

Peanut and tree nut allergy

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Among foods causing allergic reactions in children, peanut (a legume) and tree nuts (*ie*, walnut, hazel nut, Brazil nut, pecan) have attracted considerable attention for several reasons. Allergies to these foods are common, frequently have an onset in the first few years of life, generally persist, and account for severe and potentially fatal allergic reactions. Furthermore, the ubiquity of these foods in the diet makes avoidance difficult and accidental ingestions, with reactions, common. This review discusses recent and emerging information on the prevalence, clinical characteristics, natural history, genetic basis, and current treatment of these allergies. In addition, recent advances in the molecular and immunologic characteristics of these allergens, and novel therapeutic options under investigation in animal models, are reviewed. *Curr Opin Pediatr* 2000, 12:567–573 © 2000 Lippincott Williams & Wilkins, Inc.

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Abbreviations

PNA peanut allergy
RAST radioallergosorbent test

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Food allergy is defined as an adverse immunologic response to the protein, not fat or carbohydrate, in food. These allergies may manifest as acute reactions with symptoms including urticaria, angioedema, vomiting, diarrhea, rhinitis, wheezing, laryngeal edema, and, potentially, anaphylactic shock. Food-specific IgE antibodies mediate these reactions through interactions with the causal protein at the surface of mast cells and basophils, resulting in the release of a variety of potent mediators, such as histamine. These IgE antibodies are directed to numerous sites (epitopes) on any of a number of proteins in a given food. Interestingly, the detection of food-specific IgE antibody is not sufficient to diagnose clinical reactivity to a food; that is, an individual may have no clinical reaction upon ingestion of a food to which there is a positive allergy skin test or radioallergosorbent test (RAST). Food allergy is also a cause of chronic conditions such as atopic dermatitis or gastrointestinal disorders with vomiting, diarrhea, and malabsorption. While some of these disorders are also dependent upon food-specific IgE antibodies, others occur through T-cell responses mediated by the elaboration of a variety of cytokines.

Six to 8% of infants and young children are affected by food allergies [1], and the most common offending foods are cow's milk, egg, peanut, soy, and wheat. Fortunately, most of these early childhood food allergies resolve by age 3 years; however, significant allergies to peanut, tree nut, fish, and shellfish are more persistent. The ubiquitous nature of peanut and tree nuts in the food supply makes dietary avoidance difficult. This issue, compounded with the particularly severe and persistent nature of these allergies, has attracted a recent flurry of basic and clinical research that is the focus of this review.

Prevalence

The first study on the population prevalence of peanut and tree nut allergy in children was performed on a cohort of 1218 newborns followed to age 4 years on the Isle of Wight, UK [2]. The study found positive tests for IgE antibody to peanut in 13 children (1.1%) and to a tree nut in two children (0.16%) followed to age 4 years. Since sensitization (a positive skin test or RAST) does not indicate clinical reactivity, it is not surprising that only 8 of these 15 children (0.7%) had experienced a clinical reaction upon ingestion of peanut or tree nut. We sought to determine the prevalence of peanut and tree nut allergy in the general US population by admin-

istering a nationwide, cross-sectional, random digit dial telephone survey [3••]. Adult surrogates from 4374 households were interviewed, providing information for 12,032 individuals with 2998 of these being children under age 18 years. Peanut allergy was reported for 0.4% of children and 0.7% of adults. Allergy to one or more tree nuts was reported for 0.2% of children and 0.7% of adults. In a population study in the UK [4•] utilizing a survey of 2000 representative households followed by in-depth interviews of individuals reporting peanut allergy, the prevalence of reported allergy was 0.61% in children age 0 to 14 years, 0.53% in individuals aged 15 to 44 years, and 0.3% in those over 44 years. Allergy to tree nuts was reported by 0.38% of the total population. Taken together, these studies indicate that almost 1 in 150 children has a peanut and/or tree nut allergy.

Clinical characteristics

Allergic reactions to peanut and tree nuts account for most fatal and near-fatal food allergic reactions in children [5,6••]. Our population-based study confirmed that reactions to peanut and tree nuts can be severe: 81% reported respiratory or multiorgan system reactions [3••]. Rancé *et al.* [7] recently reported the clinical characteristics of food allergy in 544 children aged 0 to 15 years evaluated with oral food challenges upon referral to their medical center in France. In this selected group, 24% had peanut allergy and 4% had a tree nut allergy. Clinical symptoms attributed to peanut allergy included atopic dermatitis (46%), urticaria/angioedema (32%), asthma (15%), generalized anaphylaxis (5%), and gastrointestinal symptoms (3%). Additional characteristics of peanut-induced anaphylaxis were recently reviewed [8].

