New insights into diagnosis and treatment of peanut food allergy

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1. ABSTRACT

Peanut and/or tree nut allergy is a major health concern affecting over 1% of Americans. Although food allergy in general is the most common cause of anaphylaxis treated in emergency departments, reactions to nuts account for a disproportionate amount of deaths from food allergy. Peanut allergy is a Type I hypersensitivity (IgE mediated) immune response. Eight peanut allergens have been identified that are termed as Ara h 1 through Ara h 8. The diagnosis of peanut allergy can often be made or eliminated with a focused history and specific diagnostic testing. There is no effective method to cure peanut allergy. Therefore, the management of patients with peanut allergy focuses on 1) preventing inadvertent ingestions of peanut, 2) recognizing early signs of allergic reactions, and 3) properly treating peanut-induced symptoms should they occur. Epinephrine is clearly indicated for patients experiencing respiratory, cardiovascular, or neurologic compromise. Because inadvertent ingestion of peanut often leads to life-threatening reactions and peanut allergy is often long-lived, many investigators are focusing on decreasing clinical reactivity after peanut allergy is established.

2. INTRODUCTION

An early report of food allergy in 1948 noted adverse reactions to corn, wheat, milk, egg and other frequently ingested foods. (1) It was more than 25 years later when double-blind food challenges identified peanut as an important food allergen in children with severe asthma. (2) In the 1980’s a main focus of food allergy research was the use of unbiased food challenges to establish a precise diagnosis of food allergy and describe reproducible food-induced symptoms. It was then that peanut was identified as one of the top three food allergens in US children with atopic dermatitis. (3-6) Today, peanut and/or tree nut allergy is a major health concern affecting over 1% of Americans. (7) Although food allergy in general is the most common cause of anaphylaxis treated in emergency departments, reactions to nuts account for a disproportionate amount of deaths from food allergy. (8-10) Since there is no cure for peanut allergy, therapy focuses on peanut avoidance, early recognition of symptoms due to inadvertent ingestions, and pharmacologic treatment of adverse reactions. This approach can be unsatisfying because it does not modify the immune response to peanut, leaving even the most vigilant patient at risk for life-
threatening reactions from inadvertent ingestions of the food. For this reason, these patients are in critical need of a specific treatment for peanut allergy.

3. EPIDEMIOLOGY

As noted with other atopic diseases in westernized cultures, the prevalence of food allergy appears to be on the rise. In children, peanut sensitization tripled and reported peanut allergy doubled over only a five year period in both the United States and United Kingdom. (7,11) Studies from Canada and the United Kingdom incorporating diagnostic food challenges currently estimate that the prevalence of peanut allergy in young children may be as high as 1.5%. (11,12) The rise in peanut allergy is not limited to children. Data from a third National Health and Nutritional Examination Survey in the United States (collected from 1988 – 1994) indicate that about 8.6% of Americans are sensitized to peanuts (13). Similarly, national surveys suggest that 1.1% of Americans or three million people are allergic to peanuts, tree nuts, or both (14,15).

Methods of food preparation, increased use of antacids, patterns of peanut consumption in pregnant or lactating mothers and in childhood, as well as exposure to medicinal creams containing peanut oil have all been proposed but not confirmed as factors contributing to the recent rise in peanut allergy. (16-22) Data from the Avon Longitudinal Study of Parents and Children, a geographically defined cohort study of 13,971 preschool children, was used to identify those with a convincing history of peanut allergy and the subgroup who reacted to a double-blind peanut challenge (22). Peanut allergy was independently associated with intake of soy milk or soy formula and with the use of skin preparations containing peanut oil, although these results have yet to be confirmed in other studies. The presence of peanuts in the mother’s diet prior to delivery has been suggested to be a risk factor for the development of peanut allergy but this finding also has not been replicated (16). The explanation for the increase in the diagnosis of peanut allergy in the past several years has yet to be explained adequately. Allergic disease in general has been shown to have a genetic predisposition although arguably the development of peanut allergy has not been linked to a specific genetic predisposition (16,23,24).

