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Clinical reactivity to hazelnut may be better identified by component testing than traditional testing methods

Jacob D. Kattan, MD, **Scott H. Sicherer, MD**, and **Hugh A. Sampson, MD**

Division of Allergy and Immunology, Department of Pediatrics, Elliot and Roslyn Jaffe Food Allergy Institute, Icahn School of Medicine at Mount Sinai, New York, NY.

Keywords

Food allergy; hazelnut; birch; component testing; skin prick testing; IgE; oral food challenge; sensitivity; specificity

To the Editor:

Tree nut (TN) allergy is common and appears to be increasing among children in the US, with parent-reported prevalence rising from 0.2% in 1997 to 1.1% in 2008.[1] Among the TN allergies, diagnosis of hazelnut allergy is complicated by this nut having Cor a 1 proteins that cross react with the birch pollen allergen, Bet v 1. Beginning in 2007, one of the commercial producers of a serum hazelnut-specific IgE test (ImmunoCAP system, now Thermo Fisher Scientific) supplemented the hazelnut allergosorbent with recombinant Cor a 1, to improve the test's sensitivity for birch-related reactions to hazelnut.[2] However, the change resulted in frequent clinically irrelevant positive tests in persons with birch pollen sensitization.

The current study examines the utility of skin prick tests (SPT), hazelnut specific IgE (sIgE), and component testing for diagnosing allergy to hazelnut. Phadia Immunology Reference Laboratory (PiRL) developed commercial IgE testing to the hazelnut components Cor a 1 and Cor 8, and later added Cor a 9 and Cor a 14 to their hazelnut panel, although the latter components are not FDA cleared. In reports from the Mediterranean area, systemic reactions to hazelnut are generally mediated by IgE to Cor a 8, a lipid transfer protein.[3-4] In reports from the US and Europe, sensitization to Cor a 9, an 11S globulin, and Cor a 14, a 2S albumin, have been associated with severe hazelnut allergy in children.[5-7] Here we analyze IgE results to the components Cor a 1, 8, 9, and 14 among children in a birch-endemic area of the US.

Corresponding Author: Jacob D. Kattan, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Place Box 1198, New York, NY 10029, Telephone: 212-241-5548, Fax: 212-426-1902, jacob.kattan@mssm.edu.

The study protocol was approved by the Institutional Review Board (IRB) of the Icahn School of Medicine at Mount Sinai. A review was performed of all hazelnut oral food challenges (OFCs) at the Jaffe Food Allergy Institute, a Pediatric, university-based, outpatient practice drawing referrals from the New York City area, between January 1, 2010 and January 9, 2013. Patients were referred for open OFC by 6 allergists on the basis of their clinical impression. No cutoff age, sIgE value, or SPT size precluded challenge. Typically these patients did not have a history of objective allergic symptoms upon ingestion of hazelnut, and the likelihood of a positive reaction was thought to be less than 50%. Charts were reviewed for demographic data, hazelnut sIgE levels, SPT test results (extract from Greer, Lenoir, NC), and OFC outcomes. The OFCs were performed using whole hazelnuts or Nutella® per published guidelines, with most challenges using doubling doses every 15 minutes until an age-appropriate serving size was ingested.[8] For subjective symptoms, challenges were temporarily paused and then continued following resolution of symptoms if the supervising physician deemed it safe to proceed. Treatment decisions were based on the supervising clinician's judgment.

In addition to the chart review, hazelnut component testing was performed on sera obtained within 1 year from patients participating in an IRB-approved study evaluating component testing to a variety of foods and who either underwent an OFC to hazelnut or had a convincing history of objective allergic symptoms (urticaria, angioedema, vomiting or anaphylaxis with respiratory symptoms) with hazelnut ingestion, where OFC was deferred. IgE to hazelnut extract and the components Cor a 1, 8, 9, and 14 were measured with the ImmunoCAP system.

Demographic data and test results from 116 patients who underwent a hazelnut OFC (median age 9 yrs, 65% male) are shown in Table E1 (see Table E1 in the Online Repository). Overall, 7.8% of the challenges elicited a reaction. There was no difference between those who tolerated vs reacted to hazelnut in median age, sex, SPT (median wheal 3 mm vs 5 mm, p=0.1) or sIgE (median 6.0 kU_A/L vs 3.7 kU_A/L; p=0.8), respectively. Among 7 patients with hazelnut sIgE levels >100 kU_A/L, all 7 passed the OFC.

