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Association of tree nut and coconut sensitization

Brooke I. Polk, MD [*]; Deendayal Dinakarpandian, MD, PhD [†]; Maya Nanda, MD, MSc [*]; Charles Barnes, PhD [*]; Chitra Dinakar, MD [*]

[*] Section of Allergy/Immunology, Children's Mercy Kansas City, Kansas City, Missouri
[†] Division of Computer Science and Electrical Engineering, University of Missouri-Kansas City, Kansas City, MO

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ABSTRACT

Background: Coconut (*Cocos nucifera*), despite being a drupe, was added to the US Food and Drug Administration list of tree nuts in 2006, causing potential confusion regarding the prevalence of coconut allergy among tree nut allergic patients.
Objective: To determine whether sensitization to tree nuts is associated with increased odds of coconut sensitization.
Methods: A single-center retrospective analysis of serum specific IgE levels to coconut, tree nuts (almond, Brazil nut, cashew, chestnut, hazelnut, macadamia, pecan, pistachio, and walnut), and controls (milk and peanut) was performed using deidentified data from January 2000 to August 2012. Spearman correlation (ρ) between coconut and each tree nut was determined, followed by hierarchical clustering. Sensitization was defined as a nut specific IgE level of 0.35 kU/L or higher. Unadjusted and adjusted associations between coconut and tree nut sensitization were tested by logistic regression.
Results: Of 298 coconut IgE values, 90 (30%) were considered positive results, with a mean (SD) of 1.70 (8.28) kU/L. Macadamia had the strongest correlation ($\rho = 0.77$), whereas most other tree nuts had significant ($P < .05$) but low correlation ($\rho < 0.5$) with coconut. The adjusted odds ratio between coconut and macadamia was 7.39 (95% confidence interval, 2.60–21.02; $P < .001$) and 5.32 (95% confidence interval, 2.18–12.95; $P < .001$) between coconut and almond, with other nuts not being statistically significant.
Conclusion: Our findings suggest that although sensitization to most tree nuts appears to correlate with coconut, this is largely explained by sensitization to almond and macadamia. This finding has not previously been reported in the literature. Further study correlating these results with clinical symptoms is planned.

Introduction

Coconut (*Cocos nucifera*) is a single-seeded drupe belonging to the Arecaceae family. A staple food of many countries, coconut provides a valuable source of protein, medium chain triglycerides, and other potential health benefits, including antioxidant and antimicrobial compounds.[1,2] Despite classification as a fruit, coconut was designated as a tree nut in a 2006 addition to the Food Allergy Labeling and Consumer Protection Act[3] for food labeling purposes. Unfortunately, this label has the potential to cause confusion for the ever-increasing population of tree nut allergic patients,[4,5] who are often instructed to avoid all tree nuts and peanut because of concerns about cross-contamination.

Few studies exist to evaluate the incidence of coconut sensitization in tree nut allergic patients; hence, there is limited evidence to advise nut allergic patients about coconut consumption. Of 5,149 patients evaluated by the Food Allergy and Anaphylaxis Network Peanut and Tree Nut Allergy Registry in the United States, only 4 individuals self-reported allergy to coconut.[6] Other large-scale, survey-based studies did not further subcategorize tree nut allergy into individual nuts.[4,5] Another group of researchers did not find an association between tree nut or peanut sensitization or clinical allergy and coconut sensitization via skin prick testing in 40 patients.[7]

Although the prevalence of food allergy in children is increasing,[4,5] clinical allergy to coconut appears to be relatively rare. Since the first description in 1999 by Teuber and Peterson,[8] there have been only 10 published cases of coconut allergy.[8–15] Although findings from case reports have revealed potentially cross-reactive proteins between coconut and hazelnut, walnut, and lentils,[8,9,11,14] the significance of these findings remains unclear.

Reprints: Brooke I. Polk, MD, Section of Allergy/Immunology, Children's Mercy Hospital, 2401 Gillham Rd, Kansas City, MO 64108; E-mail: bpolk@cmh.edu.
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Because of the lack of published data, the true prevalence of coconut sensitization is poorly defined, and the association between sensitization to tree nuts and coconut is largely unknown. We sought to examine serum specific IgE (sIgE) cosensitization patterns between tree nuts and coconut and to determine whether sIgE sensitization to tree nut(s) is associated with increased odds of coconut sensitization.

Methods

Data Set

A data set that contained all food sIgE data (ImmunoCAP; Thermo Fisher Scientific, Uppsala, Sweden) obtained at a single tertiary care pediatric center between January 2000 and August 2012 (N = 5,843) was queried for coconut IgE. In the data set, 298 patients were tested for coconut. In these patients, 274 of the coconut sIgE values had been obtained as part of a standard tree nut panel order set that assessed for sIgE to almond, Brazil nut, cashew, chestnut, coconut, hazelnut, macadamia, pecan, pistachio, and walnut. Milk (n = 128) and peanut (n = 285) sIgE samples obtained from the same 298 patients were used as controls, as available.

Statistical Analyses

Descriptive statistics and sensitization incidence were calculated for coconut, tree nut, and control sIgE values. Spearman rank correlation coefficients (Spearman ρ) between coconut sIgE and sIgE to each tree nut or control were determined, excluding double-zero pairings to avoid spurious correlation. Sensitization was defined as a positive food sIgE level of 0.35 kU/L of higher. Cosensitization rates between coconut and each tree nut or control were calculated.

