Correlation of negative skin-prick test results for tree nuts and successful tree nut challenges among children with peanut allergy

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ABSTRACT

Background: *Children with peanut allergy are regularly instructed to avoid all tree nuts. However, children with peanut allergy are likely not allergic to all tree nuts.*

Objective: *In our cohort of patients with peanut anaphylaxis and who underwent oral immunotherapy, we sought to determine the correlation of skin-prick testing (SPT) results for tree nuts and the likelihood of successfully passing a tree nut challenge.*

Methods: *SPT was performed for peanut and tree nuts (macadamia, pine nut, coconut, hazelnut, brazil nut, cashew, pecan, walnut, pistachio, almond) in 27 patients with known peanut allergy. The probability of a negative SPT result (wheal < 3 mm) for each nut was determined.*

Results: *All the patients demonstrated positive results in peanut allergy diagnostics in SPT, component testing, or food challenge. Only 15.4% of the patients had a positive SPT result to peanut alone. Macadamia, pine nut, and coconut SPT had a probability of negative SPT results of 0.97, 0.97, and 0.91, respectively. The odds ratio for this group having a negative SPT was 46.22. For hazelnut, brazil nut, and cashew, the probability of a negative SPT result was 0.81, 0.77, and 0.73, respectively. Pecan, walnut, and pistachio had odds ratios of 0.68, 0.68, and 0.64, respectively. All the patients with macadamia, pine nut, and coconut negative SPT results subsequently passed 9-g food challenges without oral immunotherapy.*

Conclusion: *Despite current recommendations to avoid all tree nuts for patients with peanut allergy, the majority of patients with peanut allergy had negative SPTs and food challenges to certain tree nuts, especially macadamia, pine nut, and coconut. This pattern was seen despite most patients having multiple nut sensitizations.*

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Nut allergy is among the most common and frequently severe type of food allergy worldwide, with peanut allergy highly prevalent in the United States.[1] More than 15 million people in this country are affected.[2] The common peanut accounts for ~8% of anaphylactic reactions in children.[2] The signs and/or symptoms may increase rapidly in severity even before the reaction is recognized, so that reaction may prove lethal. Allergy to peanuts and tree nuts is the leading cause of fatal and near-fatal reactions to food.[3] The immediate treatment of choice is epinephrine.

The prevalence of peanut allergy seems to be increasing. In a national, cross-sectional, random telephone survey of 13,493 people conducted by Sicherer *et al.*,[3] the estimated prevalence of self-reported peanut allergy in children and adults from 1997 to 2002 was 1.04%. However, in children, the rate of peanut or tree nut allergy doubled, from 0.6 to 1.2%, a statistically significant increase ($p = 0.05$). Only 74% of these pediatric subjects sought medical evaluation. In a similar follow-up telephone survey conducted 11 years later by those same investigators, 13,534 subjects were questioned.[4] Another significant increase in peanut and tree nut allergies in children was observed; the rate had risen to 2.1% by 2008 compared with 1.2% in 2002 and only 0.6% in 1997. Interestingly, queries about sesame allergy showed that this was a much less common problem, reported in just 0.1% of children.

In a major pediatric survey conducted in the United States, Gupta *et al.*[2] evaluated the occurrence of food allergies in 38,480 children sampled in households from June 2009 to February 2010. Allergy to peanuts was the most prevalent, 25.2%, followed by allergy to milk and shellfish, 21.1% and 17.2%, respectively.[2] Notably, reactions were severe in 38% of the children, and multiple food allergies were noted in 30.4%; they also observed that children with multiple food allergies experienced more severe reactions than those children

