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ORIGINAL ARTICLE

The Skin Prick Test is Not Useful in the Diagnosis of the Immediate Type Food Allergy Tolerance Acquisition

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ABSTRACT

Background: Some studies have been reported about positioning of SPT in the diagnosis of food allergy. On the other hand, it is not yet clear about the positioning of SPT in the diagnosis of tolerance acquisition of the immediate type food allergy.

Methods: The retrospective study had been conducted for 236 egg allergic children (51.3 months in mean), 127 milk allergic children (53.4 months), and 96 wheat allergic children (42.6 months). The retrospective analysis of serum nonspecific and antigen-specific IgE levels, SPT, and OFC had been conducted for each allergic patient. All OFC had been conducted to verify the acquisition of tolerance against eliminated food.

Results: The OFC was positive in 61 (25.8%) hen's egg allergies, 34 (26.8%) milk allergies and 33 (34.4%) wheat allergies.

The greatest AUC for each allergen is as following; hen's egg for egg white specific IgE at 0.745, milk/histamine (wheal) index at 0.718, and wheat for wheal size at 0.597. For the predictive decision points, the highest accuracy rate was at 25.8% for an egg white wheal of 9.5 mm, at 26.8% for a milk wheal of 9.5 mm, and at 34.4% for a wheal of 6.5 mm.

Conclusions: As a result of this analysis, the diagnostic accuracy of SPT had not been satisfactory to judge the acquisition of tolerance in allergic children for eggs, milk and wheat. Therefore, this is not a strong evidence to testify the tolerance of the immediate type food allergy.

KEY WORDS

food allergy, food hypersensitivity, oral food challenge, skin prick test, tolerance acquisition

INTRODUCTION

The oral food challenge (OFC) is the gold standard used in the diagnosis of food allergy tolerance acquisition.[1,2] However, an OFC should be conducted at a medical facility because of the risk of anaphylaxis, and the procedure itself is complex and difficult to perform. Therefore, a predictive factor that can efficiently identify patients for whom OFC is indicated is needed.

The allergen-specific IgE level that is widely used in the diagnosis of food allergies has the drawback of high sensitivity, but low specificity. A large number of detailed studies have been conducted on the decision point and cutoff value to be used for correcting this problem.[3-5] The probability curves of Komata *et al.*[6] show that the positive predictive value for the allergen-specific IgE level tends to differ depending on the type of allergen and the age of the patient, and these points to a more efficient use of OFC. In contrast, the minimally invasive skin prick test (SPT) is widely used as a diagnostic indicator of food allergies.[1,7,8] The SPT and the allergen-specific IgE level have similar shortcomings, and multiple studies have been performed aimed at positioning the SPT as a more efficient diagnostic indicator. These studies have reported that the ratio between the wheal size and the positive control in SPT correlates with OFC

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results.[9-13] However, when the reports on results of SPT are compared, there are issues with both the target allergens and the number of subjects; thus, in a true sense, the positioning of SPT in the diagnosis of food allergies is still undecided.

This study investigated whether SPT results can serve as a diagnostic indicator of tolerance acquisition in patients previously diagnosed with the immediate type food allergies. This study is characterized by the fact that three types of allergens, hen's egg, milk, and wheat, were investigated, and the number of challenge tests for each was greater than in previous reports.

METHODS

A retrospective analysis of serum nonspecific IgE levels, allergen-specific IgE levels, SPT, and OFC in patients diagnosed with hen's egg, milk, and wheat allergies was conducted. The subjects were patients who were given OFC as inpatients at Sagamihara National Hospital's Department of Pediatrics. The subjects had already been diagnosed with an immediate type of food allergy to the offending food because of their accidental episodes or OFC and were on an elimination regimen. OFC was conducted to verify the acquisition of tolerance to the eliminated food. The analysis was performed on records of tests conducted from May 2006 to November 2008.

After informed consent had been obtained from the patient's legal guardian, the OFC was conducted in patients with no history of an immediate reaction to the challenge food within the past year. No upper boundary on the allergen-specific IgE level was established for conducting the OFC.

An SPT was performed at the time of OFC using a sterile bifurcated needle (Precision Medical Products, Denver, PA, USA) and commercial egg white, milk, and wheat extract (Torii Pharmaceutical, Tokyo, Japan), negative saline, and positive histamine control (10 mg/mL).[14] The use of antihistamines had been discontinued at least 24 hours before the SPT. The SPT and assessment of the skin reaction were performed by an allergist, and the maximum size of wheals was evaluated 15 minutes after the skin prick.[15] The SPT results of patients in whom the size of the positive histamine control was no greater than the size of the negative saline and of patients in whom the positive histamine control was negative were excluded from the analysis.