To further define the clinical characteristics of these allergies, we evaluated 122 children referred to our food allergy practice with acute reactions to peanut alone (68 children), tree nuts but not peanut (20 children), or both peanut and at least one tree nut (34 children) [9]. Of 54 children with reactions to tree nuts, 34 had reactions to one kind of tree nut and 20 had reactions to two or more different tree nuts, the most common being walnut, almond, and pecan. First reactions usually occurred at home at a median age of 24 months for peanut and 62 months for tree nuts. Reactions generally developed within minutes of exposure. The skin was the most common organ affected (89% of reactions, 39% as the only system involved), but the respiratory (52%) and gastrointestinal tract (32%) were also affected. Epinephrine was administered in 20% of the reactions. Accidental ingestions were common, despite education about avoidance, and occurred in 56% of peanut allergic children and in 30% of tree nut allergic children (average of two accidents per patient) over a median period of 5.5 years. Symptoms following accidental exposure were generally similar to those at initial expo-

sure. In contrast to initial reactions, accidents occurred most commonly in school, but also at home and in restaurants. Reactions occur primarily from ingestion, but mild reactions from skin contact may occur, and reactions from inhalation with large exposures in small spaces, as in commercial airliners, have been recently reported [10•]. Modes of accidental ingestion included sharing food, hidden ingredients, cross-contamination, and peanut butter projects in school. Together, these studies indicate the early-onset, severity, and frequency of reactions attributed to peanut and tree nut allergy.

Sensitization

Reactions to peanut and tree nuts are considered to have occurred upon a first known exposure in 70% of cases [9], but this is immunologically untenable since sensitization through exposure is required prior to clinical reactions. When and how does sensitization occur? Several possibilities have been investigated. A simple explanation is that an initial exposure was not recalled since there was no reaction. Another possibility is sensitization through minor exposures to ingestants or topical agents containing peanut or peanut oil. Previous studies generally indicate a low allergenic potential for refined peanut oils [11,12], but significant allergenicity for cold-pressed (extruded) peanut and tree nut oils [13,14]. A recent study of 41 peanut-sensitized children exposed to an orally administered vitamin preparation containing refined peanut oil failed to implicate this exposure as a risk for sensitization [15].

The potential for sensitization to occur *in utero* or through maternal passage of peanut protein in breast milk has been postulated. Hourihane *et al.* [16] noted that consumption of peanuts while pregnant or breast-feeding was more common among mothers of peanut allergic children aged 5 years or younger compared with mothers of peanut-allergic children aged >5 years ($P < 0.001$) and the younger children had an earlier onset of peanut allergy ($r = -0.6$, $P < 0.001$). These data imply that maternal consumption of peanut during breast-feeding could promote early sensitization and allergy. Zeiger *et al.* [17] studied the effect of avoidance of highly allergenic foods, including peanut and tree nuts, on children of mothers with strong family histories of atopy. They found that avoidance in the final trimester of pregnancy and during breast-feeding reduced atopic dermatitis and food allergy in the first 2 to 3 years of life, after which time the effect was lost. Thus, whether avoidance prevents the development of food allergy, or merely delays the inevitable, remains to be determined. It may be that sensitization occurs early and clinical expression of allergy depends upon larger oral exposures that typically occur later. This hypothesis was supported by a study measuring peanut-, hazelnut-, and Brazil nut-specific IgE in 731 nut-allergic patients [18]. The

proportion of subjects with multiple nut sensitization was similar in young children, older children (age 3–6 years), and adults.

In an attempt to determine the role of *in utero* and oral exposure to peanut on sensitization, Frank *et al.* [19] studied 43 atopic children, 25 of whom were peanut-sensitized. They found that mothers who consumed peanuts more than once a week during pregnancy were more likely to have a peanut-allergic child than mothers who consumed peanuts less than once a week (odds ratio, 3.97, 98% confidence interval 0.73–24). Peanuts or peanut butter was introduced into the child's diet from a significantly younger age in the peanut-allergic subjects ($P < 0.03$). There was also a positive correlation in the peanut-allergic subjects between age of introduction of peanuts and age at the onset of symptoms ($r = 0.63$). Unfortunately, the study did not account for the confounding factor that *in utero* exposure may have been correlated with early oral exposure. Thus, further studies are needed to better characterize a number of features of sensitization including route, dose, and timing of exposure.