4. PATHOPHYSIOLOGY

Immune responses to allergenic food proteins develop as a result of complex interactions between the food, a variety of effector cells, and their mediators. The majority of acute allergic reactions to foods are due to the engagement of allergen-specific IgE antibody with its high affinity receptor (FcεRI) that is expressed on mast cells and basophils. The overt signs of food allergy, such as urticaria or angioedema, are often the direct result of peanut protein (not carbohydrate, fat, or oil) cross-linking IgE bound to its effector cell. This antigen-specific interaction stimulates a series of events that results in release of cellular mediators and cytokines including histamine, prostaglandins, leukotrienes, and platelet-activating factor. An unexpected finding was elevated plasma histamine levels in patients with atopic dermatitis and positive food challenges but normal serum tryptase levels in patients with food-induced anaphylaxis. (9,25) Other evidence supporting the central role of basophils, rather than mast cells, in IgE-mediated food allergy is that basophils from patients with food allergy and atopic dermatitis have increased spontaneous release of histamine which declines to control levels after the causal food is restricted from the diet. (26) Additionally, tumor necrosis factor (TNF), interleukin-5, and chemokines produced at the local site result in the activation and recruitment of eosinophils. (27).

The manifestation of allergic reactions to foods not only depends upon a humoral response but is largely dependent upon preceding cellular mechanisms which are just being elucidated. The initial introduction of a food allergen generally occurs at the mucosal surface of the gastrointestinal tract. (18) Food proteins are believed to be taken up by specialized epithelial cells, M cells, transferred to antigen presenting cells such as dendritic cells, and processed into peptide fragments presented on the cell surface in the context of class II Major Histocompatibility Complex (MHC) molecules. (28,29) Peptides then are presented to naive T helper (Th) cells via MHC/T cell receptor interaction resulting in Th cell priming and activation. This event in turn initiates humoral and cellular events associated with, in this particular case, peanut allergy. In individuals at risk for allergic disease, the activation of T helper cells results in secretion of cytokines that stimulate B cells to eventually synthesize IgE antibody specific for peanut in the sensitization phase of the immune response. T helper 2 (Th2) cells cause secretion of various interleukins including interleukin-4, interleukin-5, interleukin-9 and interleukin-13.

Peanut antigen stimulates Th2 cells in peanut allergic donors but Th1 cells in children who have either outgrown their peanut allergy or who are tolerant to peanut, similar to that seen after stimulation with nonallergenic food antigens. (30) This observation that the same food stimulates T helper cells with distinct cellular phenotypes predicted by host factors and clinical reactivity suggests that food tolerance in nonatopic patients or resolution of food allergy in atopic ones is accompanied by the development of a Th1 response (high IFNγ, TNFα, and low IL-4, IL-5, IL-13). The skewed Th2 response observed in atopy may manifest early in life as a result of genetic susceptibility and intrauterine exposures. (31) Regulatory cell populations may also play a role in the development of IgE and cell mediated food allergy by failing to induce or maintain oral tolerance, although the exact mechanism remains largely unknown. (18,32-34).

5. PEANUT ALLERGENS

Foods associated with allergic reactions are generally a main component of one’s diet early in life and, therefore, differ according to age and societal eating patterns. For example, sesame seed and bird’s nest are eaten frequently in Israel and Singapore, respectively. They
are also common food allergens in those countries but peanut allergy is not as common as in the West. (35;36) The major food allergens are glycoproteins, 10-70 kd in size, that are abundant in the allergenic food. Food allergens are generally water-soluble and resistant to heat, acid, and proteolysis which enables them to sensitize the host in the gastrointestinal tract.

Eight peanut allergens have been identified that are termed as Ara h 1 through Ara h 8 (Arachis hypogaea). (37-42) Most of the peanut allergens are members of the seed storage protein families. The two peanut allergens that bind IgE in a majority of patients, Ara h 1 and 2, are part of the vicilin and conglutin family of storage proteins, respectively. Ara h 3 - 7 are minor peanut allergens. Ara h 8 is a member of the pathogenesis-related PR-10 family, primarily involved in pollen-associated food allergy. (42) Identification of individual IgE binding sites or epitopes have research utility in characterizing clinical outcomes, in the development of novel treatments, and in developing transgenic plants producing peanut proteins with reduced IgE-binding capabilities. (43-45)

