The component-specific to total IgE ratios do not improve peanut and hazelnut allergy diagnoses

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Background: Specific IgE measurement predicts the outcome of oral food challenges with considerable uncertainty when evaluating food allergy.
Objective: Our aim was to assess whether accounting for the ratio of component- or allergen-specific to total IgE can improve this prediction.
Methods: This multicenter study collected blood samples from children with suspected peanut or hazelnut allergy referred to allergy specialist clinics for food challenges. Specific IgE to peanuts, hazelnuts, and their components (Ara h 1, Ara h 2, Ara h 3, Ara h 8, Cor a 1, Cor a 8, Cor a 9, and Cor a 14) and total IgE levels were determined by using the ImmunoCAP-FEIA. Specific to total IgE ratios were compared with raw IgE levels in terms of discrimination and prediction.
Results: Eighty-eight (43%) of 207 children with suspected peanut allergy and 44 (31%) of 142 children with suspected hazelnut allergy had symptoms during food challenge. Discrimination was similar for raw and ratio measures: areas under the curve of 0.93 for Ara h 2–specific IgE versus 0.92 for the Ara h 2–specific/total IgE ratio and 0.89 for Cor a 14–specific IgE versus 0.87 for the Cor a 14–specific/total IgE ratio. The probability for a positive peanut challenge with 0.35 kU/L Ara h 2–specific IgE was 16% when the total IgE level was greater than 500 kU/L compared with 51%/48% for low/medium total IgE levels (<100/100-500 kU/L). A positive hazelnut challenge with 0.35 kU/L Cor a 14–specific IgE was estimated in 7% when total IgE levels were high compared with 34%/32% with low/medium total IgE levels.
Conclusions: Raw Ara h 2– and Cor a 14–specific IgE levels were the best single predictors for pediatric peanut and hazelnut allergies, suggesting the omission of challenges at very high levels. Calculating ratio measures did not improve prediction in this population. However, estimation of individual probabilities for challenge outcomes could be supported by total IgE levels because high levels might indicate lower probabilities at a given component-specific IgE level. (J Allergy Clin Immunol 2016;■■■:■■■-■■■.)

Key words: *Food hypersensitivity, IgE, Ara h 2 allergen, peanut, Cor a 14 allergen, hazelnut*

A food allergy can only be reliably diagnosed or ruled out with an oral food challenge.[1] With the aim of reducing the time and resources spent on these time-consuming and risky procedures, several screening methods have been evaluated to identify subjects with a very low probability of symptom development on food exposure or subjects in whom a food allergy is almost certain. Above all, sensitization markers, such as dermal reactivity (skin prick test responses) or increased serum IgE antibody levels, are widely used to predict oral food challenge outcomes.[2-4]

These single-predictor approaches come with a considerable error rate, which has led to the development of more sophisticated, multidimensional, or stratified diagnostic tools. Including information, such as age, sex, or previous symptoms, increases the predictive performance.[5] Therefore sensitization not only to any protein of a given food but also to a defined single protein, which is also known as component-resolved diagnosis (CRD),[6] can further improve the value of these models.[7] CRD has been shown to provide the best single predictors of food challenge outcomes for 2 common food allergens,[8,9] peanuts (Ara h 2–specific IgE) and hazelnuts (Cor a 14–specific IgE), superseding the use of whole allergen-specific IgE levels.[10-13]

Implications of a given specific IgE level might depend on the total IgE level, which is a potential indicator of atopy.[14] The fraction of whole allergen-specific IgE in relation to total IgE has already been used to assess the efficacy of anti-IgE treatments[15] and to predict food challenge outcomes.[16-19] Whether accounting for total IgE improves the diagnostic accuracy of component-specific IgE measurement has not been evaluated.

This analysis initially aimed to assess the diagnostic characteristics of the relative Ara h 2– and Cor a 14–specific IgE fractions in relation to peanut- and hazelnut-specific or total IgE levels in a pediatric population, which helped identify subjects who could be safely omitted from a peanut/hazelnut challenge.

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Abbreviations used
AUC: Area under the curve
CRD: Component-resolved diagnosis

The fraction of other peanut and hazelnut component–specific IgE levels and whole allergen-specific IgE levels were assessed and compared with the diagnostic performance of the raw specific IgE level. The complementing test-inherent characteristics (eg, the sensitivity, specificity, and predictive values) and pointwise probabilities for a positive challenge outcome were also estimated to improve the applicability. In addition to analysis of fractions, other approaches to account for total IgE were assessed.

METHODS

Study design and setting

Nine study centers across Germany (centers in Bonn, Wangen, Wesel, Stuttgart, Osnabrück, and Hamburg, as well as 3 centers in Berlin) performed between 7 and 100 food challenges in children suspected of having peanut or hazelnut food allergy.[10] Blood was drawn before the challenge to assess the predictive value of total, peanut/hazelnut-specific, and CRD IgE levels. Parents provided written informed consent. The local ethics committees for each study center approved the study separately.

