show negative reactions. Evaluation was withheld for subjects with mild symptoms and for those in whom ingestion was precluded by refusal or sleepiness.

Food elimination was discontinued completely in step 4 subjects with negative reactions and in step 3 children aged 1.5 years or younger at the time of elimination. Elimination was partially discontinued in step 2 and in other step 3 subjects who had negative reactions. Elimination was continued in step 2 to 4 subjects with positive reactions. In step 1 subjects with negative reactions, OFCs were conducted to subsequent steps ; food elimination was then completely or partially discontinued, or continued based on OFC results, as described above. Although criteria for continuing or discontinuing food elimination were not established in 2012, complete or partial discontinuation or continuation was evaluated for that year using the above protocol, based on challenge volumes described in the medical records.

Statistical analysis

Results were compared retrospectively between 2012 and 2013. For statistical analysis, the Fisher's exact probability test was used. A p-value below 0.05 was considered indicative of significance.

Table 1 The OFC protocol

	Total amount of challenge food	3 gradually increasing volumes
Step 1	1 g	0.15→0.3→0.6 g
Step 2	10 g	1.5→3→6 g
Step 3	30 g	5→10→15 g
Step 4	50 g	10→15→25 g

The challenge volume was chosen according to 4 steps.

Results

In 2012, the number of subjects was 32. Ages at the initial consultation ranged from 5 to 168 months (median, 22 months). In 2013, the number of subjects was 53. Ages at the initial consultation ranged from 7 to 159 months (median, 23 months ; Table 2). The total number of food items eliminated based on the results of an inquiry at consultation was 67 for the 32 subjects in 2012, and 115 for the 53 subjects in 2013

Table 2 Patients' profiles

	2012s	2013s
Number of patients	32	53
Total number of food items eliminated at the first visit	67 (average, 2.1/person)	115 (average, 2.2/person)
Sex (male : female)	21 : 11	32 : 21
Age (months) (median)	5 to 168 (22)	7 to 158 (23)

Compared the number of subjects and food items and sex, age of 2012 and 2013.

Table 3 Profiles of Patients who underwent OFCs in 2012 and 2013

	2012	2013	P
Number of patients who underwent OFCs	4	29	NS
Total number of OFCs	8	82	NS
Specific IgE (UA/ml)			
egg	0.52 to 65.3 (median, 9.9)	0.8 to 72.5 (median, 7.89)	NS
wheat	3.2 to 31.4 (13.3)	0.56 to 30.1 (2.98)	NS
milk	ND	1.38 to 8.35 (2.34)	
soybean	ND	3.07	
shrimp	ND	0.96 to 17 (17)	
squid	ND	32.9	
salmon	ND	14.8	
banana	ND	11.3	
orange	ND	0	

Comparison of OFCs of 2012 and 2013.

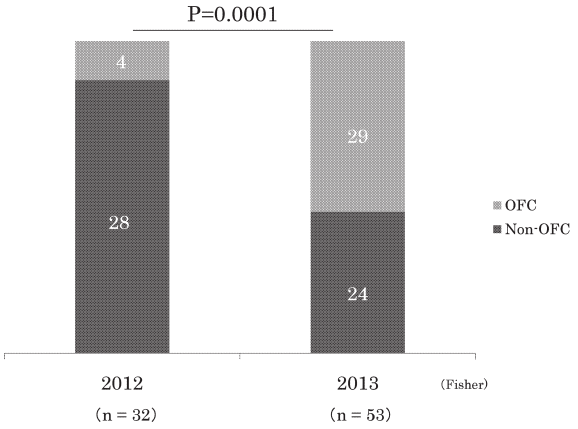

Fig. 1 Rates of patients undergoing OFCs
The proportion of subjects who underwent OFCs was significantly larger in 2013.