Natural history

The notion that peanut and tree nut allergy is permanent derives, in part, from the observation that it is an allergy that affects adults—indeed, at a rate similar to that seen in children [3••,4•]. Specific proof that peanut allergy persists was shown in a study by Bock and Atkins [20]. They reported a follow-up of 32 peanut-allergic children (confirmed by double-blind, placebo-controlled oral food challenges), followed during 2 to 14 years (mean, 7 years). None experienced resolution of the allergy (although eight were never knowingly re-exposed). The authors cautioned that larger controlled studies would be needed to determine if peanut allergy was truly permanent. Indeed, in the birth cohort studied by Tariq *et al.* [2], two children of the six who reacted to peanut (at ages 9 months and 24 months) lost their clinical reactivity and one was documented to have converted from positive to negative on prick skin test to peanut over the 4-year period of evaluation. Hourihane *et al.* [21] recently showed that peanut allergy may resolve in a subset of young children when the allergy manifested first in infancy. This group performed oral challenges to peanut in 120 children selected from 230 with peanut allergy based upon convincing histories of reactions. Selection of children for oral challenges were individualized, but included criteria such as negative skin tests and possible ingestion without reaction. Twenty-two of the 120 children (18%) passed the oral challenge; this group experienced a first reaction at a mean of 11 months of age and was challenged at a median age of 5 years. In a case-control comparison of 15 who experienced resolution to 15 subjects with

persistent peanut allergy, the former group had smaller or negative prick skin tests (a cut-off for wheal above 5 mm had a 100% positive predictive value), a longer interval since their last reaction (median 40 months vs 12 months), and fewer additional food allergies. There was no difference in severity of initial reactions. Taken together, these studies indicate that peanut allergic infants may become tolerant, but once the allergy is established in early childhood, resolution is rare. The importance of re-evaluation of the allergy, including physician-supervised food challenges, is evident.

Co-allergy and crossreactions

Our recent epidemiologic study [3••] showed a low rate (2.5%) of co-allergy to peanut and tree nuts, while our study of selected atopic children [9] with peanut or tree allergy revealed a high rate (34%) of co-allergy. These findings suggest that co-allergy to these foods in highly atopic children is due to atopic disposition in the host, rather than to cross-reacting proteins. Indeed, there have been no reports of clinically relevant proteins shared by peanut, a legume, and tree nuts. We evaluated 111 serum samples from children with peanut and/or tree nut allergies and found no strong correlation between peanut-specific IgE concentration and tree nut-specific IgE concentration for seven nuts [9]. The first anaphylactic reaction to macadamia nut was recently reported [22] and there was also no evidence of cross-reactivity with peanut. However, specific IgE concentrations did correlate strongly among several of the tree nuts (walnut with pecan, hazel with Brazil nut). Cross-reacting proteins among tree nuts or among tree nuts and other plant proteins may be relevant to allergy in some patients. For example, a subset of individuals with allergic reaction to hazelnut appear to be based upon immunologic responses to proteins shared with birch pollen [23•].

Because there are homologous proteins in peanuts and other legumes, it is not uncommon to find positive tests for IgE antibody to several of these related foods in individuals with clinical reactivity to any of them. Despite this laboratory finding, clinical observations had shown a low rate of to peanut and soybean. Bernhisel-Broadbent and Sampson [24] performed open or double-blind, placebo-controlled food challenges in 69 highly atopic children (median age 5 years; range, 1 to 21 years) with at least one positive skin test to a legume. Eighty-seven percent had a positive skin test to peanut, 43% to soy. Challenges to five legumes resulted in 43 positive reactions in 41 patients (59%). Thirty-one were challenge positive/anaphylaxis history positive to peanut. Only 2 of the 31 patients (6.5%) with severe peanut allergy had reactions to soy, and these were mild. Thus, 6.5% of the peanut-allergic children reacted to soy. These two patients lost their soy sensitivity after 3 years.