Population

Only children referred to pediatric allergy clinics for a first evaluation to demonstrate or exclude peanut allergy, hazelnut allergy, or both were eligible to participate in this study. Challenges performed to monitor already diagnosed food allergy or to prove oral tolerance were excluded from this analysis. There were no restrictions in terms of comorbidities or demographic characteristics, including age. In general, study physicians were following current international guidelines in their decision to perform a food challenge.[20,21] In detail, the inclusion criteria were as follows. First was sensitization to peanut or hazelnut, such as in children with atopic dermatitis who have never eaten peanut or hazelnut. The sensitization level (specific IgE level or skin prick test wheal size) was not accounted for as a selection criterion in these children. Second was a recent immediate-type reaction in which peanut or hazelnut was suspected as the causative agent. However, children with a severe reaction (anaphylaxis) within the last year to the first isolated consumption of peanut or hazelnut who were sensitized did not undergo food challenge testing.

IgE measurements

Venous blood samples were stored at −20°C and shipped on dry ice. The total IgE level was determined for all of the participating children. In the suspected peanut allergy cases, specific IgE levels against whole peanuts and 4 peanut proteins (Ara h 1, 2, 3, and 8) were measured, and for the suspected hazelnut allergy cases, IgE levels against whole hazelnuts and 4 hazelnut proteins (Cor a 1, 8, 9, and 14) were measured. IgE levels were determined by using a fluorescence enzyme immunoassay (ImmunoCAP 100 System; Thermo Fisher, Uppsala, Sweden), with a test-inherent upper detection limit of 100 kU/L only for the specific measurements. After all challenges were completed, analyses were performed at the study's central laboratory in Charité Berlin, Germany. Only total and whole peanut- or hazelnut-specific IgE levels measured at individual study centers using the same laboratory system were not determined again in the central laboratory.

Oral food challenges

Families were asked to discontinue the use of antihistamines 3 days before the food challenge. Native roasted peanuts and raw hazelnuts were blinded in a chocolate mousse and fed in increasing doses over 30-minute intervals (target protein amounts were 3 mg, 10 mg, 30 mg, 100 mg, 300 mg, 1 g, and 3 g) under clinical supervision and standby emergency assistance. The challenge meal ingredients were prepared centrally, distributed to each study center, and made ready for consumption on site on the day of the challenge. A positive challenge outcome was defined by objective clinical reactions (eg, urticaria/angioedema, vomiting/diarrhea, wheezing/stridor, rhinitis/conjunctivitis, and a decrease in blood pressure) during the procedure or as long as 120 minutes after the final dose, according to recent suggestions for food challenge interpretation.[20] A negative challenge outcome was ascertained by eating a cumulative dose (4.4-g protein content) without symptoms on the following day, proving clinical tolerance.[22] Interpretation of final challenge outcomes was independent of component-specific IgE levels because they were measured centrally after the clinical database was closed.

TABLE I. Baseline characteristics by assessed allergen

	Peanut		Hazelnut	
	No.	Percent	No.	Percent
Total	207		142	
Female sex	76	36.7	45	31.7
Age				
0-1 y	42	20.3	27	19.0
2-3 y	47	22.7	35	24.6
4-5 y	46	22.2	32	22.5
≥6 y	72	34.8	48	33.8
Comorbidities				
Atopic eczema	147	71.0	103	72.5
Asthma	67	32.4	50	35.2
Rhinoconjunctivitis	19	9.2	9	6.3
Other allergens challenged				
Peanut	—	—	88	62.0
Hazelnut	84	40.6	—	—
Almonds	15	7.2	18	12.7
Walnut	11	5.3	12	8.5
Hen's egg	70	33.8	61	43.0
Cow's milk	23	11.1	24	16.9
Soy	15	7.2	9	6.3
Wheat	10	4.8	4	2.8
Fish/crustaceans	7	3.4	5	3.5
Reacted to roasted allergen	179	(86.5)	18	12.7
Total IgE				
<100 kU/L	53	25.6	44	31.0
100-500 kU/L	86	41.5	61	43.0
>500 kU/L	68	32.9	37	26.1
Whole allergen-specific IgE				
<0.35 kU/L (CAP 0)	47	22.7	30	21.1
0.35 ≤ 0.70 kU/L (CAP I)	18	8.7	9	6.3
0.70 ≤ 3.5 kU/L (CAP II)	55	26.6	29	20.4
3.5 ≤ 17.5 kU/L (CAP III)	48	23.2	38	26.8
≥17.5 kU/L (CAP IV-VI)	39	18.8	36	25.4

Statistical analyses

The data set used for analyses consisted of children with available results for total IgE, Ara h 2, or Cor a 14 measurements; a defined challenge outcome (positive or negative); age (in months); and sex. Raw IgE measures are illustrated on log-scaled axes (base 10); values of less than 0.01 kU/L (including 0) and greater than 100 kU/L (upper detection limit) were shifted into these boundaries. Ratio measures were reported as percentages (multiplied by 100). By accounting for the ratio measure distributions with total IgE levels as the denominator, the data were transformed to the fifth root for depiction. Other than for total IgE levels, whole peanut/hazelnut-specific IgE levels were determined at 0 kU/L for some children (peanut, n = 16; hazelnut, n = 12). This impeded the ratio measure calculations with a specific IgE