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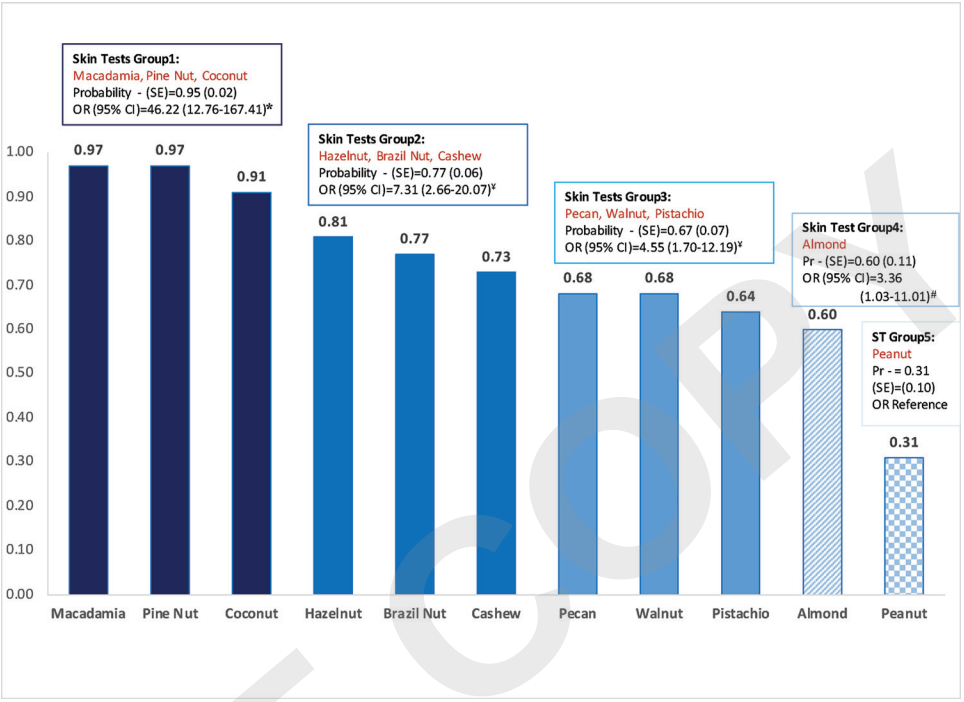

Figure 1. *Probabilities and odds ratios (odds of negative SPT result to types of tree of nuts in group verses odds negative to peanut) estimated using glimmix procedure in SAS (random intercept term specified and adjustment for repeated measures [multiple types of SPT within patient] using subject specification); *p < .05; #p < .01.*

with one food allergy.[2] Sicherer *et al.*[3] found that one in four children allergic to peanuts were also allergic to tree nuts.

Given the increasing incidence and risk prevalence, current clinical practice advises patients allergic to peanuts to avoid eating all other nuts, *e.g.*, tree nuts, regardless of the risk because the reaction could prove deadly. Children allergic to peanuts are routinely instructed to avoid eating cashews, pecans, walnuts, pistachios, almonds, macadamia nuts, pine nuts, coconut, hazelnuts, and brazil nuts. Other nuts may fall into the allergic risk, but these mentioned nuts are commonly encountered tree nuts, especially when eating in restaurants.

Irrespective of the current clinical atmosphere in food anaphylaxis, the likelihood of anaphylactic allergy to every tree nut is remote. However, few studies have addressed the risk of specific tree nut allergy in a pediatric population defined specifically as allergic to peanuts. Therefore, the goal of this study was to determine if tree nut skin-prick testing (SPT) results are indicative of a patient with peanut allergic is able to pass a tree nut challenge. At our facility, patients enrolled in food desensitization oral immunotherapy (OIT) for peanut allergy routinely undergo diagnostic assessment for specific tree nut allergy. In a cohort of patients who had experienced anaphylaxis after peanut ingestion and were undergoing OIT, we determined the correlation between SPT results obtained with tree nuts and peanuts, and evaluated the likelihood of the patient successfully passing an oral challenge with a specific tree nut.

