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Is Oral Food Challenge (OFC) test safe for preschool children?

Sait Karaman, Semiha Erdem Bahçeci, Hikmet Tekin Nacaroğlu, Canan Şule Karkıner, Demet Can

Abstract

Background: Oral food challenges (OFCs) are performed for diagnosis of a food allergy in cases where the allergy is not supported by patient history, or when a newly developed tolerance level needs to be established.

Objective: We aimed to investigate the prevalence and severity of reactions during OFCs in preschool children.

Methods: A retrospective study was conducted on children younger than 5 years, for whom OFC had been performed with milk, egg white and egg yolk. All children had been admitted to the Department of Pediatric Allergy at Behçet Uz Children's Hospital between 1 January 2010 and 31 December 2014. Any symptoms developed during the OFC were classified and recorded.

Results: A total of 122 patients who underwent an OFC were included in this study. The patients included 85 males (69.7%), and 50.8% of patients (n = 62) had a history of IgE-mediated food allergy. Co-existing allergies were found for 57.4% (n = 70) of patients. Of the OFCs performed, tests for milk, egg white and egg yolk made up 46.5, 30.5 and 23.0%, respectively. Of these, 19% (n = 33) were mild and 4.5% (n = 7) were moderate allergies in terms of symptom development. It was determined that the skin prick test (SPT) wheal size and the food-specific IgE levels did not effect in determining whether the allergic reaction would develop by OFC if the SPT wheal size and the food-specific IgE levels were below the cut-off point of a 95% positive predictive value ($p > 0.05$).

Conclusion: The severity of egg and milk allergy symptoms resulting from the frequently used OFC in preschool children are generally mild and easy to manage, particularly if the OFC is only conducted if serum-specific IgE or SPT wheal size is below the cut-off point.

Keywords: Allergy; Challenge; Egg; Food; Milk; Preschool

From:
Department of Pediatric Allergy, Behcet Uz Children's Hospital, Izmir, Turkey

Corresponding author:
Sait Karaman
Department of Pediatric Allergy, Behcet Uz Children's Hospital, Izmir, Turkey
E-mail: saitkaraman73@gmail.com

Introduction

The incidence of milk and egg allergies in preschool children is about 2.5%,[1] however, diagnosis of a food allergy can be difficult in these children. Although the frequency of non-IgE -mediated food allergies is relatively high, It may not diagnosis by the clinical history of the patient. Furthermore, the low positive predictive values of skin prick tests (SPT) and food-specific IgE.[2,3] Thus, the oral food challenge (OFC), the diagnostic "gold standard" for food allergies, is used to confirm the diagnosis.[4,5] In previous studies, symptoms developed during OFC provocation tests have been reported to vary from mild skin reactions to near fatal reactions.[6–8] It is difficult to recognize severe reactions, such as anaphylaxis, in children of this age group, particularly as it can be difficult for them to express any symptoms of nausea and stomach ache that might appear during the test. Data regarding the severity of reactions experienced by children during OFCs are limited. In the few studies in the literature that have investigated the safety of OFCs, severe reactions were found to occur in 2.2–28% of positive reactions.[9] In the present study, we aimed to determine the frequency and severity of reactions during OFCs for egg and milk allergies in preschool children.

Methods

In this retrospective study, patient files and test records of preschool children that underwent OFC to test for milk, egg white and egg yolk allergies were examined. The study included patients that had been admitted to the Department of Pediatric Allergy at Behçet Uz Children's Hospital between 1 January 2010 and 31 December 2014. Approval for the study was obtained from the ethics committee of Behçet Uz Children Hospital (protocol number 2014/05).