6. CLINICAL PRESENTATION

Peanut allergy is a Type I hypersensitivity (IgE mediated) immune response. There is a spectrum of clinical symptoms mediated by IgE which mainly involve the skin and gastrointestinal tract: urticaria, angioedema, pruritis, nausea, and vomiting, abdominal pain or cramping, and diarrhea. (3-5,46-48) Respiratory and ocular symptoms of IgE-mediated food allergy often accompany skin and gastrointestinal symptoms but rarely occur in isolation. (3,4,46,47,49) Anaphylaxis is the most severe IgE-mediated response to food. This term implies multi-system organ involvement and varies in severity from mild to fatal. (50,51)

The mean age of diagnosis of peanut allergy in children is approximately 14-18 months. (17,52) Symptoms occur following the first known peanut ingestion in 75% of those children. (52,53) The overwhelming majority of the initial reactions involve the skin, approximately one-half the respiratory tract, and a third the gastrointestinal tract. In one study, two organ systems were affected in 31% of initial reactions, and all three systems in 21% of reactions (53). Fortunately, individuals typically do not have life-ending reactions on the first known ingestion. Individuals who have life-threatening and life-ending reactions usually have asthma and frequently have a history of atopy, including food allergy in childhood, and are typically young adolescents to young adults who unknowingly ate a food to which they were allergic. (9,10,54)

7. DIAGNOSIS

The diagnosis of peanut allergy can often be made or eliminated with a focused history and specific diagnostic testing. The most supportive clinical evidence of peanut allergy includes immediate and reproducible symptoms after ingestion. Most reactions begin within seconds or minutes but may occur up to two hours after eating peanut. If allergy is suspected, peanut is then generally avoided but reproducibility of symptoms may still be assessed if there were previous ingestions or subsequent inadvertent ones. Other factors to consider for the diagnosis of peanut allergy include 1) quantity of peanut required to provoke symptoms, 2) detailed description of symptoms, 3) other foods ingested prior to development of symptoms, and 4) length of time since the last reaction or ingestion of peanut. (49)

Reproducible symptoms suggesting involvement of IgE such as urticaria, repetitive vomiting, or angioedema that occur within two hours of ingestion of peanut support the diagnosis of peanut allergy. In those cases, laboratory techniques that detect peanut-specific IgE are utilized to confirm the diagnosis. They include in vivo allergy skin prick tests and in vitro assays. Allergy skin testing is easily and safely performed, even in small infants, by applying purified food extract (1:10 or 1:20 w/v) by the prick or puncture technique. (47,55)

Allergy skin prick tests with food extracts are very sensitive but they lack specificity. (56) In patients with atopic dermatitis, the sensitivity of a peanut skin test is 100% but the specificity is only 58%. (5) And the positive predictive value of a peanut skin test is only 44% but the negative predictive value is 100%. (5) In other words, a positive skin test indicates that the patient has been sensitized, but is not definitively allergic, to peanut and a properly placed negative skin test effectively rules out peanut allergy. Because the specificity and positive predictive values are poor, interpretation of allergy skin tests requires clinical correlation to distinguish sensitization from allergy. In this regard, a positive skin test in a patient who eats peanut without adverse symptoms indicates asymptomatic sensitization. On the other hand, with anaphylaxis after ingestion of a single peanut, a positive skin test sufficiently confirms the diagnosis but a negative skin test should stimulate further evaluation.

Food-specific IgE may also be detected by in vitro methods including radioallergosorbent tests (RAST) or enzyme-linked immunosorbent assays (ELISA). In general, they are no better able to predict reactions on double blind, placebo controlled food challenges (DBPCFC) than are skin prick tests. (5) A modified in vitro assay, CAP System FEIA (Pharmacia Diagnostics; Uppsala, Sweden) increases the allergen binding capacity of previous techniques and quantitates the results as kilounits of allergen-specific IgE per liter (kUA/L). (56)

