The use of serum-specific IgE measurements for the diagnosis of peanut, tree nut, and seed allergy

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Background: The gold standard for diagnosing food allergy is the double-blind, placebo-controlled food challenge. Diagnostic food-specific IgE levels might assist in diagnosing food allergies and circumventing the need for food challenges.
Objectives: The purpose of this study was to determine the utility of food-specific IgE measurements for identifying symptomatic peanut, tree nut, and seed allergies and to augment what is known about the relationships among these foods.
Methods: Patients referred for suspected peanut or tree nut allergies answered a questionnaire about their perceived food allergies. Allergen-specific diagnoses were based on questionnaire, medical history, and, when relevant, skin prick tests and serum specific IgE levels. Sera from the patients were analyzed for specific IgE antibodies to peanuts, tree nuts, and seeds by using ImmunoCAP Specific IgE (Phadia, Inc, Uppsala, Sweden).
Results: Three hundred twenty-four patients (61% male; median age, 6.1 years; range, 0.2-40.2 years) were evaluated. The patients were highly atopic (57% with atopic dermatitis and 58% with asthma). The majority of patients with peanut allergy were sensitized to tree nuts (86%), and 34% had documented clinical allergy. The relationship between diagnosis and allergen-specific IgE levels were estimated by using logistic regression. Diagnostic decision points are suggested for peanut and walnut. Probability curves were drawn for peanut, sesame, and several tree nuts. High correlations were found between cashew and pistachio and between pecan and walnut.
Conclusions: Quantification of food-specific IgE is a valuable tool that will aid in the diagnosis of symptomatic food allergy and might decrease the need for double-blind, placebo-controlled food challenges. (J Allergy Clin Immunol 2008;122:145-51.)

Key words: *Food allergy, peanut allergy, tree nut allergy, serum-specific IgE*

Food allergies affect approximately 6% to 8% of young children,[1] and the number of children affected appears to be increasing. In fact, 2 separate studies have reported significant increases in the rates of peanut allergy. Over a 5-year period, the rate of peanut allergy in the United States appears to have doubled in young children.[2,3] Similarly, a cohort of children from the Isle of Wight was compared with a previous cohort in terms of clinical reactivity and sensitization to peanut, and a 2-fold increase in clinical reactivity and a 3-fold increase in peanut sensitization was reported.[4]

There is less information available regarding tree nut and seed allergies. Approximately 0.4% of the United States population is allergic to tree nuts.[3] It is thought that the majority of patients retain tree nut allergy throughout their lives.[5] Both children and adults are affected,[6] and reactions can be severe. In fact, tree nuts are implicated as the causative foods in a large percentage of fatal anaphylactic reactions.[7-9]

The exact prevalence of seed hypersensitivity is unknown. In 2002, the French national databank reported that 2.14% of children and 5.14% of adults were affected by sesame allergy.[10] The Anaphylaxis Campaign in the United Kingdom conducted a survey of its members who were avoiding sesame. The survey was prompted because the number of members avoiding sesame had doubled between April 2002 and December 2003. Approximately half of the persons surveyed reported clinical reactivity to sesame, with 18% of reactions characterized by symptoms consistent with anaphylaxis.[11] Recently, a report was published about the natural history of sesame allergy. The investigators of the study found that most patients had sesame allergy before the age of 2 years, and approximately 20% of those studied eventually had tolerance to the food,[12] which is similar to what is reported for peanut allergy.[13]

The diagnosis of patients with clinically reactive food allergies remains a challenge for the allergist. The double-blind, placebo-controlled food challenge is the gold standard for the diagnosis of food allergies.[14] Food challenges can be traumatic for the patient, are time-consuming, and are potentially dangerous.[15] Clinical diagnostic tests aid in the differentiation of patients who have favorable probabilities of tolerating foods during food challenges compared with those who are likely to react. The detection of food-specific IgE antibodies to certain foods (ImmunoCAP Specific IgE; Phadia, Inc, Uppsala, Sweden) has been shown to be predictive of symptomatic IgE-mediated food allergy.[16,17] Diagnostic decision points have been suggested for common food allergens, namely milk, egg, peanut, and fish. The decision points indicate reaction likelihood but do not predict reaction severity.[17] Diagnostic decision points for tree nuts and seeds that could accurately be used to diagnose symptomatic allergy would greatly assist decision making in clinical practice.

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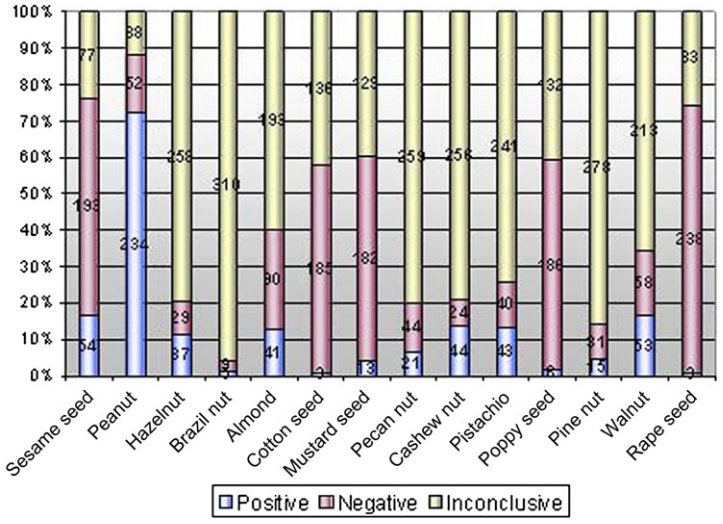

FIG 1. Characterization of the study population.

