

Utility of Ara h 2 sIgE levels to predict peanut allergy in Canadian children

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Clinical Implications

- Our study suggests that Ara h 2 specific IgE (sIgE) levels may be twice as predictive as peanut sIgE levels in diagnosing peanut allergy. This study adds further confirmation that Ara h 2 sIgE is an important diagnostic test for peanut allergy.

TO THE EDITOR:

With the increasing prevalence of peanut allergy, allergists are evaluating more children with possible peanut allergy. Up to 0.8% of adults and 1.8% of children in Canada reported a peanut allergy in a survey of nearly 10,000 individuals.¹ In an Australian study, 3.0% of infants had challenge-proven peanut allergy.² Patients may have an unclear or remote history of reaction, or have never ingested peanut but have positive skin prick test (SPT) or specific IgE (sIgE) testing to peanut. Hence, an oral challenge to peanut would need to be done to establish or disprove the diagnosis. Oral challenges are labor-intensive with a risk of anaphylaxis, and better methods for diagnosing peanut allergy are needed. Recent studies show that Ara h 2 sIgE is an important predictor of peanut allergy with improved diagnostic accuracy when compared to peanut sIgE.³⁻⁹ However, study design differences make comparison between trials difficult. In our study, we assessed if Ara h 2 sIgE could be used to predict clinical peanut allergy in Canadian patients sensitized to peanut.

Patients 3 to 18 years old ($n = 137$) referred to BC Children's Hospital Allergy clinic (Vancouver, BC) for the assessment of peanut allergy with a positive peanut SPT, between November 2011 and March 2013, were invited to participate. The vast majority had a convincing history consistent with IgE-mediated allergy to peanut (Table I). Others had known peanut sensitization from prior testing or had other food allergies and were afraid of eating peanut. Positive SPT was defined as wheal size 3 mm greater than the negative control. All children underwent sIgE testing to peanut and Ara h 2 (ImmunoCAP, Phadia 250). Patients who underwent a peanut challenge had Ara h 1, 3, 8, and 9 measured. The study was approved by the University of British Columbia Research Ethics Board (Ref. H11-00677).

Patients ($n = 47$) with Ara h 2 sIgE ≤ 10 kU/L, regardless of the peanut sIgE level, were invited for an oral challenge. Food challenges were open with a cumulative dose of 3.3-5.3 g of peanut protein. A negative food challenge was defined as no objective symptoms up to 60 minutes after the last dose of peanut. Symptom severity was classified using a previously published scoring system.³ Data were analyzed using SPSS

version 21.0 (IBM Corp, Armonk, NY) and VassarStats for statistical computation (<http://www.vassarstats.net/>).

Of the patients who consented to an oral challenge ($n = 30/47$), 20 failed and 10 had anaphylaxis. Patients with anaphylaxis had Ara h 2 sIgE ranging from <0.10 to 8.79 kU/L and peanut sIgE from 1.33 to 17.8 kU/L. The Ara h 2 level was not significantly higher in those who had anaphylaxis ($P = .18$). A patient with Ara h 2 sIgE < 0.1 kU/L developed anaphylaxis and required treatment with intramuscular epinephrine (peanut sIgE was 4.47 kU/L and SPT > 8 mm, with no previous history of reaction). This patient's main risk factor for reaction was the large SPT and history of asthma. A patient with Ara h 2 sIgE = 0.31 kU/L also developed anaphylaxis and required treatment with epinephrine (peanut sIgE 1.34 kU/L and SPT 6.5 mm, with a remote history of reaction). A patient with Ara h 2 sIgE as high as 2.43 kU/L passed the challenge (mean Ara h 2 sIgE of those who failed was 2.86 kU/L). This patient had reacted to peanut with immediate facial urticaria and oral itch 3 years earlier. For patients who failed the challenge, the average Ara h 1 was 0.94 kU/L, Ara h 3 0.18 kU/L, Ara h 8 0.94 kU/L, and Ara h 9 < 0.1 kU/L. For patients who passed the challenge, the average Ara h 1 was 0.30 kU/L, Ara h 3 < 0.1 kU/L, Ara h 8 6.46 kU/L, and Ara h 9 0.87 kU/L.

