Journal of Asthma and Allergy

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REVIEW

Current perspectives on tree nut allergy: a review

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Abstract: Tree nut (TN) allergy is common and often severe. It has become an important health concern as availability and consumption have increased. Prevalence varies by age and geographic region and appears to have increased in children. Accidental ingestion of TNs is common. Unfortunately, there is a lower likelihood of resolution of TN allergy, roughly 10%. TN-specific skin tests and serum immunoglobulin E levels can help aid in the diagnosis of TN allergy, but a careful medical history is important because a positive test in isolation is not typically diagnostic. Component-resolved diagnostic tests are being increasingly utilized and may improve accuracy. Management consists of strict avoidance of the causal nut(s) and prompt treatment of symptoms upon accidental exposure. A specific consideration with regard to the management of TN allergy is the decision to avoid all TNs or only the TNs to which a patient is clinically allergic. There are currently no data on the primary or secondary prevention of TN allergy. Treatment strategies are being evaluated.

Keywords: food allergy, anaphylaxis, food allergens, food hypersensitivity, cross reactivity, component resolved diagnostics

Introduction

Allergies to tree nuts (TNs) are common and have become an important health concern as availability has increased.[1] TNs, as a group, are one of the eight most common allergens, and allergic reactions to them can be severe.[2] TN availability has increased both in the raw form and within processed foods and bakery products; TN utilization has increased by 2.3 pounds per capita from 1980 to 2015.[3] Research has shown that the consumption of nuts has positive cardiovascular effects, such as decreasing cholesterol, triglycerides, and fasting blood glucose, and this has encouraged consumption.[4,5]

Botanically, TNs are defined as a dry fruit composed of an inedible hard shell and a seed.[6] However, the term "TN" is commonly used to describe any nut coming from a tree, and this includes foods that do not meet the botanical definition. Nine nuts account for the majority of allergies to TNs, including walnut, almond, pistachio, cashew, pecan, hazelnut, macadamia, Brazil nut, and pine nut.[6] For the purpose of labeling laws, the US Food and Drug Administration (FDA) additionally considers the following to be TNs: beechnut, butternut, chestnut, chinquapin, coconut, ginkgo nut, hickory nut, lychee nut, pili nut, and shea nut.[7] A report from the National Academies of Sciences recommends that these nuts be removed from this list since there are little data on them and they uncommonly cause allergic reactions.[8] For the purpose of this review, we will focus on the nine most common TNs that cause allergic reactions, and we do not extensively discuss peanut allergy (a legume).

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Dovepress
http://dx.doi.org/10.2147/JAA.S141636

Prevalence

There are numerous limitations to quantifying the prevalence of TN allergy. Prevalence reports are often based on self-reported allergy, rather than objective measures, which is often an overestimate.[9,10] In addition, studies regarding TN allergy often include pollen food allergy syndrome (PFS), otherwise known as oral allergy syndrome, which is characterized by mild oral symptoms, and patients may ingest the TN.[11] Another barrier to interpreting prevalence studies is that many evaluate allergy generically, querying about "nuts" without specifying which nut, and may include peanut in this category.[11]

Two systematic reviews defined the prevalence of TN allergy while taking these limitations into account. A systematic review by Zuidmeer et al[10] reported population-based cross-sectional and cohort studies published between 1990 and 2006. These studies included prevalence estimates based on self-perception, test results, and oral food challenges (OFCs). Studies performed in clinical settings were excluded to avoid bias. The prevalence of perceived reactions to TNs ranged up to 7.3%. However, most studies included were from Europe where PFS is common. When including only three studies that used OFC as an objective definition of TN allergy, the prevalence ranged from 0.1% to 4.3%. A more recent systematic review was done by McWilliam et al[11] and included studies from 1996 to 2014. Only population-based cross-sectional and cohort studies were included, and studies performed in selected patient groups or in specialty clinic settings were excluded. The majority of studies that were included were regarding children and from Europe. Probable TN allergy was defined as a reported history of an immunoglobulin E (IgE)-mediated reaction occurring ≥2 years ago or self-reports of a doctor's diagnosis of TN allergy. The prevalence of probable allergy ranged from 0.05% to 4.9%, with only one study providing data on adults. When including seven studies using the gold standard of challenge-confirmed TN allergy, the prevalence ranged from 0% to 1.6%. In both studies, the prevalence rates were lower when including only challenge-confirmed cases and ranged from 0% to 4.3%.