This quantitative method is more sensitive than previous qualitative or semi-quantitative ones. More importantly, a diagnostic level has been established for peanut that correlates well with positive outcomes on oral food challenges. (56,57) With a comparable history, a result greater than 14 kU/L (results range from <0.3.5 to >100 kU/L) supports the diagnosis of peanut allergy. As with allergy skin prick tests, negative serum tests for IgE do not always exclude peanut allergy so that a convincing history should not be disregarded.
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It is important to note that, although the likelihood of clinical reactivity increases with the size of the skin test reaction and level of food-specific IgE, they have no correlation with the severity of the reaction. (56) This point is important for patients and parents to understand so that those with higher peanut-specific IgE levels are not overwhelmed by the fear of anaphylaxis and those with lower levels are not tempted to stray from a strict peanut-elimination diet. Recent studies show that patterns of epitope binding may correlate with the severity of clinical reactions to peanut. (43, 44) IgE binding to many epitopes correlated with a history of multisystem reactions to peanut whereas IgE binding to only a few epitopes correlated with reactions limited to the skin. Assays using recombinant allergens may be more sensitive and prove to be useful for diagnosing peanut allergy. (58-60) Skin prick extracts using recombinant peanut allergens are not yet commercially available but are under investigation. The skin prick test size or IgE level to recombinant peanut allergens do not correlate with clinical symptoms but, like patterns of epitope binding, polysensitization to them may predict more severe symptoms. (60) Recent work on component resolved diagnosis suggests that in the future, with the application of understanding the hypersensitivity response to individual allergens such as Ara h 2, we may be able to determine the likelihood of the severity of the disease as well as the long lasting nature for that particular individual. (61)

Results lower than 14 kU/L do not indicate that peanut may be ingested safely. However, subdiagnostic levels combined with a convincing history of immediate IgE-type reactions may support the diagnosis of peanut allergy and justify the need to follow a strict exclusion diet. Those with low or undetectable IgE levels to peanut, especially if they have questionable clinical reactions, should undergo a supervised oral food challenge to determine clinical reactivity. Greater than 50% of patients with a peanut IgE level < 2 kU/L will have a negative peanut challenge. (62, 63)

Food challenges are performed by feeding the patient sequential, graded amounts of peanut and carefully observing for adverse effects. The initial serving size is typically less than that required to elicit symptoms (25-500 mg) and doses are increased at intervals longer than that reported between ingestion and onset of symptoms (15-60 minutes). Tolerance of 8-10 grams of peanut flour or two tablespoons of peanut butter provides strong evidence against allergy (one peanut is equivalent to 300 mg of protein). Depending upon the circumstances, oral food challenges may be open, single-blind, or double-blind. (64)

When the patients are carefully selected and the challenge is performed according to standard protocols, oral food challenges are safe procedures. Although positive reactions to oral food challenges are not infrequent, most reactions are not severe and require no treatment or antihistamine only. (49, 65) Only 10% of patients failing peanut challenges required epinephrine. (65) The majority of symptoms observed in peanut challenges were cutaneous or gastrointestinal; patients failing peanut challenges were more likely to have oral and upper respiratory symptoms compared to other foods. It is reassuring that patients failing peanut challenges were not more likely to have more severe symptoms than those failing milk, egg, soy or wheat challenges.

8. TREATMENT

There is no effective method to cure peanut allergy. Therefore, the management of children with peanut allergy focuses on 1) preventing inadvertent ingestions of peanut, 2) recognizing early signs of allergic reactions, and 3) properly treating peanut-induced symptoms should they occur.

Compliance with a food elimination diet is time-consuming, inconvenient, and requires a great deal of education and commitment on the part of the patient and all caregivers. Parents and caregivers must scrutinize all food labels for the presence of peanut. Although peanut is often an obvious component of processed foods, it can also be found in unexpected foods like gravy or salsa that are thickened with such a small amount of peanut butter that it is not detected by taste or smell. Most patients with peanut allergies will avoid the ingestion of peanut oil, although highly processed oils do not contain peanut protein and can be safely consumed by such patients. (66) Cold pressed or extracted peanut oils do contain peanut protein and could possibly induce an allergic reaction.

Children with peanut allergy are faced with many social restrictions due to the potentially life-threatening nature of their disease. The quality of life for these children is significantly impaired, even compared to children with other chronic diseases including diabetes (67). For example, they should consider avoiding high risk places where contamination with peanut is likely, including bakeries and ice cream parlors, as well the ingestion of unlabeled desserts and candies. It is important to give patients and families a written plan with the specifics of their management both for acute and chronic treatment (68). Educational materials are available through many organizations such as the Anaphylaxis Campaign (website: www.anaphylaxis.org.uk/) and the Food Allergy & Anaphylaxis Network (website: www.foodallergy.org). These organizations and their web sites are invaluable resources for patients, families and medical personnel. Registered dieticians can often provide additional educational assistance on an ongoing basis. Additionally it is also important to consider having the patient wear a bracelet or necklace noting their allergy.