To delineate sensitivities, specificities, predictive values and likelihood ratios, we calculated these values at different peanut and Ara h 2 sIgE levels (Table II). The optimal values for sensitivity and specificity for Ara h 2 sIgE were at cutoffs of 0.50 kU/L and 0.75 kU/L with an area under the curve (AUC) of 0.75 at these levels. This was the best performance identified for Ara h 2 sIgE at several cutoff levels between 0.1 and 10 kU/L on receiver operating characteristic (ROC) curves. The 95% positive predictive value for Ara h 2 sIgE was between 2 and 3 kU/L. The best performance for peanut sIgE was an AUC of 0.73 at a cutoff of 1 kU/L. For patients who underwent an oral challenge ($n = 30$), if we selected peanut SPT ≥ 3 mm and peanut sIgE ≥ 2 kU/L to predict the patients' challenge outcome, we would be correct about 32.5% of the time. If we used Ara h 2 sIgE > 0.75 kU/L to predict the challenge outcome, we would be correct 75% of the time. Using the combination of SPT ≥ 3 mm, peanut ≥ 1 kU/L, and Ara h 2 ≥ 0.75 kU/L did not improve the predictive value when compared to using Ara h 2 ≥ 0.75 kU/L alone (95% CI 0.56-0.94).

This is the first Canadian study to evaluate children with peanut challenges to assess the predictive value of Ara h 2 sIgE. Other strengths included prospective recruitment, evaluation from a single tertiary care center that accepts referrals from a large geographic area 4 times the size of Great Britain, and all oral challenges being done by the same physician. Mean Ara h 2 levels were higher in patients who were clinically allergic versus nonallergic (2.86 kU/L vs 0.53 kU/L), but we found that some with elevated Ara h 2 sIgE were tolerant and some with very low levels had anaphylaxis. A higher Ara h 2 sIgE did not help predict the severity of reaction.

A limitation of our study was its small sample size, illustrating the difficulty in adopting a prospective approach and getting patients to consent to an oral challenge with quite positive peanut SPT and sIgE results. Larger prospective studies in different geographic settings should be performed to better establish predictive values that can be generalized. Although open challenges

TABLE I. Characteristics of children enrolled in the study

Characteristic	Challengeable (n = 47)	Challenge—passed (n = 10)	Challenge—failed (n = 20)	Nonchallengeable (n = 90)
Male, no. (%)	32 (68)	4 (40)	17 (85)	58 (64)
Age in years, median (range)	7.1 (2.8-17.3)	7.3 (2-13)	7.8 (3-17)	7.75 (2.75-16.1)
Skin prick test diameter, median (range)	7 (2.5-14.5)	6.4 (4-10.5)	7.3 (1.5-14.5)	10.0 (4.5-25.5)
Peanut specific IgE (kU/L), median (range)	3.15 (0.35-33.8)	3.6 (0.1-20.5)	5.6 (0.1-32.2)	84.45 (14.7-100.0)
Ara h 2 IgE (kU/L), median (range)	1.24 (0.1-9.8)	0.53 (0.1-2.4)	2.86 (0.1-8.8)	62.7 (9.4-100.0)
Previous reaction to peanut, no. (%)	35 (75)	8 (80)	16 (80)	67 (74)
Sensitized to 2 or more foods, no. (%)	12 (26)	4 (40)	3 (15)	40 (44)
Sensitized to ≥ 1 aeroallergen, no. (%)	22 (47)	2 (20)	10 (50)	65 (72)
Personal history of eczema, no. (%)	32 (68)	7 (70)	14 (70)	46 (51)
Family history of eczema, no. (%)	20 (43)	5 (50)	10 (50)	35 (39)

Challengeable patients had Ara h 2 specific IgE (sIgE) < 10.0 kU/L.

Nonchallengeable patients had Ara h 2 sIgE ≥ 10.0 kU/L (1 patient with Ara h 2 9.4 kU/L had recent anaphylaxis to peanut and was deemed nonchallengeable).

TABLE II. Diagnostic value of peanut and Ara h 2 specific IgE (sIgE) at different cutoff points

	Sensitivity	Specificity	PPV	NPV	+LR
Peanut sIgE (kU/L)					
0.35	0.95	0.3	0.73	0.75	1.36
1	0.85	0.6	0.81	0.67	2.13
2	0.6	0.7	0.8	0.47	2
5	0.3	0.8	0.75	0.36	1.5
15	0.1	0.9	0.67	0.33	1
45	0.5	0.5	0.67	0.33	1
Ara h 2 sIgE (kU/L)					
0.25	0.85	0.6	0.81	0.67	2.13
0.5	0.8	0.7	0.84	0.64	2.67
0.75	0.7	0.8	0.88	0.57	3.5
1	0.65	0.8	0.87	0.53	3.25
2	0.5	0.9	0.91	0.47	5
3	0.25	1	1	0.4	∞

+LR, Positive likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

are not the gold standard, challenges are done this way the majority of the time in actual clinical practice, which makes our findings more relevant to those in clinical practice. Overall, using Ara h 2 sIgE at a cutoff of 0.75 kU/L to predict the outcome of a challenge was more than twice as predictive as using the combination of SPT ≥ 3 mm and peanut sIgE at a cutoff of 2 kU/L. Our findings are consistent with current studies on Ara h 2 predictive values, but a meta-analysis needs to be done before these predictive values can be generalized.³⁻⁹

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