

The natural history of tree nut allergy

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Background: Although 20% of children outgrow peanut allergy, the natural history of tree nut (TN) allergy has not been well studied.

Objective: The goals of the study were to estimate the proportion of children who outgrow TN allergy and examine predictors of outgrowing it.

Methods: Patients with TN allergy, defined as a history of reaction on ingestion and evidence of TN-specific IgE (TN-IgE) or positive TN-specific IgE level but no history of ingestion, were evaluated. If all current TN-IgE levels were less than 10 kilounits of antibody (kU_A)/L, double-blind, placebo-controlled food challenges were offered. Patients who had undergone open TN challenges as part of routine clinical care were also included.

Results: Two hundred seventy-eight patients with TN allergy were identified. One hundred one (36%) had a history of acute reactions, 12 (12%) of whom had reactions to multiple TNs and 73 (63%) of whom had a history of moderate-to-severe reactions. Nine of 20 patients who had previously reacted to a TN passed challenges, so that 9 (8.9%; 95% CI, 4% to 16%) of 101 patients with a history of prior TN reactions outgrew TN allergy. Fourteen of 19 who had never ingested TNs but had detectable TN-specific IgE levels passed challenges. One hundred sixty-one did not meet the challenge criteria, and 78 met the criteria but declined challenges. Looking at specific TN-IgE cutoffs, 58% with TN-IgE levels of 5 kU_A/L or less and 63% with TN-IgE levels of 2 kU_A/L or less passed challenges.

Conclusions: Approximately 9% of patients outgrow TN allergy, including some who had prior severe reactions. Although ideal cutoffs for challenge cannot be firmly recommended on the basis of these data, patients aged 4 years or older with all TN-IgE levels of 5 kU_A/L or less should be considered for challenge. (*J Allergy Clin Immunol* 2005;116:1087-93.)

Key words: Tree nut allergy, peanut allergy, food challenge, CAP-RAST, food hypersensitivity

In the United States, an estimated 1% to 2% of the population is allergic to peanuts, tree nuts (TNs), or

Abbreviations used

kU_A: Kilounits of antibody
PN-IgE: Peanut-specific IgE
SPT: Skin prick test
TN: Tree nut
TN-IgE: Tree nut-specific IgE

both.^{1,2} Allergic reactions to TNs are typically severe,³ and accidental ingestions by allergic individuals are common.⁴ In addition, TN allergy is generally thought to be lifelong, and as a result, patients are typically told that they should avoid TNs and carry injectable epinephrine for the rest of their lives. Furthermore, follow-up of the patient with TN allergy does not typically include routine assessment to determine whether the patient has achieved oral tolerance. Although these management practices are appropriate given the lack of evidence that these patients outgrow TN allergy, there might be a substantial number of patients labeled as having TN allergy who have outgrown their allergy.

We previously reported that as many as 20% of children outgrow peanut allergy⁵ and recommended that children with peanut allergy be re-evaluated to determine whether they have achieved oral tolerance to peanut. Furthermore, peanut-specific IgE (PN-IgE) levels have been shown to be helpful in determining the likelihood that a child has outgrown peanut allergy.^{6,7} However, there is very little information about the natural history of TN allergy that can be used to guide clinicians' long-term management of children with TN allergy. Therefore we examined a large group of children with TN allergy to develop a better understanding of the natural history of TN allergy. Our first objective was to estimate the prevalence rate of outgrowing TN allergy, and our second objective was to determine whether there were any predictors of who might outgrow TN allergy, such as TN-specific IgE (TN-IgE) levels or the presence of other food allergies or other atopic diseases. This information would provide guidance for clinicians in deciding when continued avoidance of TNs is warranted or when oral food challenges to confirm or refute clinical reactivity are needed.