Even the most vigilant patients accidentally ingest a food to which they are sensitive. (69) These inadvertent exposures will result in an allergic reaction in the average patient every three to five years, with a new study showing an annual incident rate of 14% (54, 70) These accidents occur most frequently away from the home such as in daycare, school, or restaurants where a person unfamiliar with food allergy may be responsible for determining the safety of the food. (9, 10) Cross-contamination of food may also lead to inadvertent...
ingestion of restricted foods. The food may be contaminated during the manufacture process if the same equipment used to process foods with and without a food allergen is not cleaned adequately between batches. Other settings where cross-contamination is likely to occur include bulk food bins, salad bars, or during the preparation of different foods with shared cooking utensils.

Fortunately, there is little risk from topical or inhaled environmental exposures to food allergens; generally, one must ingest peanut to have a systemic, life-threatening allergic reaction. (71,72) After applying peanut butter to the skin of peanut-allergic patients, there were no systemic reactions and one third of subjects had localized erythema or itching only. No patients had reactions to inhaled challenges with peanut butter. The risk of unanticipated exposures due to peanut allergy in the environment also appears to be low because it is removed from hands and surfaces with standard cleaning procedures. Furthermore, airborne levels were not detected around subjects who ate peanut butter and peanuts, even after shelling them. The real risk of inhaling peanut protein in airplanes with recirculated air is difficult to determine and underscores the importance of always being prepared to treat reactions (73).

Incorrect or ambiguous food labels may result in accidental ingestion of the offending allergen. The United States Food and Drug Administration requires food manufacturers to declare all functional ingredients on food labels. The Food Allergen Labeling and Consumer Protection Act (FALCPA) requires food manufacturers to explicitly state the presence of the eight major food allergens: milk, egg, wheat, soybean, peanut, tree nuts, fish and shellfish. Under this legislation, the language must be understandable to the average consumer and colorings, flavorings, or any other additives will not be exempt.

Some food manufacturers also use advisory labels such as “may contain peanut”, “manufactured on shared equipment with peanut”, or “manufactured in the same facility with peanuts” in order to warn consumers of the potential risk of peanut exposure. Practitioners often appropriately advise peanut allergic patients to avoid these products but the increase in foods with this vague warning has led patients to be complacent about excessive dietary restrictions, especially in those who previously tolerated the food in question. Although the majority of foods with these labels were actually free of peanut, the <10% containing clinically significant levels of peanut protein pose a threat to peanut allergic patients who ignore advisory labels. (74)

Because inadvertent food ingestions can not always be avoided, patients and their caregivers must be equipped to manage acute food-induced reactions. Individualized treatment plans should be prepared in advance and medications readily available. Epinephrine (0.01 mg/kg aqueous epinephrine 1:1000, maximum dose 0.3-0.5 ml) is the drug of choice for the treatment of food-induced anaphylaxis. (51) Delayed administration of this medication correlates with poor outcomes. (9,10,75) Prompt elevations in plasma epinephrine levels are desirable and achieved more readily after intramuscular injection compared to the subcutaneous route. (76,77)

The EpiPen™ (Dey; Napa, CA) contains a fixed dose of epinephrine in a self-injectable device allowing for rapid, intramuscular administration of the medication. Use of an auto-injector is preferable to withdrawing a designated dose of the medication from an ampule prior to injection because the latter method leads to imprecise dosing and delayed administration. (78) The EpiPen Jr™, containing 0.15mg epinephrine, is prescribed for children 15-30 kg while the EpiPen™ containing 0.3mg epinephrine, is prescribed for children >30 kg. Another device, Twinject™ (Verus Pharmaceuticals, Inc.; San Diego, CA), is also available for self-administration of epinephrine. It contains one of the same two fixed doses as the EpiPen™ but has the option to administer a second dose of epinephrine from the same device. The first dose is administered with an auto-injector, the second is injected manually with a pre-filled injector.