The prevalence of allergy to TNs appears to have increased in children. A US nationwide, cross-sectional, random telephone survey was conducted in 2008, and the results were compared with previous comparable surveys done in 1997 and 2002.[12] The prevalence of TN allergy in children <18 years old increased from 0.2% in 1997 to 1.1% in 2008. TN prevalence in adults was 0.5% in 2008 and was not statistically different between the surveys.

The prevalence of TN allergy varies by region and is higher in children. The US prevalence data based on telephone surveys were mentioned above and were 0.5% in adults and 1.1% in children in 2008.[12] A self-reported food allergy survey study conducted in Canada, excluding adults reporting unlikely allergies, estimated a TN allergy prevalence of 1.7% in children and 1% in adults.[13] This was similar to findings in a cross-Canada, random telephone survey, which found prevalence of perceived TN allergy of 1.22% and probable allergy of 1.14%.[14] A European systematic review that included studies from 2000 to 2012 found a pooled estimated prevalence from all age-groups of 1.3% for self-reported TN allergy and 0.5% based on OFC.[15] A study conducted in Australia, which used objective measures for diagnosis, found a prevalence of 2.3% among schoolchildren aged 10–14 years.[16] A nationwide, cross-sectional study of Korean schoolchildren found TN prevalence to be 0.32%.[17] A Mexican study found a prevalence of walnut allergy of 0.4% in adults.[18] A questionnaire study done on schoolchildren in Singapore and the Philippines found a prevalence of convincing TN allergy of 0.28% and 0.3%, respectively.[19] Overall, TN allergy appears to vary by region, age, and the definition used for diagnosis but affects ~0.05%–7.3% of the population.

Clinical manifestations

TN allergy typically develops by the age of 2 years, and the number of TNs that a patient is sensitized to can increase with age.[20] The number of nuts children eat increases with age and can explain the increasing rates of sensitization.[20] A US registry noted that the median age of reaction to TNs was 36 months, compared with peanut, which was 14 months.[21] Sixty-eight percent of these patients reacted on the first known exposure.[21] Age of initial reaction to TNs may occur later since children are often exposed to TNs later than to peanut.[22]

Reactions to TNs can be severe. Peanut and TNs account for 70%–90% of reported food-related anaphylactic fatalities, and TNs alone account for 18%–40% of cases of anaphylaxis.[23,24] Severity of coexisting atopic diseases, including allergic rhinitis, asthma, and eczema, is associated with more severe reactions to TNs.[25] Asthma may be an independent risk factor to predict severe reactions.[21]

TNs can also cause PFS. PFS is an IgE-mediated allergy due to cross-reacting homologous proteins in pollens and various foods, including nuts, fruits, and vegetables.[26] The consumption of these foods can cause localized reactions in pollen-sensitized individuals due to cross-reactivity.[27] In specific, birch-pollen-sensitized individuals may develop PFS upon

the ingestion of almond and hazelnut.[28] Symptoms of PFS are usually mild, limited to the oropharynx, and include pruritus, tingling, erythema, and mild edema of the mouth.[29] Proteins are degraded with digestion due to stomach acid and gastric enzymes, preventing systemic absorption, and reactions rarely progress.[30]

An accidental ingestion of TNs in allergic individuals is frequent. In a 5-year US follow-up telephone survey, including patients with self-reported peanut and TN allergy, 66% of individuals had more than five lifetime reactions to peanut or TN.[31] In a British study, 15% of participants had a reaction to TN and peanut after their initial diagnosis.[32] In this study, they noted that the subsequent reaction was less severe. This is in contrast to a study by Sicherer et al[21] where results showed that progressively more severe reactions occurred with repeat exposures. This study cohort had an overrepresentation of children, and the authors hypothesized that this could have been an age effect, with mild reactors outgrowing the allergy and leaving the patients with a more severe allergy in the cohort of patients with repeat reactions. In addition, older children may report symptoms that are associated with severity (eg, throat tightness).[21]