METHODS

We performed SPT to peanut as well as to 10 tree nuts by using food extracts Hollister Stier (Jubilant Hollister Stier Inc., Spokane, WA) with a multi-test prick technique in 27 patients who attended the Gallegos Food Allergy Center at Miller Children's Hospital, Long Beach, California. All the patients demonstrated a history of at least one grade II or higher episode of anaphylaxis that required epinephrine in the past 5 years. The institutional review board at Miller Children's Hospital approved the study in April 2014. Written informed consent was received from all the patients via their parents. In addition to peanuts, the patients had SPTs to macadamia nut, pine nut, coconut, hazelnut, Brazil nut, cashew, pecan, walnut, pistachio, and almond. All the patients enrolled had not been consuming any tree nuts or peanuts. We then determined the probability of a negative SPT result (wheal < 3 mm) for each nut. After SPT, each individual was challenged orally with 9 g of protein of his or her respective tree nut allergen over sequential visits, which encompassed all the nuts listed in Fig. 1, as previously described, before undergoing peanut desensitization.[5] Each individual received 9 g of his or her protein allergens without the administration of OIT.

The proportion of patients with negative test results to each of 11 allergens (10 tree nuts and peanut) based on SPT results (wheal < 3 mm) in our sample of 27 patients with known peanut allergy was determined and standard error was reported. Also determined was

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Table 1 **Demographic data**

Total no. patients	27
Girls, % (no.)	48 (13)
Ara h 2 positive (>0.3 kU/L), % (no.)	100 (27)
Anaphylaxis grade 2, % (no.)	29 (8)
Anaphylaxis grade 3, % (no.)	71 (19)
White, % (no.)	75 (20)
Median age, y	8.4

Ara h 2 = Arachis hypogaea component.

the proportion of patients positive to 0–1, 2–3, 4–5, or 6–11 allergens and the mean ± standard deviation number of positive SPT results. The Generalized Linear Mixed Model Procedure (GLIMMIX) procedure in SAS v9.2 (Statistical Analysis System, Cary, NC) further assessed the probability of a patient's negative SPT result to each allergen, and the odds of a negative SPT result in a particular grouping of tree nuts (group 1: macadamia, pine nut, coconut; group 2: hazelnut, brazil nut, cashew; group 3: pecan, walnut, pistachio) relative to odds patient SPT negative to peanut. Odds ratios were reported with 95% confidence intervals. The procedure included a random intercept term and adjustment for multiple types of SPTs performed with each patient by using subject specification.

RESULTS

All 27 individuals (14 boys and 13 girls; ages, 4–19 years; median age, 8.4 years) had previously experienced anaphylaxis, World Allergy Organization grade 2 or higher[6] after peanut ingestion (Table 1). Although all 27 patients had previously demonstrated positivity for peanut allergy on either component resolved diagnostics (Pirl Laboratories, Kalamazoo, MI) or food challenge, only 33.3% were negative results to peanut on SPT (Table 2). Interestingly, 15.4% were positive to peanut only, 30.8% tree nuts only, and 53.8% peanut plus tree nuts (Table 3). Tree nuts with the highest probability of a negative SPT result were macadamia, pine nut, and coconut (0.97, 0.97, and 0.91, respectively) (Fig. 1).

As illustrated in Fig. 1, the odds ratio for this group having a negative SPT result compared with a negative SPT result for peanut was 46.22 ($p < 0.05$). The odds of a negative test to hazelnut, brazil nut, and cashew compared with a negative test result to peanut was lower, at 7.31, although still significant ($p < 0.05$). When comparing the odds of the negative result to pecan, walnut, and pistachio versus negative results to peanut, the ratio reduced to 4.55 ($p < 0.05$), with the lowest differential observed when comparing the odds of a negative test result to almonds versus peanuts 3.66 ($p < 0.05$). Of the 10 tree nuts tested, the patients had a mean of three positive SPT results. All the patients with negative SPT results for macadamia, pine nut, and coconut passed their oral food challenges (Table 4).