METHODS

Study population

Clinic records of patients from The Johns Hopkins Pediatric Allergy Clinic who had been given a diagnosis of TN allergy were

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reviewed to collect demographic and clinical data. A diagnosis of TN allergy was defined as either a clear-cut clinical history of an allergic reaction on ingestion and a confirmatory positive test response for TN-IgE or a history of a positive TN skin prick test (SPT) response or positive TN-IgE level (>0.35 kilounits of antibody [kU_A]/L) without history of ingestion. Specific demographic and clinical data that were collected included the patient's age, sex, initial symptoms, skin test results, TN-IgE levels, previous food challenge results, other food allergies, and associated atopic diseases. Patients from this database were then contacted by mail to inquire about their interest in participating in the procedural phase of the study. Subjects who consented were offered repeat SPTs and TN-IgE measurements, and double-blind, placebo-controlled food challenges were offered to subjects 4 years or older whose current TN-IgE levels were all less than $10 kU_A/L$ and who had no history of an acute reaction to a TN in the past year. Any patients with 1 or more TN-IgE measurements of greater than $10 kU_A/L$ were considered to have ongoing TN allergy and were not challenged. Subjects who had open challenges in the clinic as part of their ongoing routine care were included in the study as well. Medications, including antihistamines (short-acting antihistamines, 72 hours; long-acting antihistamines, 7 days), β -agonists (12 hours), and cromolyn (12 hours), were restricted before skin testing and food challenges were performed. The study protocol was approved by the investigational review board of The Johns Hopkins University School of Medicine.

SPTs

SPTs were performed through a standard technique with sterile bifurcated needles (Allergen Laboratories of Ohio, Inc, Columbus, Ohio). Glycerinated TN extracts for almond, Brazil nut, cashew, hazelnut, pecan, walnut (1:20; all from Greer Laboratories, Lenoir, NC), and pistachio (1:10; ALK Abello, Inc, Round Rock, Tex); a positive control (histamine; Hollister-Stier Laboratories, Spokane, Wash); and a negative control (saline solution, Hollister-Stier) were applied. The mean diameters of both the wheal and erythema were measured after 15 minutes. To be considered positive, the wheal had to be at least 3 mm greater than that elicited by the negative control.

CAP System FEIA

Venous serum samples were analyzed for circulating IgE to almond, Brazil nut, cashew, hazelnut, macadamia nut, pecan, pine nut, pistachio, and walnut with the CAP System FEIA (Pharmacia, Uppsala, Sweden). The assay had a lower limit of detection of less than $0.35 kU_A/L$ and an upper limit of greater than $100 kU_A/L$.

TN challenges

For the double-blind, placebo-controlled food challenges, each TN was obtained from manufacturers that had an individual line dedicated to that specific TN to avoid cross-contamination: raw, shelled, and unsalted almond, Brazil nut, hazelnut, pecan, and walnut (Treasured Harvest, Los Angeles, Calif); shelled, roasted, and unsalted cashew (Just Cashews, Albuquerque, NM); raw, unshelled, and unsalted pine nuts (Liston Pine Nuts, Orem, Utah); unshelled, roasted, and unsalted pistachios (Nicholas Pistachio, Hanford, Calif); and shelled, roasted, and unsalted macadamia nuts (Langenstein Farm, Captain Cook, Hawaii). The specific TNs were ground into a fine powder with individual coffee grinders (Braun Aromatic, Model KSM 2B, Boston, Mass). The TNs were disguised in cookies that contained ground cinnamon and vanilla extract to mask the smell and taste; placebo cookies also contained molasses and more oil to create a comparable color and fat content, respectively, as the nut recipes. As a texture and volume control, ground oat flour (Old Fashioned Quaker Oats, Chicago, Ill) was used. Only one type of cookie was prepared and cooked in the oven at a time. Approximately 20 g of nuts was

used per challenge, but the amount of actual TN protein per challenge within the 20 g varied depending on the TN used: almond, 4.04 g; Brazil nut, 2.87 g; cashew, 3.37 g; hazelnut, 2.99 g; macadamia nut, 1.56 g; pecan, 2.02 g; pine nut, 4.8 g; pistachio, 4.06 g; and walnut, 3.05 g. Both the TN-containing cookies and the placebo cookies were milk, egg, soy, peanut, and wheat free.