TN allergy has a lower likelihood of resolution compared with other food allergies. A study by Fleischer et al[33] identified 101 patients in a tertiary care center with TN allergy, defined by a clear clinical history of a TN reaction as well as confirmatory positive testing. OFCs were offered to participants aged ≥4 years who had a TN specific-IgE (sIgE) <10 kU/L and had no reaction in the past year. Of the 101 patients, 20 participants underwent an OFC and 9 patients passed, demonstrating that only 9% of TN-allergic patients later became tolerant. This result can be an underestimate as 30 patients who were eligible for an OFC declined. The predictors of outgrowing TN allergies were a low TN sIgE level, a lack of other food or TN allergy, and a history of outgrowing peanut allergy. Of note, patients who developed oral tolerance to peanut may be more likely to choose to undergo a TN OFC, and this criterion can therefore be biased. No patient who passed an OFC had a history of a clinical reaction to two or more TNs, and this may be an indicator of persistent TN allergy. Severity of the initial presenting allergic reaction, a history of asthma, or a history of allergic rhinitis did not predict food challenge outcomes.[33]

Diagnosis

TN allergy is diagnosed in the same manner as other food allergies with a combination of a thorough clinical history, serum-specific IgE, skin prick testing (SPT), and OFCs.[2,9,34,35] Prior history determines clinical suspicion for allergy and helps target testing. Serum and skin tests alone are indicators of sensitization, but the history is a vital component in ascertaining if there is a clinical allergy.[9] The double-blind, placebo-controlled, food challenge (DBPCFC) remains the gold standard for diagnosis but is not indicated when there is a high clinical suspicion of allergy.

TN-specific skin tests and serum IgE are markers of sensitization and can help aid in the diagnosis when there is clinical suspicion. In a cross-sectional, observational study in the UK,[36] of 1,000 children and adults referred to an allergy clinic with a history of reaction to TNs or peanut, an SPT of ≥8 mm to TNs predicted clinical reactivity with >95% accuracy. An Australian prospective study,[37] in which 247 patients with concern for TN allergy underwent OFC, confirmed that an SPT ≥8 predicted clinical reactivity for cashew, hazelnut, and walnut. They could not determine the 95% positive predictive value (PPV) SPT for almond, pistachio, pecan, and Brazil nut and hypothesized that this was due to the small sample size for these nuts. Skin tests can vary widely among patients, institutions, and the extracts used. Therefore, each practitioner must interpret SPT values somewhat cautiously. In regard to TN sIgE, the UK observational study mentioned above found that a level of ≥15 kU/L to an individual TN had a 95% PPV for clinical allergy.[36] In the study by Fleischer et al, 63% patients with TN sIgE levels of <2 kU_A/L passed challenges.[33] In a retrospective US study reviewing open TN OFCs, 79 of 124 (89%) patients passed a challenge with a TN-specific IgE level <2 kU_A/L, whereas 10 of 16 (69%) patients passed an OFC with a TN sIgE level of ≥2 kUA (mean =5.12 kU_A/L).[38] Overall, a SPT ≥8 mm or TN sIgE ≥15 kU/L usually indicates a high risk of allergy.

Component-resolved diagnostics (CRDs), or molecular allergen analysis, are becoming more utilized and may improve accuracy for diagnosing TN allergy. While serum-specific IgE measures IgE to the whole food extract, CRD measures IgE to specific proteins within that food. This can help differentiate sensitization to clinically relevant versus irrelevant proteins and can identify reactivity as a cause for an elevated IgE.[39] For example, sensitization to an allergen that is resistant to heat or digestion, a stable protein, is more likely to cause systemic reactions. On the other hand, sensitization to proteins that are homologous to aeroallergens and are easily digested may not be clinically relevant. Identifying sensitization to allergen components may elucidate who will have a systemic reaction upon the ingestion of the TN.

