Brief report

Evaluation of early laryngeal reaction at oral food challenge

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Background: Open oral food challenge (OFC) is a commonly used diagnostic method for food allergy; however, the occurrence of uncertain reactions leads to inconclusive results.
Objective: We aimed to determine the associations between mild laryngeal symptoms and positive results in open OFCs.
Methods: We retrospectively investigated medical records of high-risk children (aged 3-15 years) who had undergone open OFC for a low dose of peanuts, hen's egg, cow's milk, or wheat. The OFC result, severity of allergic reactions, and administered treatments during OFCs were compared between the subjects with and without laryngeal symptoms. The risks of a positive OFC result were assessed by using logistic univariate and multivariate analyses, with age, sex, and serum levels of total and food-specific IgE as covariates.
Results: Among the 198 patients who underwent OFC, 25 had mild laryngeal symptoms: 8 (32%), 7 (22%), 0 (0%), and 10 (40%) in the OFC trials with hen's egg, cow's milk, wheat, and peanuts, respectively. In the peanut OFCs, univariate analyses revealed a 5-fold higher risk of a positive result (odds ratio = 5.0 [95% CI = 1.1-22.8]) in the symptomatic subjects than in the asymptomatic subjects. However, on multivariate analyses, none of the associations between the symptoms and a positive result were significant in any of the OFCs. The occurrence of anaphylaxis and adrenalin injections did not differ significantly between the symptomatic and asymptomatic subjects.
Conclusions: Laryngeal symptoms should be considered a warning sign for a positive OFC result in peanut OFCs, although not critical enough to stop the challenge. (J Allergy Clin Immunol Global 2022;1:80-4.)

Key words: *Anaphylaxis, food hypersensitivity, IgE, larynx, logistic models*

Abbreviation used:
OFC: Oral food challenge

INTRODUCTION

Oral food challenge (OFC) is the criterion standard for diagnosing food allergy.[1] In IgE-mediated food allergy, immunologic tests for allergen-specific IgE or skin prick tests have predicted positive OFC results for only a few foods.[2,3] Unnecessary dietary elimination of certain foods can lead to stunted growth and lower the quality of life.[4] Therefore, an OFC should be conducted for patients suspected of having a food allergy, despite the associated risk of allergic reactions.

In open OFC for food allergy, the patient is aware of the food being tested, and the test results are deemed positive if obvious signs emerge.[5] However, owing to concerns over more severe reactions, examiners are likely to stop when uncertain reactions occur at the start of OFC, resulting in an inconclusive result.[6] Laryngeal symptoms are among the most frequent reactions in open OFCs[7]; however, how the mild subjective symptoms are associated with OFC results is unclear. Hence, we retrospectively examined data from open OFCs for the major allergens in Japanese children (peanut, hen's egg, cow's milk, and wheat) to determine the associations between mild laryngeal symptoms and positive OFC results.

The subjects were patients aged 3 to 15 years who underwent open OFC between May 2012 and March 2020 at our university hospital, a tertiary medical center in Tokyo. The medical ethics committee of our university approved this study, which adhered to the guidelines of the Declaration of Helsinki. Informed consent was obtained by using the opt-out method. We provided OFCs following the Japanese guideline,[5] which recommends conducting tests with 3 different total target doses (low, medium, and full) with a stepwise increase (see Table E1 in the Online Repository at www.jaci-global.org). We included those OFCs with conclusive results (positive or negative) that fulfilled all of the following criteria: (1) the first OFC for IgE-mediated food allergy for each causative food, (2) OFC using the low target dose, (3) OFC administered as 2 fragmented doses at least 40 minutes apart, and (4) OFC in subjects with previous immediate reactions or specific IgE values higher than 95% of the positive predictive values (see Table E2 in the Online Repository at www.jaci-global.org).[8-11] Those OFCs that met the following criteria were excluded: OFCs associated with food-dependent, exercise-