Patients

Children were primarily referred due to a positive history of food allergy. Children that had been diagnosed as allergic and rechallenged to investigate tolerance were also included in the study. The age, clinical history and family history of each patient was considered. Children that had experienced anaphylaxis within the past 12 months were excluded from the study. Patients were only included if their cut-off values for serum specific IgE (sIgE) or SPT wheal size was below 95% of the positive predictive value. The serum sIgE cut-off point, which determines clinical reactivity with a 95% positive predictive value, was assumed to be 5 kU/L for milk and 2 kU/L for both egg yolk and egg white for subjects aged younger than 2 years, whereas values of 15 kU/L for milk and 7 kU/L for egg yolk and egg white was assumed for subjects aged 2 years or older.[10] The cut-off point for the SPT was taken to be 6 mm for milk and 5 mm for egg yolk and egg white for subjects younger than 2 years, and 8 mm for milk and 7 mm for egg yolk and egg white for subjects aged 2 years and older.[11,12]

Skin prick tests

The SPTs were performed by trained physicians on the volar surface of the forearm of each patient using a commercial extract of the suspected food (ALK Abelló, Horsholm, Denmark). A prick-by-prick (PP) technique with pasteurized cow milk and raw egg was used, always including a positive control with histamine and a negative control with saline. A mean wheal diameter of greater than 3 mm after 15 minutes of testing the allergen extracts was taken to indicate positivity. While the SPT was evaluated, the SPT wheal sizes for which the commercial extract was used were taken as the reference. In order to evaluate whether tolerance had developed or not, SPT was performed before the OFC. During the SPT, the serum sIgE level was also monitored to determine whether the PP wheal size was above the cut-off level.

Oral food challenge

After the initial SPT and serum sIgE, open OFC was applied to subjects for which the induration diameter and serum sIgE were determined to be below the cut-off point. Subjects that had a serum sIgE level or induration diameter above the cut-off point were subjected to food elimination for 6 months, after which the SPT was repeated, following open OFC was applied to subjects for which the induration diameter was determined to be below the cut-off point. For subjects with a suspected food allergy, the OFC test was performed after imposing an elimination diet for 15 days, in order to confirm the diagnosis. Both OFCs were performed under medical supervision with emergency support available. Patients were examined prior to starting feeding, as well as before each dose was administered, and their vital signs and observations for lungs and skin were recorded on clinical charts. Any signs or symptoms that occurred during the OFC were also recorded, even when mild. Clinical observations were performed for at least 4 hours after the last food dose. The initial dose for the OFC was 3 mg, as recommended by the European Academy of Allergy and Clinical Immunology food allergy and anaphylaxis guidelines, and a total of nine doses were applied to patients that showed no reactions to the logarithmic dose increase. The maximum dose included 3 g of the protein.[13] The cow's milk challenges were conducted using cow's milk (or formula milk for infants less than 12 months), and the egg provocation test was performed using a boiled egg. All reactions were scored based on their type, time of onset and severity. The OFC was stopped and considered positive when objective signs and symptoms or repeated severe subjective symptoms were noted. The rating system described by Perry et al. was used to evaluate the severity of reactions of the skin, upper respiratory, lower respiratory, gastrointestinal and cardiovascular systems (**Table 1**).[7]

Table 1. Rating the reactions

MILD	The presence of skin and/or oral mucosal symptoms
MODERATE	The involvement of upper respiratory system and/or gastrointestinal system or any of the three systems
SEVERE	The involvement of lower respiratory system and/or cardiovascular system or any of the four systems

* Perry TT, Matsui EC, Conover-Walker MK, Wood RA. The risk of oral food challenges. J Allergy Clin Immunol 2004; 114: 1164-8.

Statistical analysis

IBM SPSS version 21.0 and Medcalc (Acacialaan 22, B-8400 Ostend, Belgium) software were used for all statistical analyses. The Kolmogorov-Smirnov test was used to test the normality of variables. Parametric methods were used for analysis of variables with a normal distribution, whereas non-parametric methods were used for analysis of variables that were not normally distributed. The Pearson's chi-square and linear-by-linear association tests were used with an exact test for the comparison of categorical data. The categorical data were expressed as a percentage of the number (n) of children evaluated. The level of significance for the analyses was $p < 0.05$.