A physician, nurse practitioner, or both who were blinded to the testing materials administered the challenge in 6 divided doses. The first dose contained 5% of the total challenge dose, and subsequent doses given every 10 minutes were increased to 10%, 15%, 20%, 25%, and 25%. Up to 3 challenges were scheduled per day, 2 with TNs and 1 with placebo, and each challenge was separated by a minimum of 2 hours between the last ingestion of food in the previous challenge and the start of the next challenge. After each challenge, patients were observed for several hours. At any sign of objective or subjective symptoms deemed clinically significant, the challenge was terminated, and appropriate medical treatment was provided. The Nutrition Department of the Pediatric Clinical Research Unit of the General Clinical Research Center prepared the challenge materials and randomized each challenge.

The decision of which TNs to challenge with first was dependent on several factors. For those patients who had a prior reaction to a TN, the first day of challenges contained the TN that caused that reaction, the TN with the highest TN-IgE level, and a placebo. For those patients with positive TN-IgE levels but no history of ingestion, the challenges began with the 2 TNs that had the highest TN-IgE levels and the placebo. If the patient failed a challenge during that first day or on any future day, then the remaining challenges were aborted for that day, and the foods that were challenged were unblinded solely for that patient to determine whether a TN resulted in the reaction. If a TN-containing food was given during that challenge, then the patient was deemed allergic to TNs, no further challenges were performed, and all TNs were avoided. If the patient passed all challenges on the first day, then further challenges were conducted on other days to the other TNs in the order of the descending values of TN-IgE levels until either the patient failed a TN challenge or passed challenges to all TNs.

Statistical analysis

The primary study objectives were (1) to estimate the proportion of patients who achieve oral tolerance to TNs and (2) to examine potential predictors of oral tolerance. The study population included patients who had evidence of TN-IgE but no known TN exposure in addition to patients with both TN-IgE levels and clinical reactivity to a TN. We focused the analysis on TN-IgE levels because repeat levels were available on all subjects due to the fact that TN-IgE levels are repeated usually on an annual basis in our clinic as routine care of our patients with food allergy. SPTs were previously performed or repeated on a minority of patients and therefore were not useful in the data analysis (data not shown). For estimating the proportion of patients who outgrow TN allergy, only patients with a history of clinical reactivity to a TN were used. This minimized the possibility of overestimating the proportion of patients who outgrow their allergy by excluding those who have never ingested TNs but avoided them because they had a positive SPT response or TN-IgE level.

All patients were divided into the following 4 groups: (1) patients who passed challenges, (2) patients who failed challenges, (3) patients who were unable to be challenged because they had a TN-IgE level of greater than $10 kU_A/L$ or a recent history of a reaction, and (4) patients who declined to be challenged although they met the eligibility requirements. Several groups were also combined for further analysis: patients who were eligible for challenge, defined as patients who passed, failed, and declined challenge (groups 1, 2, and 4, respectively), and patients with ongoing TN allergy, defined