The allergen-specific IgE level was measured using the Pharmacia CAP System (Pharmacia Diagnostics, Uppsala, Sweden). For this analysis, allergen-specific IgE levels taken up to 3 months before the OFC was conducted were used. Values of 0.35 IU/mL or less were treated as 0.15 IU/mL, and values of 100 IU/mL or greater were treated as 101 IU/mL.

All OFCs were conducted under inpatient management. The test was performed so that the final ingested amounts were 1/2 heated hen's egg, 50 mL of cow's milk (milk protein 1.7 g), and 100 g of udon noodles (wheat protein 1.3 g).

Ingestion was conducted in stepwise increments equaling 1/16, 1/16, 2/16, 4/16, and 8/16 of the final amount every 15 minutes so that the total amount would be ingested in 60 min. The OFC was carried out under the supervision of an allergist and a nurse so that a sufficient response to any emergency was available, and follow-up was continued for 24 hours after the start of the OFC. The reactions induced by the OFC were judged to be positive based on the appearance of clear objective signs (remarkable hives, mucus swelling, vomit, diarrhea, wheezing, productive cough, disconciousness and so on), and treatment was provided as needed depending on the severity of the reactions induced.

The OFCs were analyzed in combination with sex difference, age at time of the OFC, and current history of bronchial asthma, eczema, allergic rhinitis, or allergic conjunctivitis.

The study was approved by the Ethics Committee of National Hospital Organization Sagamihara Hospital and was performed with consideration of all appropriate ethical issues.

For the statistical analysis, the chi-square test and Student's t-test were performed using SPSS ver. 11.0.

RESULTS

HEN'S EGG

The results for hen's egg were studied in 236 subjects (OFC positive 61, passed 175).

Significant differences between the OFC-positive group and the OFC-passed group were found in age at the time of the challenge test, egg white specific IgE levels, egg white wheal size. A significant difference in wheal size was not found in the mean egg white/histamine wheal index (Table 1a).

A receiver operating characteristic (ROC) procedure was used to derive the predictive decision points for egg white wheal size, as well as for the egg white/histamine ratio for wheal size. The AUC was the greatest for egg white specific IgE at 0.745. Significant differences were also seen in the egg white wheal and egg white/histamine (wheal) index (Fig. 1, Table 2). The predictive decision points were a wheal size of 9.5 mm, but the accuracy for both was low, at about 25.8%. No satisfactory values were found for either the positive or negative likelihood ratio (LR) (Table 3).

MILK

The OFC for milk was conducted on 127 subjects (OFC positive 34, passed 93).

Significant differences between the OFC-positive group and the OFC-passed group were found in mean IgE level, milk-specific IgE level, milk wheal size, as well as in the milk/histamine ratio for wheal size. No

Table 1a Comparison of laboratory and clinical characteristics between children who passed and those who failed OFCs to hen's egg

	passed	failed	*p* value
n	175	61	
mean age (SD), months	48.2 (38.4)	60.0 (32.1)	0.033
male sex, %	54.9	62.3	0.369
mean IgE level (SD), IU/mL	656.7 (1065.2)	741.5 (922.9)	0.585
mean egg white-specific IgE level (SD), UA/ml	7.50 (12.8)	16.9 (19.9)	<0.001*
mean egg white wheal (SD), mm	10.3 (5.5)	13.1 (6.1)	0.001
mean egg/histamine wheal index (SD)	1.8 (1.4)	2.0 (1.0)	0.235

*Statistically significant: $p < 0.05$.

Table 1b Comparison of laboratory and clinical characteristics between children who passed and those who failed OFCs to milk

	passed	failed	*p* value
n	93	34	
mean age (SD), months	51.5 (41.1)	58.7 (38.1)	0.378
male sex, %	57.0	70.6	0.219
mean IgE level (SD), IU/mL	1064.2 (1431.7)	614.1 (625.5)	0.018
mean milk-specific IgE level (SD), UA/ml	3.6 (6.5)	9.4 (13.8)	0.024
mean milk wheal (SD), mm	6.4 (5.5)	10.1 (5.3)	0.001
mean milk/histamine wheal index (SD)	1.0 (0.9)	1.9 (1.5)	<0.001*

*Statistically significant: $p < 0.05$.

Table 1c Comparison of laboratory and clinical characteristics between children who passed and those who failed OFCs to wheat

	passed	failed	*p* value
l	63	33	
mean age (SD), months	43.0 (32.4)	41.9 (29.7)	0.873
male sex, %	65.1	63.6	1.000
mean IgE level (SD), IU/mL	938.7 (1222.4)	1269.4 (2233.0)	0.435
mean wheat-specific IgE level (SD), UA/ml	6.9 (10.5)	15.1 (26.8)	0.042
mean wheat wheal (SD), mm	6.7 (5.3)	8.7 (5.7)	0.089
mean wheat/histamine wheal index (SD)	1.2 (1.2)	1.4 (1.0)	0.443

*Statistically significant: $p < 0.05$.

significant differences in clinical background characteristics were found (Table 1b).