TNs have two major types of proteins, metabolic and storage proteins. The seed storage proteins are the allergens associated with many cases of severe, anaphylactic TN allergy. Seed storage proteins include the prolamin superfamily (including 2S albumins) and the cupin superfamily that consists of the legumin-group proteins (the 11S globulins) and vicilins (the 7S globulins).[40] Additional TN proteins, also known as pan-allergens, include lipid transfer proteins (LTPs), profilins (structural proteins), pathogenesis-related proteins, and heveins, and these are similar to proteins in pollens, seeds, fruits, and vegetables and are associated with IgE-mediated cross-reactivity.[41] Sensitization to these proteins may lead to PFS, although systemic reactions are also possible, particularly for LTP or 2S albumins.

Individual TNs

CRD is available for many individual TNs. Here, we will review prevalence data specific to individual TNs as well as the known component proteins (Table 1).

Hazelnut

Hazelnut, also known as filbert, is from the genus *Corylus* and belongs to the Betulaceae, or birch, family. In a systematic chart review, hazelnut was found to be the most common TN allergy in Europe.[11] However, many studies in this review included PFS reactions to TNs. Hazelnut, along with walnut, was also found to be the most common TN allergy in Spain.[42] Hazelnut is often consumed in pastries and chocolates. Some hazelnut butters, such as the brand Nutella®, are not cross-contaminated with other nuts and therefore may be of interest to patients allergic to a TN other than hazelnut.

CRD has been useful in differentiating primary hazelnut allergy from sensitization to pan-allergens with homology to birch pollen. Sensitization to the hazelnut components, Cor a 9, an 11S globulin; and Cor a 14, a 2S albumin, is more specific for hazelnut allergy compared with total hazelnut sIgE.[43,44] Cor a 9 was detected in 86% of the patients with hazelnut allergy and a history of systemic reactions.[45] A Dutch study found that an IgE level to Cor a 9 of ≥1 kU_A/L in children and adults or a level to Cor a 14 of ≥5 kU_A/L in children and ≥1 in adults had a specificity of >90% in diagnosing hazelnut allergy.[46] Similar results were found in a US study where a Cor a 9 of ≥2.0 kU_A/L or Cor a 14 of ≥1.0 kU_A/L had a sensitivity of 92% and specificity of 93% for diagnosing clinical reactivity.[44] Cor a 8 is an LTP that is heat-stable and not cross-reactive to pollen. Sensitization to Cor a 8 is a risk

Table 1 Individual tree nut components

Tree nut	Protein family	Component	Protein type	Clinical relevance
Hazelnut	Pan-allergens	Cor a 1	PR-10	Homolog of Bet v 1; PFS
		Cor a 2	Profilin	Homolog of Bet v 2; PFS
		Cor a 8	LTP	Systemic reactions in children from Mediterranean areas
	Storage proteins	Cor a 9	11S globulin	Systemic reactions
		Cor a 11	7S globulin	
		Cor a 14	2S albumin	Systemic reactions
Cashew	Storage proteins	Ana o 1	7S globulin	
		Ana o 2	11S globulin	
		Ana o 3	2S albumin	Systemic reactions
Pistachio	Storage proteins	Pis v 1	2S albumin	Homolog of Ana o 3; systemic reactions
		Pis v 2	11S globulin	Homolog of Ana o 2; systemic reactions
		Pis v 3	7S globulin	
		Pis v 5	11S globulin	Homolog of Ana o 1
Walnut	Storage proteins	Jug r 1	2S albumin	Systemic reactions
		Jug r 2	7S globulin	Systemic reactions
		Jug r 4	11S globulin	Systemic reactions
	Pan-allergens	Jug r 3	LTP	Systemic reactions in Mediterranean individuals
		Jug r 5	Profilin	
Pecan	Storage proteins	Car i 1	2S albumin	Homolog of Jug r 1
		Car i 2	7S globulin	Systemic reactions
		Car i 4	11S globulin	Homolog of Jug r 4
Almond	Storage proteins	Pru du 6	11S globulin	
	Pan-allergens	Pru du 3	LTP	
		Pru du 4	Profilin	
Pine nut	Storage proteins	Pin p 1	2S albumin	Systemic reactions
Brazil nut	Storage proteins	Ber e 1	2S albumin	Systemic reactions
		Ber e 2	11S globulin	

Abbreviations: LTP, lipid transfer protein; PFS, pollen food syndrome.