Table 2 **Negative SPT results to tree nuts in patients with known peanut allergy (*N* = 27)***

Allergy	Patients with Negative (q) Results to a Specific SPT, % ± SE#
Tree nut	
Macadamia	96.3 ± 0.04
Pine nut	96.3 ± 0.04
Coconut	88.9 ± 0.06
Hazelnut	77.8 ± 0.08
Brazil nut	74.1 ± 0.08
Cashew	70.4 ± 0.09
Pecan	66.7 ± 0.09
Walnut	66.7 ± 0.09
Pistachio	63.0 ± 0.09
Almond	59.3 ± 0.09
Peanut	33.3 ± 0.09

SE = Standard error; SPT= skin prick test; SQRI=square root.
**Negative SPT result was defined by a wheal < 3 mm.*
#SE = SQRT ([p × q]/n).

Table 3 **Positive SPT results to tree nuts in patients with known peanut allergy (*N* = 27)***

Allergy	Patients with Positive SPT Result#
Type of allergy, % ± SE	
Peanut only	15.4 ± 0.07
Tree nuts only	30.8 ± 0.09
Peanut plus tree nuts	53.8 ± 0.10
No. SPTs (0–11), % ± SE	
0–1	29.6 ± 0.09
2–3	37.0 ± 0.09
4–5	18.5 ± 0.07
≥6	14.8 ± 0.07
Positive SPTs, mean ± SD, no.	3 ± 2.3

SE = Standard error; SD = standard deviation; SPT = skin prick test; SQRI = square root.
**Positive SPT result defined by wheal > = 3 mm.*
#SE = SQRT ([p × q]/n).

DISCUSSION

Difficulty remains for children and adults allergic to peanuts to avoid accidental exposure. Most anaphylactic reactions occur at home, despite caution taken in preparing food for the individual with an allergy. The U.S. Peanut and Tree Nut Allergy Registry reports that 13.7% of such individuals experienced reactions after

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Table 4 **Description of patients who passed on the first attempt at open challenge to individual tree nuts**

Tree Nut	Patients Who Passed First Challenge, no.	Patients with Negative SPT Results Who Passed First Challenge, no.	Highest Grade of Symptoms on Failed Challenges (1–4)	Reactions that Required Use of an EpiPen (Mylan Inc., Canonsburg, PA), no.
Macadamia	27	26	0	0
Coconut	27	26	0	0
Pine nut	27	24	0	0
Hazelnut	22	20	3	1
Brazil nut	24	20	2	0
Cashew	19	19	3	1
Pecan	19	17	2	0
Walnut	18	18	2	0
Pistachio	18	17	2	0
Almond	16	16	2	0

SPT = Skin-prick test.

eating in an establishment that served food.[7] Furlong *et al.*[8] reported that restaurants (nearly 20% of them Asian) as well as buffets, food bars, and bakeries can present a risk to these patients. The investigators obtained details for 156 episodes of allergic reactions from 129 subjects or their surrogates who attended these establishments.[8] Most reactions were caused by peanut (67%) or, to a lesser extent, tree nut (24%); for some reactions, a combination of peanut and another nut was the cause in 9% or the cause was unknown.[8] Symptoms began ~5 minutes after exposure and were severe in 27%; antihistamines were administered to 86%, whereas only 40% received epinephrine.[8] The variability of clinical reactivity is reflective of food anaphylaxis heterogeneity among individual allergens.

The frequency of tree nuts and peanut exposure in the dietary and nondietary environment is a known risk that mandates diagnostic evaluation. Peanuts or other nuts can be present in desserts, in sauces, ice cream, dressings, or egg rolls, or even as contaminants on cooking utensils. According to Sicherer *et al.*,[3] a patient who is allergic to peanuts is 25 to 40% more likely to be allergic to tree nuts. GLIMMIX procedure analysis assessed the probability of negative tree nut and peanut SPT results among a peanut anaphylactic cohort. Tree nuts were organized in the analysis, based on deciles of probability, into four separate tree nut groups, with the fifth group being peanut (Fig. 1). Of note, the >90% probability decile identified macadamia, pine nut, and coconut as most likely to have a SPT negative result despite known peanut anaphylaxis.