In contrast to this study, a recent report from Sweden argued that peanut-allergic individuals may react to soy with severe consequences [6••]. These investigators reviewed the medical records of all fatal or life-threatening reactions sent to them by physicians during a 3-year period. In 1993 to 1996, four fatal food-allergic reactions were reported and the authors reviewed these and two additional fatal cases that occurred less than a year before the study began. Two deaths caused by peanuts and four deaths presumably caused by soy were evaluated. These subjects were aged 9 to 18 years and all had previously diagnosed severe peanut allergy, underlying asthma, but no reaction to previous soy ingestion. In the four fatal reactions in peanut-allergic individuals who apparently reacted to soy despite previous tolerance, the causal foods were hamburger in three cases (2.2–3% soy), and kebab in one case (7% soy). The findings have raised concern among patients with peanut allergy and their physicians.

However, there are several unusual aspects in these case reports. The peanut-allergic children were tolerating soy all of their lives without reactions and the causal foods were similar (processed ground beef), raising a concern that these foods were contaminated with peanut protein. In addition, most of the children had high peanut-specific IgE and moderate soy-specific IgE. Additional issues concerning cross-reactions between soy and peanut were recently reviewed [25] and it does not appear warranted at this time to remove soy from the diet of children with peanut allergy who are currently tolerating the food. On the other hand, several recent reports from Europe indicate that lupine, another legume that has been used in flours, does have significant clinical cross-reactivity with peanut and may cause a reaction for some, but not all, peanut-allergic individuals [26,27].

Genetics

A number of studies have shown that peanut or tree nut allergy is likely to occur in individuals with other atopic diseases (asthma, atopic dermatitis, other food allergies). Hourihane *et al.* [16] delved more closely into the specific genetic influence of peanut allergy among families with a peanut-allergic proband and found that 7% of siblings shared the allergy. Assuming a population prevalence of peanut allergy of 0.5%, the heritability risk (λ_s) for peanut allergy for siblings, a ratio comparing the risk to siblings with that of the general population, is approximately 14, which is relatively high for a complex trait (similar to insulin-dependent diabetes). Two studies [28,29] have addressed the role of human leukocyte antigen, a potential candidate gene because it plays a role in immune processing of proteins, in peanut allergy and showed evidence for an association.

We have recently collected data on monozygotic and dizygotic twins with peanut allergy (PNA) to determine

the impact of genetics on this disease [30]. Among the monozygotic pairs ($n = 14$), nine were concordant for PNA (pairwise concordance, 64.3%) and among dizygotic pairs ($n = 44$), three were concordant for PNA (pairwise concordance, 6.8%; $\chi^2 = 21.38$, $P < 0.0001$). Heritability of PNA was estimated at 81.6% (95% CI, 41.6–99.7%) indicating a significant genetic influence on PNA.

Treatment

Before the institution of treatment, peanut or tree nut allergy must be confirmed based upon a convincing clinical history and evidence of specific IgE antibody to the suspected food (or by physician-supervised oral food challenges in cases of possible alternative explanations for reactions or for monitoring for resolution of allergy). Once the diagnosis is secured, the treatment is avoidance of the causal food protein and preparedness to treat reactions from accidental ingestions. These apparently simple tenets of treatment are actually quite complex. Frequently, the assistance of a dietitian is helpful in instructing families on avoidance, including careful label reading and issues of cross-contamination in industry and restaurants. The Food Allergy Network (Fairfax, VA, www.foodallergy.org, 800-929-4040) [31] is a lay organization that is helpful for families with food allergies and can provide additional information on issues of food avoidance. Our studies of highly atopic children [9] indicate that peanut and tree nut allergy may coexist in almost one third. This, and the knowledge that accidental ingestions occur frequently because of cross-contamination, hidden ingredients, and substitution of ingredients, has lead us to frequently advise avoidance of all tree nuts in young children with peanut or tree nut allergy. However, we would generally not disallow previously tolerated nuts when eaten in isolation, rather than in bakery products or in restaurants.

The mainstay of treatment for accidental ingestions is the prompt administration of epinephrine in the event of severe reactions, or a history of severe reactions. Prompt transport to a medical facility is also crucial. Antihistamines are helpful, but do not provide the cardiovascular and respiratory support needed in a severe reaction. Self-injection devices containing premeasured doses of epinephrine, such as the Epi-Pen, Epi-Pen Junior, and Ana-Kit, are available and should be on hand at all times. Unfortunately, a recent study [32] of 101 families prescribed these devices for severe food allergy found that only 71% of this group had epinephrine on hand, 10% had devices beyond the labeled expiration date, and only 32% of the participants correctly demonstrated the use of the device. Attending pediatricians were also generally not familiar with the technique of administering the medication from these devices. The study pointed out the need for improved patient and physician education, and frequent review of

the indications and technique of administration to ensure proper use of this lifesaving medication.