An ROC procedure was used to derive the predictive decision points for milk wheal size, as well as for the milk/histamine ratio for wheal size. Significant differences were seen in all parameters (Fig. 1, Table 2). The predictive decision points were a wheal size of 9.5 mm, but the accuracy for both was low, at about 26.8%. No satisfactory values were found for either the positive or negative likelihood ratio (LR) (Table 3).

WHEAT

The results for wheat were investigated in 96 subjects (OFC positive 33, passed 63). Significant differences between the OFC-positive group and the OFC-passed group were found in wheat-specific IgE level. No significant differences were found in wheat/histamine ratio or clinical background characteristics (Table 1 c).

An ROC procedure was not used to derive the predictive decision points for wheat. A significant difference for wheal size was also found, but there was no significant difference in histamine ratio (Fig. 1, Table 2). The predictive decision points were a wheal size of 6.5 mm, but the accuracy for both was low, at about 34.4%. No satisfactory values were found for either the positive or negative likelihood ratio (LR) (Table 3).

DISCUSSION

The present analysis differs from those previously re-

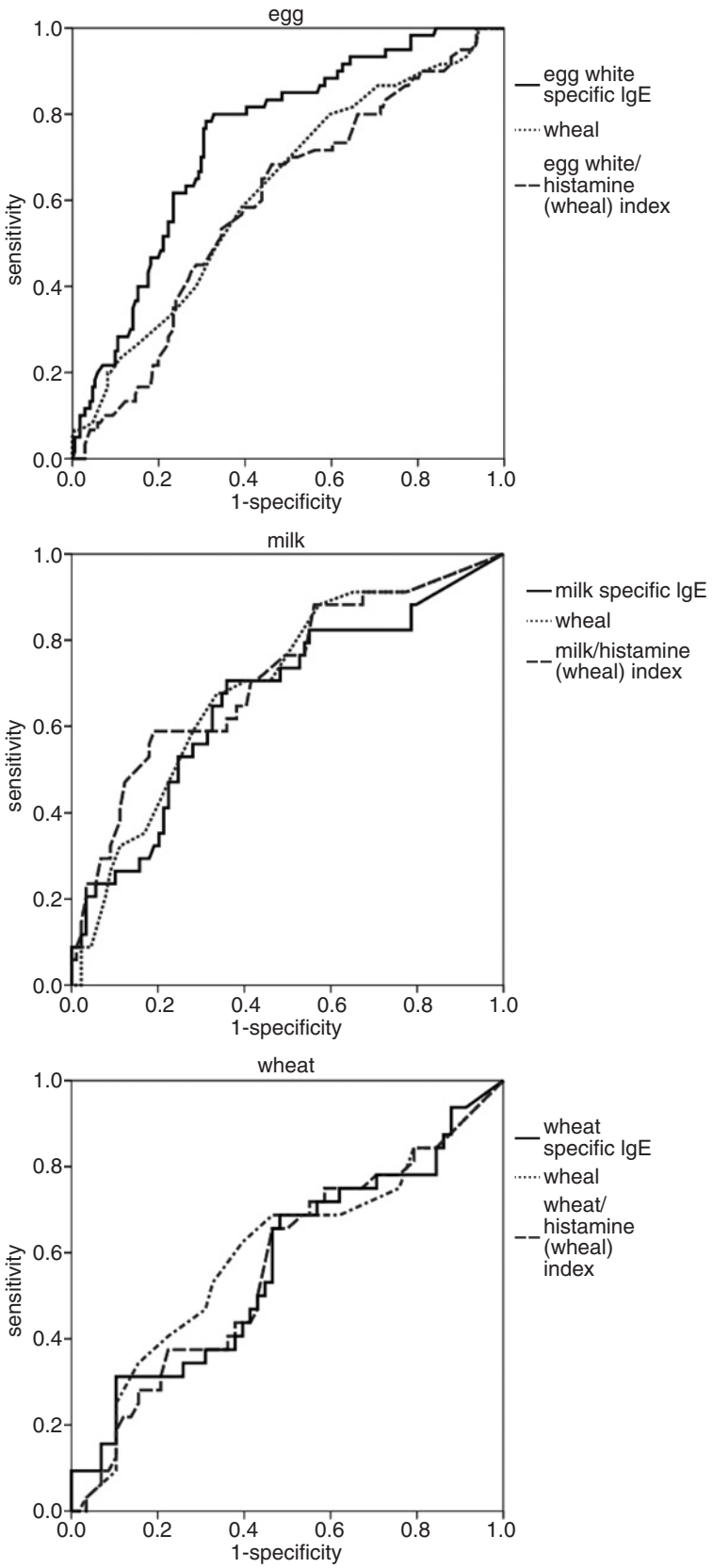

Fig. 1 ROC curve between children who passed and those who reacted OFCs to every allergen.