The purpose of this study was to determine the usefulness of peanut-, tree nut–, and seed-specific IgE measurements (ImmunoCAP Specific IgE) for the diagnosis of symptomatic allergies and to learn more about the relationships among these food proteins.

METHODS

Children, adolescents, and adults referred to the Mount Sinai Pediatric Allergy Clinic and the Boulder Valley Asthma and Allergy Clinic in Boulder, Colorado, for evaluation of suspected IgE-mediated peanut, tree nut, or seed (sesame, mustard, poppy, rape, and cotton seed) hypersensitivity were enrolled in the study. The Mount Sinai informed consent procedure was used for all patients enrolled in the study. The physicians involved in the study protocol determined the diagnosis of food allergy. A physician's diagnosis of allergy (positive, negative, or inconclusive) was determined for peanut, each tree nut, and each seed based on the available clinical information. A patient was labeled as having a positive diagnosis if he or she had a history of clinical reactivity to the individual food, and when questionable, this reaction was supported by serologic or skin test evidence of IgE-mediated allergy to that food; a patient was considered to have a negative diagnosis if he or she could tolerate ingestion of the food; and a patient was considered to have an inconclusive diagnosis if it was unknown whether the patient could tolerate the food regardless of serologic or skin test evidence of IgE mediated allergy. A questionnaire was administered to the patients prospectively pertaining to their food allergies. Questions included demographic information, age of onset of allergy, number of accidental exposures, severity of reactions, history of concurrent food allergies, resolution of other food allergies, and history of other atopic diseases. Subjects were enrolled in the study if they had a history of a reaction that was attributed to a peanut, tree nut, or seed; had evidence of food allergy, as demonstrated by an increased serum specific IgE level and, when relevant, by skin prick testing; or both. Food challenges were not performed on the majority of patients. Although considered the gold standard methodology for the diagnosis of food hypersensitivity, the investigators did not judge food challenges to be ethically justified, and parents frequently refused to allow challenges in this highly allergic study population, which consisted predominantly of pediatric patients.

Serum samples from all patients were collected at the time of the visit and analyzed for food allergen–specific IgE antibodies by using the ImmunoCAP Specific IgE, as previously described.[16] In brief, venous blood samples were collected and analyzed with the automated ImmunoCAP System. Fifty microliters of standards or patients' sera was added to the solid matrix (ImmunoCAP) and incubated for 30 minutes. After washing, enzyme-labeled anti-IgE was added to the ImmunoCAP and incubated for 2.5 hours, after which it was washed again, and then 50 μL of developing solution was added to each sample. After a 10-minute incubation, stopping solution was added, and fluorescence was determined and compared with values from the standard curve.

The study was approved by the Mount Sinai School of Medicine Institutional Review Board.

All statistical tests were 2-sided, and a P value of less than .05 was regarded as statistically significant. In patients with tree nut allergy, the Fischer exact test was used to test the hypothesis of an enhanced prevalence of allergy to a specific tree nut in relation to peanut allergy.

For single nuts and seeds, the relationship between diagnosis (positive or negative) and allergen-specific IgE antibody levels was estimated by using logistic regression. Observations with inconclusive diagnoses were not included in the analyses. The logistic regression models were formulated as the probability of receiving a positive clinical diagnosis as a function of the natural logarithm of the specific IgE concentration. Fitted predicted probability curves, using the results derived from the logistic regression models, were plotted. Performance characteristics (sensitivity, specificity, efficiency, and positive and negative predictive values) of ImmunoCAP Specific IgE were calculated at allergen-specific IgE antibody levels with a fitted predicted probability of 90% and 95%.

The Spearman rank order correlation coefficient was used to measure the strength of the relationship between allergen-specific IgE levels to peanut, tree nuts, and/or seeds.

RESULTS

Three hundred twenty-four patients with suspected peanut, tree nut, and/or seed allergies were enrolled in the study. The patients ranged in age from 2.4 months to 40.2 years (median, 6.1 years), and the majority of patients were male (male/female ratio, 198:126). Fifty-seven percent of patients had atopic dermatitis at some point in their lifetimes, and 58% had asthma. Many patients had other food allergies (either "outgrown" or present at the time of inclusion in the study), which occurred with the following frequencies: egg, 36.8%; milk, 29.6%; soy, 17.9%; fish, 13.3%; shellfish, 11.7%; and wheat, 10.5%.

Seventy-two percent of the patients reported and had a convincing history of peanut allergy. Fewer patients had convincing histories of tree nut allergy; however, the majority of