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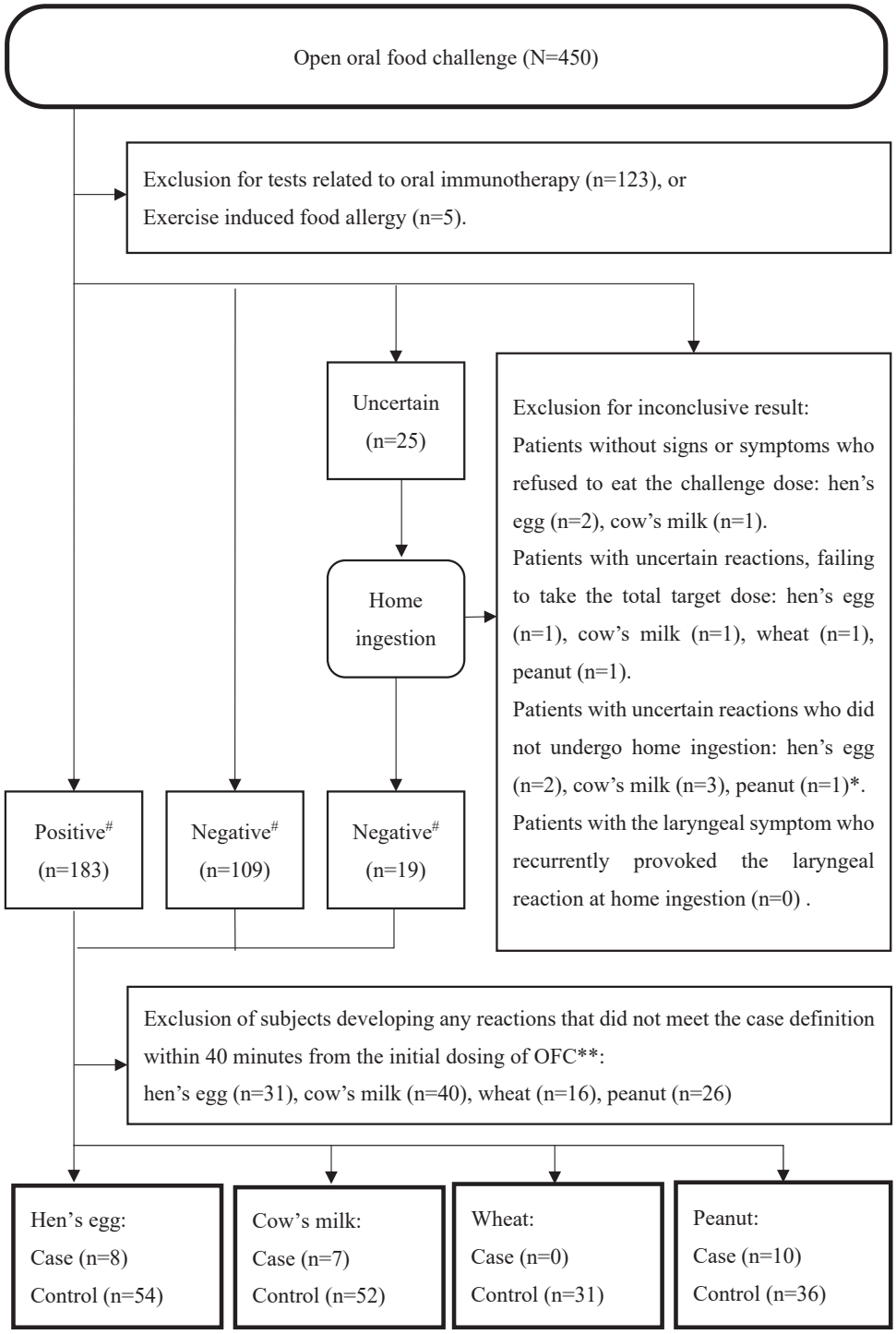

FIG 1. Flowchart for interpretation of open OFC. *Of these children, 2 met the criteria of laryngeal symptoms with cow's milk (n = 1) or peanut (n = 1). **The case patient group included children who developed the following laryngeal symptoms within 40 minutes of the initial dosing: patient-reported nasopharyngeal or pharyngeal discomfort or pruritus. #The tests with conclusive results (positive or negative) involved 72 peanut, 93 hen's egg, 99 cow's milk, and 47 wheat OFCs.

induced anaphylaxis or with a decision of oral immunotherapy induction (eg, patients tested for the initial dose of oral immunotherapy) and OFCs in which subjects developed any reactions that did not meet the case definitions within 40 minutes from the initial OFC dosing. Children who developed the laryngeal symptoms (ie, patient-reported mild nasopharyngeal or pharyngeal discomfort or pruritis) within 40 minutes of the initial dosing were defined as the case patient group (see also the Supplementary Material in the Online Repository at www.jaci-global.org). The control group consisted of patients without any reactions within 40 minutes of the initial dosing. The initial doses were 1/96 of a cooked whole egg, 1 mL of pasteurized milk, 1g of

TABLE I. Comparison of clinical characteristics between patients with laryngeal symptoms and the control group