Table 2 AUC (area under the curve) between children who passed and those who reacted OFCs to every allergen

allergen	item	passed	failed	AUC	SE	*p* value	95%CI (range)
egg white	wheal	175	61	0.624	0.041	0.004	0.543-0.705
	specific IgE			0.745	0.035	<0.001	0.676-0.813
	egg white/histamine (wheal) index			0.595	0.041	0.028	0.514-0.677
milk	wheal	93	34	0.697	0.052	0.001	0.595-0.799
	specific IgE			0.664	0.057	0.005	0.553-0.775
	milk/histamine (wheal) index			0.718	0.053	<0.001	0.613-0.822
wheat	wheal	63	33	0.597	0.065	0.273	0.043-0.697
	specific IgE			0.570	0.065	0.128	0.469-0.725
	wheat/histamine (wheal) index			0.567	0.064	0.298	0.041-0.692

Table 3 Wheal size of decision point to every allergen

	egg white	milk	wheat
decision point, mm	9.5	9.5	6.5
sensitivity, %	19.7	32.3	36.4
specificity, %	59.4	33.3	40.0
false negative, %	80.3	67.6	63.6
false positive, %	40.5	66.7	60.2
accuracy, %	25.8	26.8	34.4
positive likelihood ratio	0.48	0.49	0.60
negative likelihood ratio	1.35	2.03	1.60

ported and is unique in several ways. First, the subjects of analysis were patients who had already been diagnosed with a food allergy, and the diagnostic value of SPT was investigated based on the results of an OFC conducted to verify tolerance acquisition. In addition, three types of allergens, hen's egg, milk, and wheat, were investigated, and the number of cases analyzed was larger than in previous studies.

This analysis differs from those reported elsewhere because, although a significant difference in SPT wheal size was found between the mean values of the positive and passed groups in the OFCs conducted to diagnose tolerance acquisition, that result cannot be used efficiently as a predictive decision point, and the severity of the positive reaction was not useful as a predictive factor. Similarly, no usefulness was found in the examination of an index using a positive control.

A significant difference in the mean value of wheal size between the OFC-positive group and the OFC-passed group was found for hen's egg and milk.

In the ROC procedure based on the OFC results, the AUC was highest for milk wheal size of 0.697, but the accuracy based on the calculated best cut off value of each allergen was not necessarily satisfactory. In a previous study, an OFC was performed in 104 patients with suspected milk allergy, and a 95% PPV of milk SPT was calculated from the results in 28 positive patients.[10] It is likely that this does not show the true usefulness of SPT because the subjects were those with a suspected milk allergy, and the number of subjects was small. Compared to a different report that attempted to calculate the PPV for hen's egg and milk wheal size from 735 OFC results in the same manner,[11] it is likely that different results from the findings in this study were derived because the purpose of the OFC was for allergen diagnosis rather than verification of tolerance acquisition, and the average age of the subjects was 22 months.

While some reports up to date assumed that SPT was useful as a predictor of the result of OFC[9]), these OFCs were conducted for diagnostic purposes and SPTs are not applicable to results of OFCs for the purpose of confirmation of acquired tolerance. The results of the present analysis differ from previous reports on the predictive factor of SPT results on OFC results, and they do not strongly point to the usefulness of SPT. One possible reason for this is that the subjects were patients undergoing OFC for tolerance acquisition, and the number of subjects was larger than in other studies. Other causes may lie in the fact that a different allergen solution was used, as well as in racial differences, etc. However, because the number of OFCs that was analyzed related to obvious, immediate-type food allergy patients based on OFC results, which are the most frequent among previous reports, the present results can be considered analytical results indicating the positioning of SPT as a predictive factor for results of OFC for tolerance acquisition. These analytical results do not conclude that SPT has no overall value for the diagnosis of food allergy. Topics for future research will focus on differences in the allergen solution and racial differences that were noted above, and whether the same conclusion is reached through the examination of allergens that were not investigated in this study. We need to examine desirable about usefulness of SPT in the complete resistance then. This study presents problems on washout period of 24 hours before SPT, for antihistamine, the homogeneity of the antigen solution and other points. An altered prospective study, with consideration and improvements of above problems, is required in future.

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