factor for systemic reactions in children from Mediterranean areas.[47,48] Cor a 1 (PR-10) is a profilin and homolog of Bet v 1, which is a major birch pollen allergen. Sensitization to Cor a 1 is elevated in patients with PFS to hazelnut.[49,50] It was found that all patients with PFS to hazelnut were sensitized to Bet v 1 and >97% to Cor a 1, with no patients being sensitized to Cor a 9 or Cor a 8.[50] Cor a 2, another profilin, correlates to Bet v 2, which can also cause PFS in patients sensitized to certain birch and grass pollens.[51] Cor a 11, a 7S vicilin, is less well defined.[52]

Cashew and pistachio

Cashew and pistachio belong to the Anacardiaceae family and are botanically related. Cosensitization often exists to these nuts. Coallergy often exists as well, although pistachio allergy is somewhat less common, and patients with a cashew or pistachio allergy are often counseled to avoid the related nut.[53,54] One study showed that cashew nut–sensitized children were cosensitized to pistachio nut in 98% of cases. They challenged a subset of these patients and found that only 34% of the cashew-sensitized patients reacted to pistachio.[55] In another study, all of 42 pistachio-allergic participants had a positive challenge to cashew.[54]

Cashew and pistachio allergies commonly cause severe reactions with very small exposure. In a retrospective chart review including 27 patients with cashew allergy, 74% experienced anaphylaxis upon cashew ingestion.[56] In a case-matching study that compared patients who presented primarily for cashew allergy to patients who presented for peanut allergy, more patients in the cashew-allergic group reported wheezing and cardiovascular symptoms, and they required intramuscular adrenaline more frequently.[57] Interestingly, proteins homologous to cashew may be found in fruit seeds, such as apple and orange, with rare reports of reactions among people with severe cashew allergy if these seeds are eaten.[58–60]

The prevalence of cashew and pistachio nut allergies seems to be common in industrialized countries where these nuts are being used with increasing popularity. Cashew nuts can be found in Asian meals, cakes, and chocolates, and they are being used in commercially prepared pesto sauces.[57] In a US registry of patients with TN allergy, which included mostly children, cashew was the second most common cause of TN allergy, and this allergy was found in 20% of TN-allergic patients.[21] Two other studies also identified cashew, along with walnut, as being the most common TN allergen in the USA.[11,33] In a 3-year follow-up study involving 139 TN-allergic adults from the Netherlands, 20% were allergic to cashew, and in France, there was an estimated frequency of 10.3%.[61,62] Pistachio nut allergy is less prevalent in the USA and was estimated in 7% of TN-allergic patients.[21] In Turkey, pistachio allergy was found in 6.7% of patients with food allergy.[63]

Cashew allergen components include Ana o 1, a vicilin; Ana o 2, a legumin-like 11S globulin; and Ana o 3, a 2S albumin. Sensitization to Ana o 3 is the best predictor of clinical allergy.[64] In Greek children, IgE sensitization to Ana o 3 was detected in 93% of cashew-allergic children and in only 6% of cashew-tolerant patients.[65] In addition, Ana o 3 can be used to diagnose pistachio allergy. For Ana o 3, an optimal cutoff point of 0.16 kU_A/L was reported as indicative for cashew nut and pistachio allergies with high sensitivity and specificity.[65]

Pistachio components Pis v 1 (2S albumin) and Pis v 2 (11S globulin) are homologous to Ana o 3 and Ana o 2, respectively, and have shown to cause sensitization in pistachio-allergic patients.[66] Of 28 pistachio-allergic patients, 68% were sensitized to Pis v 1 and 50% to Pis v 2.[66] Pis v 3 (7S vicilin) showed correlation with Ana o 1.[67] Pis v 5 is another 11S globulin, but less information is known about this allergen.

