Previous history of immediate reactions changes predictive accuracy for pediatric peanut allergy

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Running title

Previous history of immediate reaction and peanut allergy

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To the Editor

Peanuts are one of the most common food allergens.[1] In Japan, 5.1% of all food allergy cases are peanut allergies.[2] Although oral food challenge (OFC) is the gold standard to diagnose peanut allergy, severe reactions sometimes occur.[3]

Recently, specific immunoglobulin E (sIgE) to peanut allergen components can be measured. *Arachis Hypogaea* (Ara h) 2 is one of the peanut allergen components, and sIgE levels to Ara h 2 could be a predictive marker in diagnosing a peanut allergy.[4] However, predictive values were different between studies, because these values depend on disease prevalence as well as patient age.[5]We have reported that a previous history of immediate reactions may change the predictive decision point (PPV) of positive buckwheat OFC.[6] Similarly, one Australian study of 1-year-old infants showed that a previous history of peanut reactions altered the 95% PPV of peanut sIgE for peanut allergy; however, no study has evaluated the influence of the presence of a previous history of immediate reactions on PPV of Ara h 2 sIgE and 5% PPV of peanut sIgE.[7] Here, we evaluated it in children.

This study retrospectively analyzed data from subjects aged <18 years who underwent a 3 g peanut (containing 750 mg peanut protein) OFC on admission between March 2010 and March 2016 at Sagamihara National Hospital.

Overall, 128 patients, with a median age of 6.7 years, were assessed (See Supplementary Figure S1, Patient Enrollment and Background Characteristics and Supplementary Table S1). The median levels of peanut sIgE and Ara h 2 sIgE were 9.7 kU_A/L and 1.1 kU_A/L, respectively. Of 128 patients, 49 patients (38%) had a history of immediate reactions to peanuts, and 16 (12%) had a history of anaphylaxis due to peanuts.

Among 128 patients, 50 patients (39 %) reacted and 18 patients (36%) presented with an anaphylactic reaction during OFC. Statistically significant differences were observed between patients with positive and negative OFC results depending on whether they had a previous history of immediate reactions to peanuts, a previous history of anaphylactic reactions to peanuts, atopic dermatitis and total IgE level. Patients with positive results had significantly higher levels of peanut sIgE (11.4 vs 7.3 kU_A/L, $p = 0.038$) and Ara h 2 sIgE (9.84 vs 0.19 kU_A/L, $p < 0.001$) (Supplementary Table S2).

Multivariate analyses were performed with adjusting by three statistically significant predictors for positive OFC results: age, a previous history of immediate reactions to peanuts, and atopic dermatitis (Supplementary Table S3). Peanut sIgE level (adjusted odds ratio: 4.5, 95% confidence interval [CI]: 1.7–12.1, $p = 0.002$) and Ara h 2 sIgE level (adjusted odds ratio: 8.3, 95% CI: 3.7–18.3, $p < 0.001$) were significant risk factors for positive OFC results. The areas under the peanut sIgE and Ara h 2 sIgE receiver operating characteristic curves (AUC) were also calculated (Supplementary Table S4). The AUC of peanut and Ara h 2 sIgE were 0.735 and 0.829 in patients with a previous history of immediate reactions and 0.673 and 0.899 in patients without a history, respectively.

We also developed fitted probability curves for patients with and without a previous history of immediate reactions (Figure 1). The 95% PPV for peanut and Ara h 2 sIgE levels were 96.3 and 38.4 kU_A/L in patients with a previous history of immediate reactions, whereas those in patients without a history could not be obtained. However, the 5% PPV for peanut and Ara h 2 sIgE levels were 0.70 and 0.23 kU_A/L in patients without a previous history of immediate reactions, respectively, whereas those in patients with a history could not be obtained (Table 1).

In this study, we found that the presence of a previous history of immediate reactions changed PPV for a peanut allergy.

In patients with a previous history of immediate reactions, peanut and Ara h 2 sIgE levels higher than 96.3 kU_A/L and 38.4 kU_A/L, respectively, were correlated to a high likelihood of positive OFC results. These patients may not need OFC to be diagnosed with peanut allergy. On the other hand, we could not calculate the 5% PPV, therefore patients with a previous history of immediate reactions should undergo an OFC even if their specific IgE levels are low. Especially we should mind that approximately 20% of patients with a negative Ara h 2 sIgE developed symptoms in OFC in our fitted probability curve.