Advances in molecular and immunologic characterization of allergen

For the purpose of creating better diagnostic tools and therapeutic interventions, it is crucial to understand the characteristics of the proteins in these foods and their interaction with the immune system. Three major allergens have been identified and characterized in peanut: Ara h 1 (64.5 kDa, vicilin family of seed storage proteins) [33], Ara h 2 (17.5 kDa, conglutin family of seed storage proteins) [34], and Ara h 3 (60 kDa, glycinin-like seed storage protein, a preproglobulin) [35]. Studies on the biochemical, structural, and immunologic characteristics of these proteins, using native proteins or cDNA clones and allergic sera, have further elucidated important features of these proteins with implications for therapeutic intervention [35–37,38]. For example, Ara h 1 forms a stable trimer that may add stability to the protein, an important characteristic for allergens [36]. In addition, heating does not alter the allergenicity of this protein [39]. Further, epitope analysis reveals that binding of IgE to linear, as opposed to conformational or folded, epitopes is prominent and may account for the increased allergenicity; however, single amino acid substitutions of IgE binding sites often lead to a loss of binding to these epitopes, a finding with important therapeutic implications [36]. Recent work has also expanded knowledge of the major allergens in walnut [40,41].

Future therapies

It is frustrating for patients and families to live with peanut or tree nut allergy knowing that resolution is rare, reactions are severe, and accidental ingestions are virtually inevitable. Research into more definitive therapies for these allergies is underway. One strategy that may be considered allergen nonspecific is treatment with anti-IgE antibodies. These engineered, humanized IgG antibodies are directed to circulating, unbound, IgE molecules and, when infused, make IgE antibodies unavailable for binding to mast cells and basophils. Recent studies [42] show safety and efficacy for the treatment of steroid-dependent allergic asthma and the study of the efficacy of this injection therapy for treatment of food allergy is underway.

Therapies that are allergen specific have been attempted for peanut allergy. Allergen immunotherapy (allergy shots) are given to induce an alteration in the immune response, away from allergic responses through injection of gradually increasing amounts of the allergenic protein. Efficacy of this treatment for allergy to aero-allergens (pollen, animal dander) is well established, but attempts to perform immunotherapy with peanut protein [43] have resulted in severe reactions to

the injections themselves, precluding their use. Thus, alternatives to classical allergen immunotherapy are under investigation. As noted above, site-directed mutation of major allergenic epitopes in peanut can abrogate IgE binding-but not T cell response-this could potentially allow immunotherapy without the side effects previously noted. Digestion of peanut protein into smaller peptides may also facilitate this approach [44].

Another strategy that has been investigated in murine models of peanut allergy is the injection or oral administration of plasmid DNA encoding relevant major peanut proteins. The theory is that the endogenous production of peanut protein in the host could act to alter immune responses toward tolerance rather than atopy. When used as a treatment prior to sensitization with peanut, allergic immune responses were downregulated [45•], but the affect appears to be dependent upon the strain of mouse [46•]. Thus, such an approach may have different efficacy in different individuals. Additional strategies being tested are the use of immunologically altered peanut proteins, peanut protein injected in combination with molecules that direct nonatopic immune responses (cytokines or immune stimulatory DNA sequences), and combinations of these approaches.

Conclusions

Recent studies have defined the prevalence and clinical characteristics of peanut and tree nut allergy. It is crucial to confirm the diagnosis, since treatment entails significant lifestyle changes. The allergy is potentially fatal and accidental reactions are common—mandating that the pediatrician carefully review issues concerning food avoidance and the administration of emergency medications. Although much has been learned about sensitization, this area remains open to further work to better define interventions that may be successful in preventing or delaying clinical allergy. The notion that peanut allergy is permanent has been dispelled as a subset of infants and young children with peanut allergy may achieve tolerance, a new finding that a number of additional unpublished studies have confirmed. However, better methods to identify those who will become tolerant are needed. Finally, advances in molecular biology, genetics, and trials of novel therapies using animal models of food allergy show promise for improved diagnosis and definitive therapies for these allergies in the future.

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