TABLE I. Patient characteristics

	Passed challenge (n = 23)	Failed challenge (n = 16)	Unable to challenge (n = 161)	Met criteria for challenge but declined (n = 78)	Total (n = 278)
Male sex	14 (61%)	12 (75%)	103 (64%)	51 (65%)	180 (65%)
Female sex	9 (39%)	4 (25%)	58 (36%)	27 (35%)	98 (35%)
Current age (y)					
Range	5.8-15.7	4.3-19.5	3-21.6	3-17.3	3-21.6
Median	10	8.4	6.8	6.8	6.9
Current TN-IgE level (kU _A /L)					
Range	<0.35-7.83	<0.35-4.98	<0.35->100	<0.35-8.95	<0.35->100
Median	0.79	1.17	32.5	2.81	12.1
No. diagnosed only by positive RAST or SPT response	14	5	110	48	177
No. diagnosed by history of acute reaction to a TN	9	11	51	30	101
Age at initial diagnosis (y)					
Range	0.5-5	0.6-5	0.3-15.8	0.3-13	0.3-15.8
Median	1.2	1.8	1.3	1.5	1.3
Initial TN-IgE level (kU _A /L)	n = 10	n = 8	n = 101	n = 40	n = 159
Range	<0.35-5.99	0.67-16.1	0.41->100	<0.35-45.2	<0.35->100
Median	1.1	3.28	22.3	3.26	9.79
Current peanut allergy	1 (4%)	3 (19%)	137 (85%)	49 (63%)	190 (68%)
Outgrown peanut allergy	11 (48%)	6 (38%)	6 (4%)	6 (8%)	29 (10%)

as those who failed challenges and those who could not be challenged (groups 2 and 3). Predictors of challenge outcome were analyzed by comparing patients who passed challenges with those who failed (groups 1 vs 2), regardless of whether they had previously reacted to a TN. Predictors of outgrowing TN allergy were performed by comparing patients who passed with those who had ongoing TN allergy (groups 1 vs 2 plus 3). The Mann-Whitney *U* test was used for analysis of continuous variables, the χ^2 test was used for categorical variables, and the Fisher exact test was used when the expected number in a cell was less than 5. The Cuzick test for trend was used to examine challenge outcomes across strata of TN-IgE levels. Negative TN-IgE levels of less than 0.35 kU_A/L and TN-IgE levels of greater than 100 kU_A/L were assigned levels of 0.1 and 100, respectively, for the purpose of analysis. All analyses were performed with StataSE 8.0 (College Station, Tex). A *P* value of less than .05 was considered statistically significant.

RESULTS

Study population

A total of 278 patients, with an age range of 3 to 21.6 years (median, 6.9 years) at the time of evaluation, were enrolled in the study and are described in Table I. There were 180 male (65%) and 98 female (35%) patients, and their TN allergies had been diagnosed between the ages of 3 months and 15.8 years (median, 1.3 years). The initial diagnosis was made on the basis of a history of an acute reaction to a TN or multiple TNs in 101 patients, 13 of whom had positive SPT responses and 88 of whom had positive TN-IgE levels. Of the remaining 177 patients, 170 were given diagnoses on the basis of a positive TN-IgE level, and 7 were given diagnoses on the basis of a positive SPT response. Peanut allergy status is described

in Table I, and associated atopic disorders are listed in Table E1 in the Online Repository in the online version of this article at www.jacionline.org. Overall, the study population was highly atopic because 96% of patients had an atopic disorder other than food allergy, and only 3% of patients had no other food allergy and no other atopic disorder. Sixty percent of patients had asthma, 67% had allergic rhinitis, and 66% had atopic dermatitis.

The 101 patients who were given diagnoses of TN allergy on the basis of previous clinical reactivity had a total of 115 allergic reactions: 10 patients reacted to 2 different TNs, and 2 patients reacted to 3 different TNs. The number and type of TNs causing reactions in these patients are depicted in Fig E1 in the Online Repository in the online version of this article at www.jacionline.org. Nine (8%) patients reacted to almond, 3 (3%) to Brazil nut, 34 (30%) to cashew, 6 (5%) to hazelnut, 5 (4%) to macadamia nut, 16 (14%) to pecan, 2 (2%) to pine nut, 5 (4%) to pistachio, and 35 (30%) to walnut. The number and type of organ systems involved in the reactions are described in Table E2 in the Online Repository in the online version of this article at www.jacionline.org. Ninety-seven (84%) reactions involved the skin, 52 (45%) involved the respiratory system (3% upper and 42% lower), 58 (50%) involved the gastrointestinal system (17% oral and 33% lower gastrointestinal), and 4 (3%) involved the cardiovascular system. Sixty-nine (60%) of the reactions involved more than one organ system. Two patients had multiple organ system allergic reactions involving cardiovascular compromise, one of whom had similar reactions to 3 different TNs. The severity of TN reactions in relation to the type of TN ingested is described in Table II.