Results

The study included 122 patients who had received OFC, and a total of 174 OFCs were performed. Of these tests, 59% were performed to verify the diagnosis and 41% to determine whether or not tolerance had developed. Of the patients, 69.7% (n = 85) were male, and the average age of patients was 15 months (3–60 months), 20 months (7–60 months) and 22 months (7–60 months) for the milk, egg yolk and egg white tests, respectively. Tests for milk, egg white and egg yolk allergies made up 46.5, 30.5 and 23.0%, respectively. A history of IgE-mediated food allergy was present for 50.8% of the patients (n = 62). Development of a rash 1–2 hours after food intake was observed in 48 subjects, vomiting was observed in 10 subjects,

and coughing and wheezing was observed in four subjects. Seventy of the patients (54%) had co-existing diseases (e.g. atopic dermatitis or wheezing) in addition to a food allergy, and 58 patients had a medical history of familial atopy (**Table 2**). Patients developed reactions in 41 of the tests (23.5%), and reactions were observed for 32.5% of patients who received oral milk provocation, 22.5% of patients who received egg yolk provocation and 11.3% of the patients who received egg white provocation. For subjects that developed reactions, the median amount of protein that subjects took in the OFC tests was 300, 200 and 250 mg for milk, egg white and egg yolk, respectively. No reaction was observed for 133 (76.5%) of the OFC tests, whereas mild and moderate reactions were determined for 33 (19%) and eight (4.5%) tests, respectively. Furthermore, none of the patients developed a severe reaction (**Table 2**). Antihistaminic therapy was used for patients that developed a reaction, but epinephrine was not required.

There were no significant differences for the diameter of induration in the SPT and serum Ig-E values between the patients that developed or did not develop reactions to food ($p > 0.05$; **Table 3**).

Table 2. General characteristics of the patients

	n	%
Gender (male)	85	69.7
Age of Oral Provocation Test (month)*		
Milk	15 (3-60)	
Egg yolk	20 (7-60)	
Egg white	22 (7-72)	
Oral Provocation Tests		
Milk	81	46.5
Egg yolk	40	23.0
Egg white	53	30.5
Medical history of Type I reaction with suspected food	62	50.8
Urticaria	48	39.3
Vomiting	10	8.2
Cough/wheezing	4	3.3
OFC indication		
In order to confirm the diagnosis	103	59
In order to evaluate whether tolerance developed or not	71	41
Coexisting disease	70	57.4
Familial atopic	58	47.5

*Median (range)

Discussion

Oral food challenges for milk and eggs are the most commonly used tests for food allergies, and have been found to be safe for preschool children.

Although double blind OFCs are the gold standard for food allergy diagnosis, objective reactions that appear in open oral food provocation tests are adequate for most cases,[13] as found in our study. Furthermore, the number of subjective symptoms was relatively low due to the psychological interactions in the preschool group, and therefore, it was not necessary to perform double blind OFCs.

In a study by Rolinck Werninghaus et al., a total of 869 OFCs were performed, and the authors reported relationships between the reaction severity and the dose that was applied during the provocation, and between high serum levels of sIgE and a positive OFC.[14] In the present study, there was no significant difference between serum sIgE and the diameter of induration in the SPT, therefore, these parameters probably had no effect on the reactions.

Another criterion that reveals the severity of reaction is epinephrine or antihistamine administration during the OFC. In an OFC performed on 521 patients, Lieberman et al. found that allergic reactions to suspected foods developed in only 18.8% of cases, and epinephrine was used in 1.7% of the patients that developed reactions.[15] Calvani et al. performed a total of 544 OFCs, in which 48.3% patients developed reactions,

Table 3. The effects of the induration diameter of Skin Prick Test and food-specific Ig-E values on patients without any reaction