Walnut and pecan

Walnut and pecan are members of the Juglandaceae family, and allergies to these nuts often coexist, with pecan allergy being slightly less common.[53] Andorf et al[54] showed that all participants who were allergic to pecan were also allergic to walnut, while 9% of walnut-allergic participants tolerated pecan. Walnut is the most common TN allergen among TN-allergic patients in Spain and the USA, where it was found to range between 3% and 34%.[21,33,42]

Proteins in Juglans regia (English Walnut) include Jug r 1 (2S albumin), Jug r 2 (7S vicilin), Jug r 3 (LTP), Jug r 4 (legumin-like 11S globulin), and Jug r 5 (a profilin).[68] Jug r 1 is related to Ana o 3.[69] Sensitization to Jug r 1 and Jug r 2 was found among 75% and 60% of patients with severe clinical presentations, respectively.[70,71] Jug r 1 had improved specificity over walnut extract for diagnosing walnut allergy.[72] Jug r 4 was positive in 21 of 37 individuals with walnut allergy (>57%).[73] Jug r 3 was recognized in 78.2% of Italian walnut-allergic patients and may have more importance in Mediterranean patients. However, this study included both patients with PFS and systemic reactions.[74]

Pecan components include Car i 1 (2S albumin) and Car i 4 (11S legumin).[75,76] These components have been found to be cross-reactive with Jug r 1 and Jug r 4.[75,76] IgE to Car

i 2, a 7S vicilin, was detected in 6 of 25 patients with pecan allergy confirmed by double-blind, placebo-controlled food challenges.[77]

Almond

Almond is from the Rosaceae family. In the USA, almond allergy is reported by 9%–15% of TN-allergic individuals.[21,33] Almond, along with walnut, was the most common TN allergy in allergic individuals in the UK, and the prevalence ranged from 22% to 33%.[11] Almonds are often consumed roasted or in almond milk and butters, of which certain brands can be purchased easily without cross-contamination with other nuts. Sensitization to almond correlates strongly with birch sensitization; however, it does not necessarily translate into clinical reactivity.[28] Almond components, such as Pru du 6 (11S globulin), Pru du 3 (LTP), and Pru d 4 (profilin), have been recognized, but little clinical information is available about them.

Pine nut

Pine nuts, otherwise known as pignoli, are seeds of the Pinaceae family. Pine nuts can be found in salads, Italian dishes such as Italian pesto and pignoli cookies, and Middle Eastern cuisines, such as kibbeh and baklava. Pine nut allergy is less prevalent, and among TN-allergic patients in the USA, <5% reported allergy to pine nut.[33] In a retrospective chart review in Korea, among 126 patients with anaphylaxis to peanut, TNs, and seeds, pine nut allergy accounted for 7% of the reactions.[78] However, patients can still be monosensitized to pine nut, and pine nut can trigger severe reactions.[79] Pine nut allergen Pin p 1 is a 2S albumin and was recognized by IgE from 6 of 8 pine nut-allergic patients.[80]

Brazil nut

Brazil nuts belong to the genus *Bertholletia*, and they are most often found in mixed nut packages. While in the USA, the prevalence is reported as <5%, in the UK, the prevalence ranges from 24% to 33% among TN individuals.[11,33] Brazil nut components include Ber e 1 (2S albumin) and Ber e 2 (11S globulin). Sensitization to Ber e 1 showed improved sensitivity over whole extract for the diagnosis of Brazil nut allergy in a small study.[81]

Macadamia and other nuts

Macadamia nuts are from the Proteaceae family. They are found in baked goods and ice creams. Macadamia nut allergy was reported in <5% of US TN-allergic patients.[33] Case reports of reactions to macadamia nut have been reported, and symptoms range from PFS to severe reactions.[82–84]

Coconut, a drupe, is incorrectly considered a TN. Coconut has demonstrated cross-reactivity with walnut, hazelnut, almond, and macadamia nut in vitro.[85–87] Despite this, coconut is an uncommon allergen, and allergy to it has not been shown to clinically correlate with TN allergy.

The FDA also listed shea nut as a TN. However, there have been no reported reactions to shea nut. In addition, topical shea butter, which is the common usage of shea nuts, is not allergenic due to its minimal amount of protein; there was undetectable IgE binding to shea nut found in shea butter extracts by Western blot and enzyme-linked immunosorbent assay.[88]

Coallergy among TNs

Patients with TN allergy can have cosensitization and coallergy to other TNs. Specific TN allergies coexist more commonly, such as cashew with pistachio as well as walnut with pecan.[28,54,89] Among 101 individuals in a tertiary care center with TN allergy, 12% had at least one additional TN allergy.[33] In a recent study by Couch et al,[38] 67 patients were identified from a US tertiary care center who had a clinical history of TN allergy that were challenged to another TN to which they were sensitized but had not previously ingested. The study found that 76% passed the OFC. Of note, 90% of these patients had an sIgE <2 kU/L and at least half had a level <0.35 kU/L. Twenty-five patients had an SPT of at least 3 mm, and 56% of these passed their OFC. This study was limited by the fact that it was retrospective, the challenges were performed without blinding, and there was a possible preference to perform TN OFCs with little or no sensitization.