TABLE II. Severity and type of TN ingested in 115 reactions

TN	Mild	Moderate	Severe
Almond	8 (19%)	0	1 (2%)
Brazil nut	1 (2%)	0	2 (4%)
Cashew	9 (21%)	8 (35%)	17 (34%)
Hazelnut	1 (2%)	3 (13%)	2 (4%)
Macadamia	0	3 (13%)	2 (4%)
Pecan	4 (10%)	5 (22%)	7 (14%)
Pine nut	2 (5%)	0	0
Pistachio	1 (2%)	0	4 (8%)
Walnut	16 (38%)	4 (17%)	15 (30%)
Total (n = 115)	42 (37%)	23 (20%)	50 (43%)

Mild, Skin symptoms and/or oral symptoms only; *Moderate*, upper respiratory and/or gastrointestinal only OR any 3 systems; *Severe*, respiratory lower and/or cardiovascular OR any 4 systems.

Almost two thirds of the reactions were moderate to severe, and reactions to cashew and walnut accounted for approximately two thirds of the severe reactions.

Of the 278 patients, 117 met challenge eligibility requirements on the basis of history and TN-IgE levels, whereas 161 did not. In the 161 patients who were unable to be challenged, whose ages ranged from age 3 to 21.6 years (median, 6.8 years), current TN-IgE levels ranged from less than 0.35 to greater than 100 kU_A/L (median, 32.5 kU_A/L). Fifty-one of the 161 patients were given diagnoses on the basis of a history of an allergic reaction to a TN on ingestion, and 110 patients were given diagnoses solely on the basis of a positive test result for TN-IgE. Four patients in this group had TN-IgE levels of less than 10 kU_A/L but were not able to be challenged because they had an allergic reaction to a TN within the past year. Of these 4 patients, one reacted to Brazil nut with urticaria and angioedema (Brazil nut-specific IgE 8.08 kU_A/L), and one reacted to walnut with angioedema and coughing accompanied by wheezing (walnut-specific IgE 5.17 kU_A/L). The remaining 2 patients both reacted to cashew; one experienced urticaria and coughing with wheezing (cashew-specific IgE <0.35 kU_A/L; positive SPT response), and the other had a severe anaphylactic reaction requiring intubation (cashew-specific IgE 1.55 kU_A/L). Initial TN-IgE levels, which were available in 101 of the 161 patients, ranged from 0.41 to greater than 100 kU_A/L (median, 22.3 kU_A/L). Both the current and initial median TN-IgE levels of patients who were unable to be challenged were significantly higher than the median levels in those groups of patients who met the challenge criteria ($P < .0001$).

Of the 117 patients who met the challenge criteria, 78 with ages ranging from 3 to 17.3 years (median, 6.8 years) and current TN-IgE levels of between less than 0.35 and 8.95 kU_A/L (median, 2.81 kU_A/L) declined challenges. Thirty of the 78 patients had been given diagnoses of TN allergy on the basis of an acute reaction to a TN, whereas 47 were given diagnoses on the basis of a positive TN-IgE level and 1 on the basis of a positive SPT response. Patients who declined challenges had significantly higher current TN-IgE levels than those who were challenged (2.81 kU_A/L vs 0.84 kU_A/L, $P < .0001$). Patients

who declined challenges were also significantly more likely to both have current food allergies and significantly less likely to have outgrown other food allergies compared with patients who were challenged ($P < .0001$ and $P = .03$, respectively). Furthermore, patients who were eligible for challenges were significantly less likely to have current other food allergies compared with patients unable to be challenged ($P < .0001$). Finally, patients who declined challenges were significantly more likely to have current peanut allergy and significantly less likely to have outgrown peanut allergy compared with patients who were challenged (both $P < .0001$).