	Group without reaction (n=133) sIgE (kU/L)*	Group with reaction (n=41) sIgE (kU/L)*	*p* value#	Group without reaction (n=133) SPT wheal (mm)*	Group with reaction (n=41) SPT wheal (mm)**	*p* value#
Milk	1.6 (0.7-2.6)	1.8 (0.8-6)	0.051	4 (3-5)	4 (3-5)	0.490
Egg white	2.2 (0.7-3)	2.6 (0.6-3)	0.72	4 (3-5)	4.5 (4-5)	0.101
Egg yolk	1.5 (0.7-1.7)	1.7 (1-2.5)	0.089	3 (3-4)	4 (3-5)	0.165
The group to which OFC was applied in order to evaluate whether tolerance developed or not						
Milk	1.6 (1.2-8)	2.7 (0.8-7)	0.975	4 (3-6)	3 (3-4)	0.271
Egg white	2.1 (0.8-6)	2.4 (0.8-7)	0.825	4 (3-5)	4 (3-5)	0.751
Egg yolk	1.8 (1-2.5)	1.6 (0.4-6)	0.672	3 (3-4)	4.5 (3-5)	0.624
The group to which OFC was applied in order to confirm the diagnosis						
Milk	1.1 (0.7-2.2)	1.9(1.4-3.4)	0.052	3 (3-4)	4 (3-5)	0.069
Egg white	1.7 (0.8-2.4)	1.4 (0.6-3)	0.720	3 (3-5)	4 (3-5)	0.059
Egg yolk	1.4 (0.4-1.7)	1.9 (1.7-2)	0.056	3 (3-4)	3.5 (3-5)	0.595

*median (IQR), # Mann-Whitney test

and epinephrine was required for 2.7% of patients.[9] In another study by Calvani et al., OFC was performed on 66 patients, 42.4% of whom developed reactions, of which 16.7% had a generalized reaction (reactions affecting two or more systems, namely, skin, gastrointestinal and upper respiratory systems) and 9.1% had a severe generalized reaction (reactions affecting two or more systems, including cardiovascular or lower respiratory tract involvement). In their study, 24% of patients received intramuscular epinephrine.[16] The frequency of allergic reactions found in our study was similar to that reported by Lieberman et al., however, in contrast to the three other studies, we did not observe any severe reactions. Therefore, epinephrine was not given to any of the patients in the present study, and antihistamine was only given to 15% of patients.

In 1237 OFCs conducted by Jarvinen et al., food reactions developed in 436 (34%) tests, for which epinephrine was given to 11% of those patients. Of these reactions, 16% of reactions developed in response to egg provocation and 12% to milk provocation. In contrast to these results, the frequency of reactions was higher for milk OFC in the present study.

Elevated serum levels of sIgE were observed in patients with food allergies. This may be explained by the larger induration diameter in the SPT and the presence of a severe reaction history in patients with food allergies, which are the major limitations of performing OFCs.[4] Nowadays, the recommended levels of serum sIgE and diameter of induration should be below the 95% positive predictive value in order to avoid unnecessary OFCs.[18–20] In the present study, patient selection was performed according to the suspected food allergy of the patients, and only those with serum sIgE and SPT levels below the 95% positive predictive value were included. None of the previous studies in the literature that have evaluated the severity and frequency of OFCs have required these conditions. As a consequence, the frequency of performing OFCs for milk and egg allergies was found to be lower in our study compared to those reported in the literature. In a study including 382 patients by Perry et al., 584 OFCs were performed and 43% of patients developed reactions, of which 56 and 42% developed in response to milk and egg provocation, respectively. Furthermore, mild, moderate and severe reactions to oral milk provocation were observed in 37, 37 and 27% of cases, respectively, and 32, 30 and 38% of reactions were mild, moderate and severe, respectively, in the egg provocation test. Of the patients that developed an allergic reaction to food, 11% received epinephrine.[7] In our study, the proportion of patients that developed reactions to food was lower than that observed by Perry et al., in which the same parameters for determining the severity of reactions were used. The lower number of reactions and reduced proportion of severe reactions may be explained by our patient selection criteria, as mentioned above.

A limitation of our study may be data loss, due to the nature of retrospective studies. Moreover, only patients with egg and/or milk allergies were included in the study, and therefore, other common allergens and their severity and frequency were not evaluated.

In conclusion, OFCs for suspected milk and egg allergies was found to be safe for use in preschool children, provided that the serum sIgE and SPT results are below the 95% positive predictive values prior to the test.

Conflicts of interest

The authors have no conflicts of interest to declare.

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