Characteristic	Peanut			Hen's egg			Cow's milk		
	Case patients (n = 10)	Controls (n = 36)	*P* value	Case patients (n = 8)	Controls (n = 54)	*P* value	Case patients (n = 7)	Controls (n = 52)	*P* value
Age (mo), median (range)	118(78-154)	74(56-94)	.07	64(52-78)	47(41-61)	.02	69(49-116)	69(49-116)	.40
Sex (male), no. (%)	6 (60%)	26 (72%)	.46	6 (60%)	51 (68%)	.57	4 (57%)	32 (62%)	.82
Reasons for elimination, no. (%)									
Objective allergic reactions, no. (%)	9 (90%)	22 (61%)	.09	6 (75%)	45 (83%)	.56	6 (86%)	43 (83%)	.84
Allergic complications, no. (%)									
Asthma	3 (30%)	9 (25%)	.75	3 (38%)	16 (30%)	.65	4 (57%)	15 (29%)	.13
Atopic dermatitis	1 (10%)	9 (25%)	.31	2 (20%)	34 (46%)	.12	4 (57%)	26 (50%)	.72
Allergic rhinitis	4 (40%)	6 (17%)	.11	3 (38%)	3 (6%)	.004	2 (29%)	3 (6%)	.04
Total IgE level, median (range)	563(326-886)	1036(240-2085)	.27	1146(583-1659)	893(354-1905)	.27	1122(742-1940)	665(278-1236)	.36
Specific IgE level (kU_A/L) for crude antigens median (range)	24.1(3.0-52.6)	15.2(3.4-27.8)	.70	54.2(19.0-97.0)	54.0(24.5-101)	.79	72.2(17.2-100)	24.0(13.9-70.1)	.52
Specific IgE level (kU_A/L) for component antigens, median (range)	23.8(0.8-43.2)	1.5(0.3-7.4)	.27	46.7(17.8-82.7)	33.8(13.8-101)	.55			

P values were calculated by using the Mann-Whitney *U* test or chi-square test. Specific IgE value for crude antigens shows the level of serum-specific IgE against egg white, cow's milk, or peanut in OFC for hen's egg, cow's milk, and peanut, respectively. Specific IgE value for component antigens shows the level of serum-specific IgE value against *Arapis hypogaea* 2 or ovomucoid in the peanut and hen's egg OFCs.
Of the 46 subjects who underwent peanut OFC, 25 (54%) had results for *Arapis hypogaea* 2 IgE values.

TABLE II. Comparison of OFC outcomes

Variable	Peanut			Hen's egg			Cow's milk		
	Case patients (n = 10)	Controls (n = 36)	*P* value	Case patients (n = 8)	Controls (n = 54)	*P* value	Case patients (n = 7)	Controls (n = 52)	*P* value
Positive OFC result, no. (%)	5 (50%)	6 (17%)	.03	4 (50%)	22 (41%)	.62	5 (71%)	24 (46%)	.21
Cumulative dose resulting in OFC termination, no. (%)			.32			.11			<.001
One-third of the target dose	1 (10%)	1 (3%)		1 (13%)	1 (2%)		2 (28%)	0 (0%)	
From one-third to all of the target dose*	0 (0%)	0 (0%)		0 (0%)	0 (0%)		1 (14%)	3 (3%)	
Full target dose	9 (90%)	35 (97%)		7 (87%)	53 (98%)		4 (57%)	49 (94%)	
Anaphylaxis, no. (%)	1 (10%)	1 (3%)	.32	0 (0%)	2 (4%)	.58	1 (14%)	4 (8%)	.54
Adrenalin injection, no. (%)	1 (10%)	2 (3%)	.32	0 (0%)	2 (4%)	.58	1 (14%)	4 (8%)	.54
Symptoms resulting in termination of OFC, no. (%)			.16			.60			.14
Skin	1 (10%)	2 (6%)		1 (12%)	4 (7%)		3 (42%)	10 (19%)	
Gastric	3 (30%)	3 (8%)		3 (38%)	12 (22%)		1 (14%)	1 (2%)	
Respiratory	1 (10%)	1 (3%)		0 (0%)	6 (11%)		1 (14%)	10 (19%)	
First treatment for symptoms resulting in termination, no. (%)			.10			.40			.51
Oral antihistamines	3 (30%)	3 (8%)		1 (13%)	7 (13%)		2 (29%)	6 (12%)	
Inhaled bronchodilator	1 (10%)	1 (10%)		0 (0%)	10 (19%)		2 (29%)	10 (19%)	
Adrenalin injection	0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	1 (2%)	

The total target doses for peanut, hens' egg, and cow's milk OFC were 1 g of roasted peanuts, 1/32 of a cooked whole egg, and 3 mL of pasteurized milk. The total challenge dose was administered as 2 fragmented doses, amounting to one-third and two-third portions of the total target dose, respectively, with a 40-minute interval between them.
*In all, 1 and 3 subjects in the case patient and control groups for cow's milk OFC stopped the intake at 1.5 mL of the cumulative dose, respectively.