A diagnosis of nut allergy still presents a challenge. Although SPT is practical, it is imperfect. It cannot predict the risk of anaphylaxis after ingestion of a specific nut species. Nevertheless, SPT for nuts coupled with oral nut allergen challenge, as was used here, is presently the standard for diagnosing a common and potentially dangerous anaphylactic reaction to peanuts and their tree-nut associates. Based on classifications of plant globulins and associated protein structures, including lectins and defenses, phylogenetic structures among tree nuts and peanuts can immunologically trigger cross sensitization.

In this study, we evaluated the negative predictive value of SPT in patients with a history of peanut anaphylaxis. In a study similar to ours but that relied instead on challenge with oral allergens that included tree nuts, Elizur *et al.*[9] diagnosed 60 patients ages 4–15 years with multiple allergies. The investigators found little evidence to exclude tree nuts from the diet, with acute reaction rates of only 5.9% for tree nuts versus 20–40% for other foods.[9] Retesting after 7 years (average) showed that some individuals indeed had developed tree nut allergies by then.[9] Newer tests, such as the component level approach, offer promise for a more precise diagnostic evaluation in the separation of various tree nut allergy diagnoses.

Our previous study of 74 patients who had experienced anaphylactic episodes on peanut ingestion[10] correlated their Radioallergosorbent Test (RAST), component levels, SPT results, and therapeutic epinephrine requirements. Although we found positive correlations between levels of certain components as well as epinephrine usage in assessing their risk for the number of episodes of peanut anaphylaxis, SPT data did not support such correlations.[10] However, specific directives for the use of component-level testing remain to be established. Our study demonstrated that, in peanut allergy, the highest probability of a negative SPT result was for macadamia, pine nut, and coconut. This odds ratio placed the patients at minimum risk for food challenge. To our knowledge, ours was the first study

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to further stratify such results in patients with peanut allergy across various tree nuts. Our results indicated certain tree nuts may be outright safely challenged in the office setting among individuals with peanut allergy.

Limitations of our study included a relatively small test sample ($N = 27$). Further, some of the children tested showed the onset of allergy at 9 or 10 years old, whereas others were infants at onset of allergy. The maturity of these children at the time of their first diagnosis could have influenced our subsequent diagnostic test results. Also, follow-up testing of our pediatric subjects might reveal probability data for allergy to tree nuts that differ from the present findings. Also, one may question the consistency and quality of our SPT antigens. To avoid problems in variability, our technicians were trained to use the same antigens from the same companies in SPT for peanuts and tree nut allergies.

The statistical approach to SPT results described here allowed for a more precise evaluation of the risk of tree nut sensitivity in patients with peanut sensitivity, which made it possible to render specific clinical advice regarding tree nut consumption or avoidance. Despite the current recommendations for these patients to avoid eating all tree nuts, the overwhelming majority of individuals will have negative SPT results as well as negative food challenges to certain tree nuts, especially to macadamia, pine nut, and coconut, which was the observed pattern in our patients with multiple nut sensitizations.

CONCLUSION

The present study provided a model for additional research. The heterogeneous nature of food anaphylaxis is dependent on multiple factors that involve variables within plant protein structures, epigenetic modification, and early environmental influences. Given the rise in food allergy diagnoses, it is important to determine the safety and efficacy in accurately diagnosing patients. To date, to our knowledge, no study has attempted to define the risk associated with patients with peanut allergy and the consumption of tree nuts. As we demonstrated in this study, avoidance of all tree nuts in patients with peanut allergy was not necessary. Indeed, several tree nuts were safe to challenge outright in an office setting. However, further compilation of comprehensive data across heterogeneity of this condition will improve the ability to predict which patients can safely be challenged and which patients require specific avoidance.

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