Component testing was performed on 42 patients, 29 who passed a hazelnut OFC, 4 who failed and 9 based on a history of an allergic reaction. Of the 4 patients who failed the challenge, 3 developed urticaria and 1 developed an intermittent cough and lip swelling. While we would have liked to perform component testing only on patients who underwent an OFC, due to a lack of positive challenges, we tested the serum of an additional 9 subjects with a history of objective symptoms with ingestion of hazelnut. Of these 9 patients, 4 reported anaphylaxis with respiratory distress, 3 reported angioedema, 1 reported hives, and 1 reported vomiting. All 42 patients had detectable sIgE (>0.10 kU_A/L, the lower limit of detection in the commercially available component testing from PiRL, Portage, MI) to hazelnut extract, but reactive subjects were more likely to have detectable Cor a 9 (92% vs 55%, p=0.03) and Cor a 14 (85% vs 35%, p=0.006) (Table I) and had higher median sIgE only to Cor a 9 and Cor a 14 (Table II). Sensitivity and specificity to Cor a 9 and Cor a 14 were calculated for different IgE levels (see Table E2 in the Online Repository). A result ≥ 2.0 kU_A/L for Cor a 9 or ≥ 1.0 kU_A/L for Cor a 14 had a sensitivity of 92% and specificity of 93% for clinical reactivity. Using these cutoffs, only 1 of the 13 patients with a history of

objective symptoms with hazelnut ingestion would have been misdiagnosed as tolerant, while only 2 of 29 who passed the OFC would have been misdiagnosed as allergic.

In summary, SPT and sIgE testing for hazelnut allergy results in many false positive tests and unnecessary dietary eliminations. In this birch endemic area of the US, the specificity of hazelnut testing is greatly improved when utilizing hazelnut components if it includes Cor a 9 and Cor a 14. These components are both highly sensitive and specific for predicting clinical reactivity to hazelnut, particularly when utilized in combination.

There are several limitations in this study. Outpatient OFCs were performed openly, and at the discretion of the allergists, which could introduce bias. A recent Dutch study by Masthoff et al reported that IgE levels to hazelnut were significantly higher in children with objective symptoms compared to those with no or subjective symptoms.[7] We did not observe this distinction, possibly because our clinicians did not routinely challenge children with the highest sIgE levels who did not also have elevated birch sIgE levels. In the performance of component testing, we were limited by not having serum samples or consent for component testing from all patients who underwent hazelnut OFCs and therefore included patients reporting objective symptoms without performing an OFC, although this also reflects routine practice. Since only approximately 9% of children with tree nuts allergy outgrow their allergy,[9] it was unlikely that these patients would be tolerant.

This study reports the limitations of skin prick testing and food specific IgE levels in making a diagnosis of hazelnut allergy as demonstrated by over 100 hazelnut OFCs, and it is the first to report the benefits of using serum IgE levels to hazelnut components in a US population. While it is not necessary to perform hazelnut component testing in all patients with suspected allergy to hazelnut, there are many patients who are likely to benefit from this modality. In patients who do not have a history of objective symptoms upon ingestion of hazelnut, and whose elevated hazelnut sIgE levels may be attributed to elevated birch sIgE levels, component testing could give a better indication of patients who are clinically reactive to hazelnut. Additional studies with larger cohorts in different geographic regions will be needed to establish specific diagnostic protocols.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Clinical Implications

SPT and sIgE testing for hazelnut allergy produces many false positive results. When elevated hazelnut sIgE levels may be attributed to elevated birch sIgE levels, component testing that includes Cor a 9 and 14 may better indicate clinical reactivity.

Table I

Percent of patients showing sensitization to hazelnut and hazelnut components

	Clinically Nonreactive(n=29)	Clinically Reactive (n=13)	
	N (percent)	N (percent)	P value
Hazelnut Extract IgE ≥0.10 kU_A/L	29 (100)	13 (100)	1.00
Cor a 1 ≥0.10 kU_A/L	23 (79.3)	11 (84.6)	1.00
Cor a 8 ≥0.10 kU_A/L	6 (20.7)	6 (46.2)	0.14
Cor a 9 ≥0.10 kU_A/L	16 (55.2)	12 (92.3)	0.032
Cor a 14 ≥0.10 kU_A/L	10 (34.5)	11 (84.6)	0.006

Table II

Median IgE levels to hazelnut components

	Clinically Nonreactive (n=29)	Clinically Reactive (n=13)	
	Median IgE Level kU_A/L (range)	**Median IgE Level kU_A/L (range)**	**P value**
Hazelnut Extract	4.36 (0.21->100)	12.5 (5.26->100)	0.039
Cor a 1	3.91 (<0.10->100)	2.26 (<0.10-63.70)	0.60
Cor a 8	<0.10 (<0.10-0.55)	<0.10 (<0.10-13.30)	0.046
Cor a 9	0.18 (<0.10-3.66)	5.31 (<0.10-38.80)	<0.001
Cor a 14	<0.10 (<0.10-.86)	2.18 (<0.10-68.20)	0.001