TN challenges

The remaining 39 of 117 patients who met the challenge criteria, with an age range from 4 to 19.5 years (median, 9.2 years), underwent TN challenges. TN-IgE levels at the time of challenge ranged from less than 0.35 to 7.83 kU_A/L (median, 0.84 kU_A/L), and initial TN-IgE levels available in 18 of the 39 patients ranged from less than 0.35 to 16.1 kU_A/L (median, 1.44 kU_A/L). The age of diagnosis of the challenge group ranged from 6 months to 5 years (median, 1.5 years).

Twenty-three (59%) of the 39 patients who underwent challenges passed. TN-IgE levels for those who passed challenges were similar to levels in the group who failed challenges (median, 0.79 vs 1.17 kU_A/L, respectively; $P = .44$). The age of diagnosis for those who passed was not significantly different than the age of diagnosis for those who failed ($P = .54$). Initial TN-IgE levels, which were available in 10 of the patients who passed and in 8 of the patients who failed, were significantly higher in the group that failed challenges (median, 1.1 vs 3.28 kU_A/L, respectively; $P < .03$).

Twenty of the 39 patients who were challenged had previously ingested and reacted to a TN, 9 (45%) of whom passed. Two of these 9 patients had previously failed a TN challenge, and another 2 patients had previously reacted to 2 different TNs, both to walnut and pecan. Four of these 9 patients outgrew cashew, 3 outgrew pecan, and 2 outgrew walnut allergies. Nineteen patients who were challenged had never eaten a TN but were given diagnoses of TN

allergy on the basis of detection of TN-IgE. Fourteen (74%) of them passed, and 5 failed.

Estimated proportion of patients with resolved TN allergy

Of the 101 patients who had both clinical reactivity and evidence of TN-IgE, 9 of 20 passed TN challenges, so that we could confirm that at least 8.9% (95% CI, 4% to 16%) of these 101 patients acquired oral tolerance. If the analysis was not restricted to those patients who had previously reacted to a TN, so that all 278 patients were included regardless of the method of TN allergy diagnosis, then at least 23 (8.3%; 95% CI, 5% to 12%) of the 278 patients outgrew their TN allergy.

TN-IgE levels and challenge outcome

The ability of TN-IgE levels to predict challenge outcome was also evaluated (Table III). Twenty (63%) of 32 patients with TN-IgE levels of less than 2 kU_A/L and 22 (58%) of 38 patients with TN-IgE levels of less than 5 kU_A/L passed challenges, but only 1 patient passed with a TN-IgE level of greater than 5 kU_A/L. TN challenge pass rates tended to decrease with increasing TN-IgE levels, but the trend was not statistically significant ($P = .28$). Three (75%) of 4 patients with negative TN-IgE levels passed challenges, 17 (61%) of 28 patients with TN-IgE levels of between 0.35 and 2 kU_A/L passed challenges, and 2 (33%) of 6 patients passed with TN-IgE levels of between 2 and 5 kU_A/L.

Predictors of TN allergy resolution and challenge outcome

The initial presenting allergic reaction did not predict resolution or persistence of TN allergy. Of the 9 patients with a history of TN ingestion who passed challenges, 5 had previously had mild reactions, 1 had previously had a moderate reaction, and 3 had previously had severe reactions. Of the 11 patients with a history of TN reactions who failed challenges, 5 had had mild, 2 had had moderate, and 4 had had severe reactions previously.

Similar rates of asthma and allergic rhinitis were observed in patients who passed and failed challenges, as well as in patients who were unable to be challenged and declined challenge. Although 69% of patients with atopic dermatitis failed challenges and 43% of patients with atopic dermatitis passed challenges, this difference was not statistically significant ($P = .19$). However, patients who passed challenges had a significantly lower rate of atopic dermatitis than those with ongoing TN allergy ($P = .009$).