Coallergy to peanut

Peanut is botanically related to legumes and not to TNs, but despite this, reported coallergy between TN and peanut ranges between 20% and 68%.[20–22,32,33,89] Major allergens in peanut have homologs in many TNs; however, these have not been shown to be responsible for clinical reactivity.[90] Peters et al[91] enrolled peanut-allergic patients from the population-based, longitudinal HealthNuts Study and found that, in patients with OFC-proven peanut allergy at the age of 4 years, the TN sensitization rate was 61% for cashew, almond, or hazelnut. Among 234 patients with physician-diagnosed peanut allergy, 86% were sensitized to at least one TN, whereas 34% had reported clinical allergy.[89] However, the majority of patients enrolled had never ingested TNs; therefore, this can be an underestimation of clinical allergy. In a US prospective study, 12 of 19 peanut-allergic patients confirmed by DBPCFC had a positive skin test to TNs, but

all had a negative TN challenge.[92] In the abovementioned study by Couch et al,[38] 46 patients had peanut allergy and TN sensitization, and 20% of these patients had a history of clinical allergy to TN. When peanut-allergic patients were challenged to a TN to which they were sensitized to but had not ingested, 96% passed their challenge, questioning the previously estimated prevalence of coallergy. However, only 14 of the 68 TN OFCs performed in this group had a TN sIgE level of at least 2 kU_A/L and/or an SPT wheal of at least 3 mm. While considering cosensitization and coallergy between peanuts and TNs, many studies point out that select peanut-allergic patients may tolerate TNs, and OFC can be considered.

Management

Avoidance

The two pillars of food allergy management are strict avoidance of the index nut and prompt treatment of symptoms upon accidental exposure. Epinephrine is the first-line treatment for anaphylaxis, and it must be administered promptly for anaphylaxis. Patients with potential anaphylaxis to TNs should have ready access to epinephrine auto-injector in the outpatient setting.[93]

Important components of food avoidance are reading food labels and recognizing the allergen. The Food Allergy Labeling and Consumer Protection Act of 2004 mandates that manufacturers in the USA identify the presence of any of the eight most common food allergens, including TNs. Many companies also choose to add precautionary statements, such as "may contain," or "made in a shared facility," but there is no regulation as to what these mean and consumers do not often recognize this.[94] Another important component of allergen avoidance is recognizing the food itself, but many people cannot recognize TNs.[95,96] When 1,105 subjects were shown 19 different pictures of peanuts and TNs, the mean number of correct responses was 8.4.[96] There was no difference in correct response rate between TN-allergic subjects compared with nonallergic subjects, and only half of the patients with a TN allergy correctly identified all forms of TNs to which they are allergic.[96]

A specific consideration with regard to the management of TN allergy is the decision to avoid all TNs or only the TN to which a patient is clinically allergic (Table 2). Avoiding all nuts simplifies the management. It may also decrease the risk of reactions secondary to cross-contamination or misidentification, which is common as mentioned above. However, it is possible that patients can become sensitized and clinically allergic to TNs during their period of avoidance. The charts of 60 patients who were enrolling for multiple-food oral immunotherapy (OIT) were reviewed, and it was found that TN elimination was often recommended due to concern for cross-contamination of another TN or peanut to which the patient reacted to.[97] There was a lower rate of clinical reaction to the TNs and higher rate of negative skin test and specific IgE at the time of diagnosis when compared to peanut, milk, egg, soy, sesame, and wheat. SPT and serum-specific IgE increased significantly over time to TNs, and most OFCs performed later were positive. This suggests that sensitization developed during the period of elimination.