The association between individual tree nut sensitization and coconut sensitization was examined by univariate and multiple logistic regression analysis on the entire cohort and randomly generated subsets. Corresponding unadjusted and adjusted odds ratios (ORs) were calculated with 95% confidence intervals (CIs) and the *P* value for differing from 1. Hierarchical clustering of antifood allergen sIgE levels was performed using Spearman correlation as the measure of distance between foods, including peanut and milk sIgE values as negative controls. Average linkage was used to determine the distance between clusters. This procedure was repeated multiple times on random subsets of the data and the consensus clustering reported.

Decision tree analysis to predict coconut positivity was performed after dichotomizing the sIgE measurements as negative or positive based on a threshold of 0.35 kU/L. Gini impurity was used as the criterion for splitting. Cross-validation with pruning was performed to determine the optimal tree. Analyses were performed using R statistical software, version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria), and SAS statistical software, version 9.4 (SAS Institute Inc, Cary, North Carolina). Exempt status was obtained from our institutional review board.

Results

The demographic profile of children attending our institution during the 12-year study period was 1 in 2 white, 1 in 4 African American, and 1 in 10 Hispanic. During the study period, 298 patients underwent testing for coconut sIgE, with a median age of 5.7 years (range, 2.1–30.7 years; interquartile range, 4.7 years). There were slightly more males than females (57.6% vs 42.4%). Coconut sIgE values ranged from 0 to greater than 100 kU/L (interquartile range, 0.46 kU/L), and 90 patients (30.2%) had a positive coconut sIgE test result (Table 1). Sensitization rates varied for each food, with peanut having the highest sensitization incidence, followed by pistachio and hazelnut. In general, the highest rates of sensitization were observed in the 5- to 10-year age range (Fig 1).

Table 1
Descriptive Statistics for Coconut, Tree Nut, and Control Specific IgE Values

Nut or control	No. of patients	No. (%) with positive test results	Mean	Median	IQR
Coconut	298	90 (30.2)	1.70	0	0.46
Almond	281	91 (30.5)	1.29	0	0.65
Brazil nut	272	82 (27.5)	1.59	0	0.52
Cashew	277	135 (45.3)	5.11	0.28	2.75
Chestnut	221	96 (32.2)	1.83	0.14	1.28
Hazelnut	270	146 (49.0)	6.96	0.47	3.33
Macadamia	270	103 (34.6)	1.71	0	0.86
Pecan	279	109 (36.6)	4.12	0	23.2
Pistachio	275	151 (50.7)	6.30	0.47	1.31
Walnut	278	117 (39.3)	4.03	0	4.04
Peanut	285	182 (61.1)	18.88	1.93	1.42
Milk	128	56 (18.8)	3.57	0.12	1.42

Abbreviation: IQR, interquartile range.

Coconut cosensitization rates (Table 2) were highest for macadamia (71%) and almond (69%). Spearman correlation analysis was performed in lieu of Pearson correlation to identity monotonic associations that were not necessarily linear and to minimize the effect of outliers. The Spearman correlation coefficient with coconut was highest for macadamia ($\rho = 0.77$, $P < .001$) followed by hazelnut ($\rho = 0.56$, $P < .001$) and almond ($\rho = 0.52$, $P < .001$) (Table 3). Correlation between coconut and peanut was quite weak ($\rho = 0.26$, $P < .001$), and no significant correlation was found between coconut and milk ($\rho = -0.0025$, $P = .98$).

Unadjusted ORs had a significant association between sensitization to each tree nut and coconut. Adjusted multiple logistic regression analysis, however, yielded a significant association only between almond and coconut sensitization (adjusted OR, 5.31; 95% CI, 2.18–12.95; $P < .001$) and between macadamia and coconut sensitization (adjusted OR, 7.39; 95% CI, 2.60–21.02; $P < .001$) (Table 4).

Hierarchical clustering revealed that coconut is the closest to macadamia in terms of sIgE levels (Fig 2). Additional evidence of the robustness of the clustering results is based on the fact that pistachio and cashew also tended to cluster together, as did pecan and walnut. Multiple trials of clustering were performed on random subsets of the data to minimize the chance of coincidental findings. The clustering association among the nuts was largely preserved, with milk and peanut being isolated from the nuts.

Decision tree analysis on the dichotomized data for prediction of coconut sensitization based on the results of testing for tree nut sensitization resulted in a very simple rule: “If macadamia tests positive, then coconut tests positive.” The corresponding positive predictive value and negative predictive value for sensitization were 0.75 and 0.96, respectively. The sensitivity and specificity of predicting a coconut sensitization based on the presence of sensitization to macadamia were 0.93 and 0.86, respectively.

Given the significant association between macadamia and coconut sensitization from the adjusted OR, clustering, and decision tree analysis, we performed linear regression between the corresponding levels of macadamia and coconut sIgE. Although the fit was statistically significant for the entire data set, Figure 3 highlights the fit to the 95% of data that have values less than 10 kU/L for both coconut and macadamia sIgE.

Discussion

Contrary to its name, the coconut fruit is not a nut. In botanical terms, a nut is a hard-shelled fruit that contains a single seed. Chestnut and hazelnut are nuts, although coconut is considered a drupe. Also known as a stone fruit, a drupe is an indehiscent fruit in