In patients without a previous history of immediate reactions, we could not calculate the 95% PPV. Peanut sIgE and Ara h 2 sIgE levels lower than 0.70 kU_A/L and 0.23 kU_A/L, respectively, are correlated to a high chance of ingesting peanuts without experiencing symptoms. These patients may not need an OFC and they may try consuming peanuts in their diets. In our fitted probability curve, more than half of patients without a previous history of immediate reactions to peanuts had negative OFC even if they had 100 kU_A/L of peanut sIgE. Therefore, in patients without a previous history of immediate reactions to peanuts, high levels of peanut sIgE alone should not lead to avoiding peanuts and testing for Ara h 2 sIgE levels is useful in determining whether to undergo peanut OFC. Using the above information, we can assess a patient suspected of peanut allergy with a flowchart (Supplementary Figure S2).

Peters *et al.* have reported the probability for a positive peanut food challenge, by peanut sIgE and Ara h 2 sIgE.[8] In the study, although OFCs were performed with 6 g of peanuts and the ratio of patients with a history of immediate reactions to peanuts was not described, the 95% PPV of peanut and Ara h 2 sIgE was 87.9 kU_A/L and 42.2 kU_A/L, respectively. These values were similar to the results of our study. One Australian study found that 95% PPV of peanut sIgE to peanut allergy was 1.0 kU_A/L and 39 kU_A/L with and without a previous history of immediate reactions, respectively.[7] These PPVs were lower than those in our study. The reasons for this difference were considered as follows. First, 9 g of peanut was used for the OFC. Second, all participants were 1 year old while in our study the ages ranged from 1 to 17 years. It has been reported that infants are more likely to have lower 95% PPVs than children aged 2 or older.[5] Considering that age may influence PPVs, we developed fitted probability curves for patients <6 years and those 6 years or older. There was no obvious difference between these groups (Supplementary Figure S3).

This study has some limitations. First, although older children were included, OFCs were open-challenge tests and not double-blind placebo-controlled food challenge tests. Second, analysis of the skin prick test could not be performed because only a small number of participants underwent this test. Third, this study presented fitted predictive probability curves for the positive outcome of a 3 g peanut OFC. These probability curves should not be used for predicting results of OFC using >3 g of peanuts. Finally, potential risks of bias and limitations related to the retrospective study design cannot be ruled out.

In conclusion, a previous history of immediate reactions changes the predictive accuracy for peanut allergy in children. The presence of a previous history of immediate reactions should be considered when performing OFC.

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IMPACT STATEMENT:

Our study is the first to show that a previous history of peanut reactions altered the predictive decision point of Ara h 2 and peanut specific IgE for positive peanut oral food challenge in children. Having a previous history of immediate reactions should be considered when we performing OFC.

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Tables:

Table 1: Predictive decision points for positive peanut food challenge results by peanut specific IgE and Ara h 2specific IgE

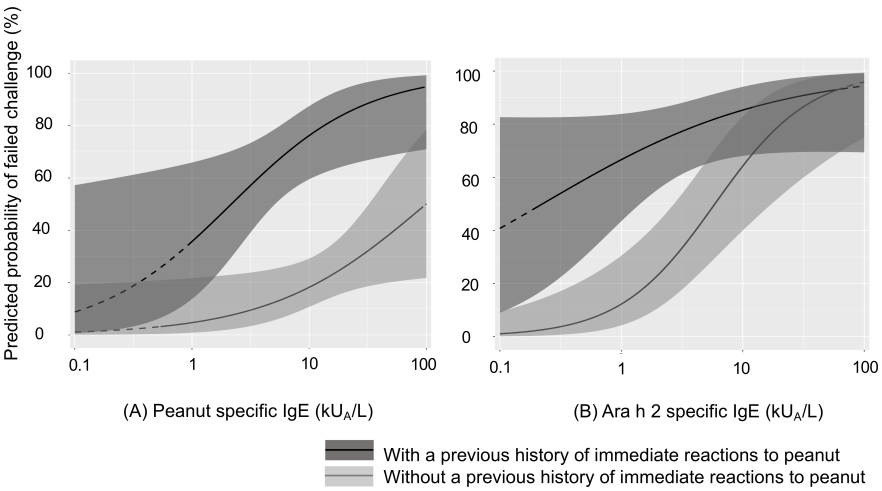
Predictive decision point (PPV)	With a previous history of immediate reactions to peanuts	With a previous history of i
	Peanut specific IgE (kU_A/L)	Ara h 2 specific IgE ($kU_A/$I
5% PPV	NA	NA
10% PPV	NA	NA
90% PPV	36.9	13.7
95% PPV	96.3	38.4

PPV, predictive decision point; NA, not applicable

Figure Legends:

Figure 1: Probability of positive peanut oral food challenge by peanut specific IgE (A) and Ara h 2 specific IgE (B) for patients with and without a previous history of immediate reactions

The solid lines indicate the range of probability calculated by specific IgE levels of our subject, the dashed lines indicate the range of probability calculated by extrapolation. The surrounded grayed area indicates 95% CI.



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