Approximately one third of the 278 patients had outgrown other food allergies, and approximately 75% had other ongoing food allergies. Patients who passed TN challenges were significantly less likely to have other current food allergies than those who failed challenges ($P = .03$) and those with ongoing TN allergy ($P < .0001$). Overall, 190 (68%) patients had ongoing peanut allergy

TABLE III. TN-IgE levels and pass rates

TN-IgE levels at challenge (kU _A /L)	Pass rate (%)
≤5	58
2.01-5	33
≤2	63
0.35-2	61
<0.35	75

(peanut allergy was diagnosed by using the same criteria as for TN allergy), whereas only 29 (10%) had outgrown peanut allergy. Patients who had outgrown peanut allergy were significantly more likely to outgrow TN allergy compared with patients with ongoing TN and peanut allergies ($P < .0001$).

DISCUSSION

These findings confirm that a subset of children with TN allergy outgrow their allergy over time, although the resolution rate appears to be less than in peanut allergy. The data suggest that children with TN allergy should be re-evaluated periodically to assess whether they have acquired oral tolerance. In addition, TN-IgE levels can be used to estimate the likelihood that a patient has outgrown his or her TN allergy and guide selection of appropriate candidates for TN challenges.

Our estimate that 9% of children with TN allergy outgrow their allergy was calculated using only the subgroup of patients who had both clinical reactivity and evidence of TN-IgE. We restricted the calculation to the subgroup with clear-cut TN allergy to derive a conservative estimate of the true resolution rate. However, this result could be an underestimate of the true resolution rate. First, only 20 of the 50 patients with a history of reaction after ingestion who met the challenge criteria were actually challenged because 30 patients declined, despite being eligible to undergo challenge. Although the median TN-IgE level for those who declined challenge, 2.81 kU_A/L, was significantly higher than the median of those patients challenged, 0.84 kU_A/L ($P < .0001$), some patients in the group who declined challenge would likely have passed. If we were to assume that the pass rate for those who declined challenge was the same for those challenged (45%), the resolution rate would increase to 21.8% (95% CI, 14% to 31%). It is also possible that even a few of the patients who had TN-IgE levels of greater than 10 kU_A/L could have passed if they were challenged. Furthermore, because our clinic site is in a tertiary-care facility, our patient population might be skewed to more severe cases of food allergy and therefore might not be typical of all patients with TN allergy.

As seen for other food allergies,⁵⁻⁷ TN-IgE levels are likely to be the best guide to determine which patients should be considered for oral food challenges. Although we have not challenged as many patients with TN allergy, the pass rates at different TN-IgE levels were very similar

to the pass rates at the same cutoffs for PN-IgE levels.^{5,7} In this study, 58% of children with TN-IgE levels of 5 kU_A/L or less, 63% with TN-IgE levels of 2 kU_A/L or less, and 75% with negative TN-IgE levels passed an oral challenge. The minimum age of 4 years that was used for inclusion in this study was selected to maximize safety and avoid a possible risk of increased sensitization if challenged too young. In addition, TN-IgE levels might also be helpful in assessing the likelihood that a patient will acquire oral tolerance in the future. For example, the highest initial TN-IgE level of any patient who outgrew TN allergy was 7.83 kU_A/L. Although we did not study enough patients to make a definitive conclusion, it is unlikely that many patients with TN allergy will eventually outgrow their allergy if their TN-IgE levels increase to greater than 10 to 20 kU_A/L, as has been the case in our patients with peanut allergy.^{5,7}

The potential for severe anaphylactic reactions to TNs, which has been reported in other studies,^{4,8,9} was confirmed in this study. The majority of the 115 allergic reactions were graded as either moderate (20%) or severe (43%). Initial reactions to TNs, however, were not predictive of future TN allergy status. Looking at the number of organ systems involved in the 115 reactions, 40% involved only 1 organ system, 43% involved 2 organ systems, 17% involved 3 organ systems, and 1% involved 4 organ systems. These percentages are similar to those found in the TN registry study by Sicherer et al.¹