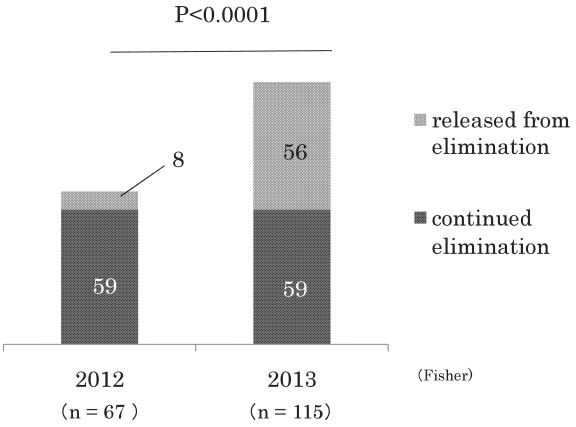

Fig. 2 Rates of discontinued food elimination
As for the results of OFCs, all subjects (8/8) showed negative reactions in 2012. However, challenge food volumes were small. Food elimination was partially discontinued in all subjects. In 2013, negative reactions were noted in 56 of 82 subjects. In 19% of all subjects in 2013, food elimination was completely discontinued. The proportion of subjects in whom food elimination was either completely or partially discontinued also increased in 2013.

(Table 2).

In 2012, 8 OFCs were conducted in 4 subjects. In 2013, 82 OFCs were performed in 29 subjects. No difference in the allergen-specific IgE concentration was observed between the 2 groups of subjects (Table 3). The proportion of subjects who underwent OFCs was significantly greater in 2013 (Figure 1).

The number of suspected allergens decreased by introducing OFC protocols we have devised. As for the results of OFCs, all subjects (8/8) showed negative reactions in 2012. However, challenge food volumes were small. Food elimination was partially discontinued in all subjects. In 2013, negative reactions were noted in 56 of 82 tests. In 19% of all subjects in 2013, food elimination was completely discontinued. The proportion of subjects in whom food elimination was either completely or partially discontinued also increased in 2013 (Figure 2).

In 2013, 15 subjects had positive reactions to : eggs in 8, wheat in 3, milk in 2, soybeans in 1, and bananas in 1 (Table 4). Table 5 shows the classification of anaphylaxis defined in the Guidline.[1] Anaphylaxis occurred in 6 patients, all of whom had histories of ingestion and induced symptoms. One required the subcutaneous injection of epinephrine (Table 6). No

Table 4 Results of OFCs

	2012		2013				
	Egg	Wheat	Egg	Wheat	Milk	Soybean	Others
Positive (Grade-number)	0	0	8 (I-3, II-5)	3 (II-2, IV-1)	2 (I-1, II-1)	1 (II-1)	1 (III-1)
Negative	4	4	36	4	7	3	6
Holding	0	0	6	0	2	1	2

In 2013, 15 subjects had positive reactions : to eggs in 8, wheat in 3, milk in 2, soybeans in 1, and bananas in 1.

Table 5 Classification of anaphylaxis

Grade	skin	Digestive organ	Respiratory organ	Circulatory organ	Nerve
1	〈Localized〉 • pruritus, erythema, urticaria, angioedema	• Oral itch and/or discomfort • Swelling of lips	• Pharyngeal pruritus and/or discomfort	—	—
2	〈Systemic〉 • 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 coughing	—	• 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 • Wheezing • Dyspnea • Hoarseness • Cyanosis • Barking • Cough • Dysphagia	• Arrhythmia • Decreased blood pressure	• Unrest • Fear of death
5	Above symptoms	Above symptoms	• Respiratory arrest	• Severe bradycardia • Marked decrease in blood pressure • Cardiac arrest	• Unconsciousness

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.

positive reactions were noted in 2012.

Discussion

Food allergy is classified into 5 types : non-IgE-mediated gastrointestinal food allergy in neonates and infants, infantile atopic dermatitis caused by food allergy, immediate allergic reactions such as anaphylaxis, exercise-induced anaphylaxis, and oral allergy syndrome, although the term most often refers to immediate-type symptoms.[1] The diagnosis involves clinical history, allergen-specific IgE determinations in serum, skin tests, and OFCs. Conclusive diagnosis cannot be achieved when the description of symptom development by parents is not clear, or

Table 6 Anaphylaxis (An) history

Age	Sex	Eating history	History of An	History of reactions	Food	Dose	Grade	Specific IgE antibody	Use of epinephrine
10M	female	YES	NO	NO	wheat	50 g	2	0.56	NO
1Y	male	YES	NO	YES	egg	10 g	3	20.7	YES
1Y	male	YES	NO	YES	wheat	30 g	2	14.1	NO
3Y	male	YES	YES	YES	banana	1 peace	3	11.3	NO
4Y	male	YES	NO	YES	egg	50 g	2	4.48	NO
10Y	male	YES	YES	YES	wheat	10 g	2	30.1	NO