Udon noodles, and 0.3 g of dry roasted peanut. The laryngeal symptoms were regarded as uncertain reactions, and children with symptoms that resolved during the observation period consumed a fragmented subsequent dose. Children with only uncertain reactions during OFC were instructed to take the same amount of food several times at home (home ingestion). The test results were recorded as positive, negative, or inconclusive.[5] Children with only uncertain reactions were classified has having a negative result if they had no reactions after several home ingestions. Otherwise, the children were classified as having an inconclusive result (see the Supplementary Material). To assess the risk of a positive OFC result and the severity of the subsequent allergic reactions, we investigated OFC outcomes between the case patient and control groups, including the ratios of a positive OFC result, anaphylaxis, and treatments. To evaluate the significance of the presence of the mild laryngeal symptoms for the positive

TABLE III. Risk of a positive OFC result among children with early laryngeal symptoms

	Peanut				Hen's egg				Cow's milk			
Variable	**OR**	***P* value**	**aOR**	***P* value**	**OR**	***P* value**	**aOR**	***P* value**	**OR**	***P* value**	**aOR**	***P* value**
Laryngeal symptoms	5.0(1.1-22.8)	.04	8.4(0.8-84.5)	.07	1.5(0.3-6.4)	.49	1.3(0.2-7.2)	.79	2.9(0.5-16.4)	.23	7.2(0.6-81.2)	.11
Age (mo)	1.0(0.99-1.0)	.20	1.0(0.99-1.0)	.15	1.0(0.98-1.0)	.85	1.0(0.97-1.03)	.93	0.98(0.97-1.0)	.15	0.99(0.97-1.0)	.54
Sex (male)	1.2(0.3-5.5)	.79	5.6(0.5-65.2)	.17	1.7(0.5-5.2)	.38	1.8(0.6-6.0)	.32	1.5(0.5-4.2)	.49	1.5(0.4-6.4)	.56
Total IgE level (IU/mL)	1.0(0.5-1.7)	.88	0.6(0.2-1.4)	.21	0.9(0.6-1.4)	.62	0.8(0.4-1.5)	.54	1.0(0.7-1.6)	.90	0.7(0.4-1.5)	.38
Specific IgE level for crude or component antigen (kU_A/L)	2.3(1.1-4.6)	.02	3.7(1.4-9.8)	.01	1.1(0.7-1.8)	.67	1.2(0.6-2.4)	.54	1.9(1.1-3.2)	.03	2.4(1.0-5.6)	.04

aOR, Adjusted odds ratio; *OR*, odds ratio.

Univariate and multivariate logistic regression was used. The number shows odds ratio and 95% confidence interval. The following variables were included in the multivariate analysis: age, sex, serum levels of total IgE and specific IgE (ovomucoid, cow's milk, or peanut). Total raw IgE and specific IgE values were log-transformed (log(x + 1)) before the analyses. Analysis of *Arapis hypogaea* 2 IgE values was omitted because half of the subjects had missing values.

OFC results, we constructed a prediction model using logistic regression; the model included age, sex, allergens, and presence of laryngeal symptoms (see also the Supplementary Material).