Of the different TNs, cashew, walnut, and pecan accounted for the vast majority of reactions: 30%, 30%, and 14%, respectively. These values are also similar to those reported in the TN registry when there was an isolated ingestion of a single nut.¹ In this study cashew, pecan, and walnut were responsible for approximately 75% of the moderate (35%, 22%, and 17%, respectively) to severe (34%, 14%, and 30%, respectively) allergic reactions, whereas almond, cashew, and walnut accounted for about three quarters of the mild reactions at 19%, 21%, and 38%, respectively. Even though our clinic site is a major referral center for patients with food allergy, our patient population appears to be similar in many regards to patients in the TN registry.¹ Why these particular nuts are so highly represented is most likely a manifestation of both allergenicity and their relative use.

Overall, 68% of our patient population allergic to TNs was also allergic to peanut. The percentage of patients with peanut allergy in this study is higher than reported in other studies in which both peanut and TN allergies were found in 41% of 62 patients,⁸ 28% of 122 patients,⁴ 40% of 223 patients,⁵ and 49.5% of 622 patients.¹⁰ This discrepancy might be explained by the fact that a large number of our patients given diagnoses of TN allergy were identified during an evaluation for peanut allergy and had no history of prior TN ingestion, so that some of them might not have true TN allergy.

Other notable findings in this study are that none of the patients who outgrew their TN allergy had a history of having clinical reactions to more than 2 different TNs and

that having outgrown peanut allergy was significantly associated with an increased chance of outgrowing TN allergy. This latter result remained statistically significant ($P < .0001$) when we analyzed the subgroup of patients with peanut allergy who had either ingested peanut and reacted or had a PN-IgE level of greater than 14 kU_A/L (95% positive predictive value cutoff)¹¹ and never ingested peanut (data not shown). Although this latter finding is intriguing, it could be due to a biased association. For example, parents of children who had outgrown peanut allergy might have been more willing to consent to TN challenges. Furthermore, parents might have had preconceptions of whether their children truly ever had TN allergy or still had ongoing TN allergy, and these potentially valid preconceptions could have affected the parents' willingness to consent to a TN challenge. Although some clinical cross-reactivity between peanut and TN proteins have been found and could explain the association between outgrowing peanut allergy and outgrowing TN allergy,¹² more data from patients who outgrow these allergies is needed before definitive conclusions can be made.

Overall, 78% of the patients had ongoing allergies to other foods, whereas 37% had outgrown other food allergies. Whether a patient with TN allergy had outgrown other food allergies did not seem to affect whether they outgrew their TN allergy. However, only 13% of patients who passed TN challenges had current other food allergies, which was significantly less than in those who failed TN challenges (44%), those who were unable to be challenged (91%), and those with ongoing TN allergy (87%). In their peanut allergy study, Skolnick et al⁵ also found that patients who passed peanut challenges were significantly less likely to have current other food allergies than those who had ongoing peanut allergy. This might reflect the fact that because only approximately 10% to 20% of patients outgrow TN and peanut allergy, respectively, those patients who do outgrow peanut and TN allergies might be more likely to have a general tendency to not only outgrow food allergies in general but also to possibly outgrow them sooner.

We conclude that approximately 9% (95% CI, 4% to 16%) of children with TN allergy outgrow their allergy, including patients who have previously failed a challenge and patients who have had severe anaphylactic reactions in the past. Patients who are allergic to more than 1 or 2 different TNs are unlikely to eventually outgrow their allergy. Whether patients who have outgrown peanut allergy are truly more likely to outgrow their TN allergy needs to be studied further as we challenge more patients with TN allergy over time. Although the potential for a severe reaction exists and the ideal TN-IgE cutoff has not been definitively established, patients 4 years or older with all TN-IgE levels of less than 5 kU_A/L or less should be considered for challenge in the proper setting with trained personnel. However, it might be more prudent to delay challenges until the TN-IgE levels are 2 kU_A/L or less because this might further increase the odds of a successful outcome.

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