Anaphylaxis occurred in 6 of the patients, all of whom had histories of ingestion and induced symptoms. All patients experiencing anaphylaxis in this study had a history of induced symptoms before OFCs.

after the apparent gradual acquisition of tolerance. Although IgE and skin tests are considered specific to immediate allergic reactions, these reflect the state of sensitization alone and cannot determine the presence or absence of food allergy-induced symptoms developing through the processes of digestion and absorption in vivo.[3]

In particular, specific IgE measurement has been used routinely in general medical examinations since the 1990s. The simplicity of scoring the results in classes 0 to 6 based on the IgE concentration has contributed to the attractiveness of specific IgE as a diagnostic indicator. As a result, food elimination is still prescribed frequently based on the IgE concentration alone. IgE determinations are useful for screening after the occurrence of apparent allergic symptoms without an identified cause. IgE concentrations are correlated with the likelihood of allergy, as indicated by probability curves[1,4]; the spontaneous acquisition of tolerance is usually unlikely in such instances.[1] However, food elimination should not be prescribed based solely on the putative sensitization on a specific IgE level alone, given insufficient information about the onset of allergic symptoms. The use of OFCs was supported by a double-blind, placebo-controlled food challenge test that was reported from the US in the 1970s[5]. In Japan, OFCs have been conducted in increasing numbers of cases since the late 1980s. OFCs for inpatients and outpatients became covered by Japanese health insurance system in 2006 and 2008, respectively. Challenge test guidelines were also proposed in 2009. Because food allergy diagnosis has the short history yet, there is a difference in thinking between doctors and hospitals.

In this study, we examined the possible effectiveness of OFCs before and after the introduction of an OFC protocol in a single center. Introduction of the standardized protocol greatly increased the use of OFCs and also increased the amount of food used in challenges. These changes may have resulted from an improved understanding of OFC. After the adoption of the protocol, patients could eat the food which had been eliminated based on results of OFC. Elimination diets compromise the quality of life of patients and their families; such treatments also provoke anxiety, as previously reported in Japan.[6,7] The increase in the rate at which an elimination diet was discontinued was significant after the introduction of the standardized OFC.

In high-risk patients, OFCs initially use food volumes smaller than those on daily intake, as was done generally in 2012. When negative reactions are obtained using reduced amounts, it is necessary to conduct OFCs using standard intake volumes. When OFCs with an insufficient volume show negative reactions, ingestion with an increased volume may induce allergic symptoms to patients. In 2013, positive reactions and sometimes anaphylaxis occurred in the patients by actively doing OFCs. This may be related to an increased number of OFCs as well as a greater challenge volume.

When performing OFCs, emergency medicine, oxygen, and electric monitors should be at hand. All patients experiencing anaphylaxis in this study had a history of induced symptoms before OFCs (Table 6). Obtaining such pre-OFC information is important; if an OFC yields a positive reaction, attending personnel are better prepared to alleviate the stress on children and their families. However, OFCs should be conducted according to the given protocol, considering the benefits of possibly discontinuing dietary restrictions, accurately identifying allergens and their

amounts that provoke symptoms, and possibly confirming the acquisition of tolerance.

In this study, food elimination often could be discontinued based on the results of OFCs. In some of these patients, food elimination may have been inappropriate. Previously, inappropriate elimination according to non-evidence-based methods was frequent (e.g., beef elimination in patients with milk allergy). If the elimination is inappropriate, it should be discontinued. When a diagnosis of food allergy is made based on sensitization alone, a food-related onset should be confirmed. Additionally, the spontaneous acquisition of tolerance is a possibility that should be assessed using OFCs.

This study confirmed the usefulness of OFCs in the diagnosis of food allergy. OFC methods should continue to be refined to improve their safety and utility. We will continue to build a system so that many food allergy patients can receive appropriate medical care.

Acknowledgments

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Conflicts of Interest

We have no conflicting interest regarding the present study.

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