Another approach is to encourage patients to eat the TNs to which they are determined to be clinically tolerant. This decreases unnecessary food avoidance and expands the patient's diet. It may circumvent the observation noted above about increasing sensitization to avoided nuts, but no studies have addressed this possibility. Whether adding the nuts early would "prevent" allergy development is also unknown. The Learning Earning about Peanut Allergy (LEAP) trial showed that in high-risk infants, early introduction of peanut, compared with avoidance, was protective of peanut allergy.[98] It is not known whether a similar approach to TNs would be protective, but there is a theoretical possibility. Practically speaking, introducing all TNs to infants and toddlers may be limited since whole nuts can be choking hazards and nut spreads or baked good with nuts must be used, and if the dose matters (as it may have for peanut), it could be difficult to achieve a large amount of so many different foods. Studies are needed to determine whether an early feeding prevention approach is safe and effective.

A third approach patients and allergist have taken is to avoid all TNs, except the ones that the patient has already tolerated or selected ones that are easy to obtain without cross-contact. While this approach does not necessarily expand the diet, it simplifies management and decreases the need for OFCs to determine clinical tolerance. The decision to avoid all or select TNs should ultimately involve the patient and their family. Decisions may be influenced by many factors including the patient's age, risk, their developmental ability, and motivation of undertaking OFCs.

Prevention and treatment

There are currently no data on the primary or secondary prevention of TN allergy. However, available data have changed current recommendations regarding specific avoidance of allergenic foods. In 2000, the American Academy of Pediatrics (AAP) suggested delaying introduction of highly allergenic food in high-risk infants and recommended avoiding peanuts

Table 2 Alternatives for avoidance in tree nut allergy

Avoidance strategy	Pros	Cons
Eat selected tree nuts to which they are clinically tolerant	• Limit unnecessary food avoidance and expand the diet • Possibility that regular consumption of an allergenic food can avoid allergy	• Increase need for oral food challenges to assess clinical tolerance • Increases risk of cross-contamination and misidentification • Practically must avoid whole nuts in infants and toddlers since they are choking hazards
Avoid all tree nuts even if clinically tolerant to select nuts	• Simplifies management • Decreases need for oral food challenges to assess clinical tolerance • Decreases risk of cross-contamination and misidentification	• Concern of developing sensitization and clinical allergy during the period of avoidance

and TNs until the age of 3 years. In 2008, the AAP amended this statement to say there is no current convincing evidence that delaying introduction of allergenic foods had a significant protective effect.[99] There are no data to delay TN introduction, and they can be introduced based on family preference in age-appropriate forms. There is no current curative therapy for TN allergy, but approaches being tested such as OIT, sublingual immunotherapy, and epicutaneous immunotherapy could be applicable as research advances.[100,101]

Conclusion

TN allergy is common, and reactions range from mild itching of the mouth to anaphylaxis. When including only challenge-confirmed cases of TN allergy, prevalence rates ranged up to 4.3%. TNs account for 18%–40% of cases of anaphylaxis. TNs can cause pollen food syndrome in pollen allergic individuals, most commonly to almond and hazelnut in birch-allergic individuals. Twelve percent of patients with a TN allergy have at least one additional TN allergy, and specific TN allergies coexist more commonly, such as cashew with pistachio as well as walnut with pecan. Physician-supervised OFCs are needed to differentiate sensitization from clinical allergy. CRDs improve diagnostic accuracy by differentiating sensitization to clinically relevant versus irrelevant proteins. The patient and clinician must decide whether to avoid all TNs or only the ones the patient is clinically allergic to. Risk of cross-contamination and misidentification must be weighed against the benefit of expanding a patient's diet and the possibility of decreasing risk of allergy by consumption. There are no data on primary prevention of TN allergy but, based on data from studies on primary prevention of peanut allergy, delayed introduction is no longer recommended. More studies are needed to find curative therapy for IgE-mediated food allergies.

Disclosure

Tamar Weinberger reports no conflicts of interest in this work. Scott Sicherer receives royalties from UpToDate, a stipend from the American Academy of Allergy, Asthma and Immunology as Associate Editor of the Journal of Allergy and Clinical Immunology in Practice, and his institution receives grants from HAL Allergy Group and the National Institute of Allergy and Infectious Diseases for his research.

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