RESULTS AND DISCUSSION

Of the 450 subjects who underwent the initial low-dose OFC, 311 (75%) had conclusive results; 198 of them (44%) were included in the study (Fig 1). Among the 198 patients who underwent OFC, 25 had mild laryngeal symptoms: 8 (32%), 7 (22%), 0 (0%), and 10 (40%) in the OFC trials with hen's egg, cow's milk, wheat, and peanuts, respectively. In all, 23 subjects complained of laryngeal discomfort and 2 subjects complained of laryngeal pruritus. Among the subjects with conclusive results, the case proportion was highest for peanut (10 of 72 [14%]), followed by hen's egg (8 of 93 [9%]), cow's milk (7 of 99 [7%]), and wheat (0 of 47 [0%]) ($P = .06$). Given the small number of cases associated with wheat, the tests for wheat allergy were excluded from further analyses. The comparisons between case patients and controls (Table I) showed significant differences in age (case patients vs controls: 64 [range 52-78] vs 47 [range 41-61] months; $P = .02$) for the hen's egg OFC and in the proportions of allergic rhinitis for the hen's egg OFC (3 [38%] vs 3 [6%]; $P = .004$) and the cow's milk OFC (2 [29%] vs 3[6%]; $P = .04$) (Table I). The rate of a positive OFC result (5 [50%] vs 6 [17%]; $P = .03$) was higher in the case patient group than in the control group in the peanut OFCs only (Table II). The cumulative dose that resulted in test termination was significantly lower in the case patient group for cow's milk OFCs. The most frequent systemic reactions resulting in test termination were gastric symptoms such as abdominal pain in the peanut OFC (30%) and hen's egg OFC (38%) and skin symptoms (rush or urticaria) in the cow's milk OFC (42%). Oral antihistamines were most frequently administered as the first treatment in the case patient groups for all of the OFCs. No significant differences were observed in the frequency of anaphylaxis, adrenalin injection, symptoms resulting in test termination, and the type of the first administered treatment between the groups in all of the OFCs.

Univariate analyses revealed that laryngeal symptoms were associated with increased risk of a positive result (odds ratio = 5.0 [95% CI = 1.1-22.8]; $P = .04$) in the peanut OFCs. However, the association was not significant on multivariate analyses (Table III). The area under the curve of the prediction model for a positive OFC result was 64%, and the positive predictive value was 57% (Fig 2).

This study revealed that the frequency of having mild laryngeal symptoms at open OFC might have differed between the peanut, hen's egg, cow's milk, and wheat tests (0%-14%). Subjects with laryngeal symptoms in the peanut OFCs had a 5-fold higher risk of a positive OFC result than did those subjects without the symptoms. However, there were no significant differences in the rates of anaphylaxis and adrenalin injections, and the predictive models based on the laryngeal reactions had poor robustness. A previous study reported that in a general setting, laryngeal symptoms might have little association with OFC outcomes.[12] Our findings confirmed that even in high-risk patients, the laryngeal symptoms might be poor predictors of OFC outcomes. OFCs in children with these reactions can be continued under careful observation.

This study has limitations regarding the low number of cases for each antigen and the lack of results based on a double-blinded placebo-controlled food challenge. The low statistical power to detect significant differences may attenuate the reliability of our conclusion regarding the association between laryngeal symptoms and OFC results. However, the low frequency of anaphylaxis and adrenalin injections in the case patient group suggests that the provocation of mild laryngeal symptoms is not critical enough to stop OFCs. A previous study based on double-blinded placebo-controlled food challenges for cow's milk allergy showed that in 90% of children laryngeal symptoms were followed by objective signs,[13] suggesting that the laryngeal symptoms should be considered a warning for further allergic reactions. Finally, our study did not evaluate whether the degree of processing of food proteins influenced the significance of the laryngeal symptoms for each antigen. The lack of this evaluation weakens the generalizability of our findings, given that OFCs with different degrees of processing of food proteins may alter the importance of the laryngeal symptoms.

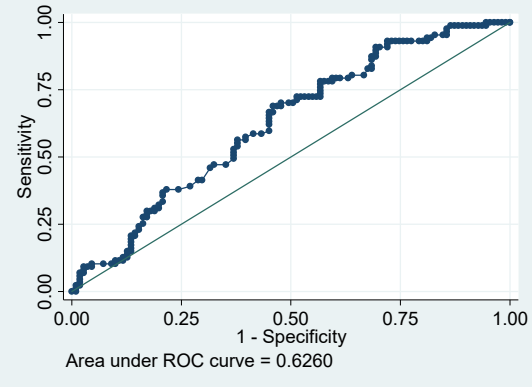

FIG 2. Receiver operating characteristic curve for a prediction model for a positive. OFC result. A prediction model for a positive OFC result was constructed by using logistic regression with age, sex, allergens, and the presence of laryngeal symptoms included as predictors.

To prevent inconclusive results in open OFCs, physicians should balance the benefits of acquiring definitive diagnoses with the risk of triggering severe allergic reactions.[6] Our findings indicate that it may be acceptable to continue OFC under careful supervision when early laryngeal symptoms occur.

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Clinical implications: Subjective laryngeal symptoms that emerge during open OFC have a weak relationship with a positive OFC result, although it is not critical enough to stop the challenge.

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