Epinephrine is clearly indicated for patients experiencing respiratory, cardiovascular, or neurologic compromise but more specific guidelines for its use have not been established. (51) The importance of gastrointestinal symptoms is particularly controversial because they may signify a more serious reaction or quickly resolve without any medical intervention. (50) In uncertain situations the decision to treat with epinephrine not only depends upon the symptoms that the patient is acutely experiencing but also upon factors known to correlate with outcomes of food-induced anaphylaxis. A history of a previous life-threatening reaction, allergy to peanut, concomitant diagnosis of asthma, or a reaction occurring outside of the home all correlate with poor outcomes; patients with these risk factors should be treated aggressively. These factors may also be considered when determining which of the two fixed doses of epinephrine to prescribe for children. (51,79) Children between 20 and 30 kg with risk factors for severe food-induced anaphylaxis may be prescribed 0.3 mg which will provide more epinephrine than the recommended 0.01 mg/kg rather than a subtherapeutic dose. (51) The importance of asthma as a risk for fatal food-induced anaphylaxis is particularly important and not limited to those with poorly controlled respiratory symptoms.

9. FUTURE DIRECTIONS

Because inadvertent ingestion of peanut often lead to life threatening reactions and peanut allergy is often long-lived, many investigators are focusing on decreasing clinical reactivity after peanut allergy is established. A Phase I trial with humanized, monoclonal anti-IgE antibody (TNX-901) proved beneficial for some patients with peanut allergy by increasing the threshold dose of peanut required to elicit symptoms but it remains under investigation for the treatment of peanut allergy. (80) Subcutaneous immunotherapy demonstrated efficacy in some patients with peanut allergy but significant adverse reaction rates made it unsuitable for clinical use. (81,82) Therefore, immunotherapy utilizing alternative routes of allergen...
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administration with a more favorable risk benefit ratio is desirable.

Immunotherapy by the sublingual route (SLIT) was successful in adults with hazelnut allergy and has prompted studies of its use in peanut allergic patients. (83,84) Although the mainstay of therapy for peanut allergy is avoidance of the allergen, some investigators believe that routine ingestion of increasingly larger amounts of peanut may actually induce tolerance. This method of treatment, oral immunotherapy (OIT), has shown promise for egg allergy. (85) Similar studies of OIT for peanut allergy, which differs significantly from egg allergy in that it is not usually outgrown, are now being conducted (86-88). The potential of anaphylaxis during OIT is significant, so this therapy should not be attempted as yet. These studies hold promise for the possibility of at least hyposensitization (raising the threshold of the amount of peanut that it would take to cause a life-threatening allergic reaction) or desensitization (preventing an allergic reaction while peanut was routinely ingested). Whether these types of treatments are likely to cause clinical tolerance to develop and persist after active treatment is discontinued remains to be seen. It is extremely likely that in the next five years there will be some type of specific immunotherapy available for peanut allergic individuals.

The main risk of immunotherapy, regardless of the route of administration, is anaphylaxis to the administration of whole allergens. Novel immunotherapeutic strategies aim to reduce this risk while still altering the immune system’s response to the specific allergen. An example is the use of overlapping T-cell peptides for cat allergy. These short peptides do not bind IgE and, instead, inhibit allergic reactions to the whole cat allergen. (89,90) An increase in IL-10 production suggests a role for T regulatory cells in tolerance induction using T-cell peptides. The use of engineered peanut allergens in studies has similar utility to the short peptides in that the mutated peanut allergens (recombinant Ara h 1, 2 and 3) bind less peanut-specific IgE but retain the critical T-cell epitopes needed for effective immunotherapy (91-94). Another method of immunotherapy that is well tolerated and may produce greater clinical benefit beyond the period of active therapy utilizes heat-killed Listeria or E. coli (HKL, HKE) as an adjuvant for the peanut protein or modified peanut allergen. Immunotherapy with HKL or HKE and peanut allergen in dogs and mice rapidly induced the innate immune system via toll-like receptors and simultaneously modified adaptive immunity with a decline in peanut-specific IgE production. (94,95) Clinical correlates in the animals included reduced skin test reactivity to peanut and mild or no symptoms after oral food challenges.

Cytokine-modulated immunotherapy, immunostimulatory sequence-conjugated protein-modulated immunotherapy, and plasmid DNA immunotherapy also attempt to curb the Th2-type response and induce tolerance by increased Th1 and T regulatory cytokine production responses to peanut allergen. (96-98) Other studies have shown the possibility of utilizing similar or cross-reacting proteins in soybeans for immunotherapy in peanut allergic mice. (99)

10. NATURAL HISTORY

Historically, allergy to peanut is not thought to be outgrown but the natural history of peanut allergy in young patients is still evolving. (100,101) It is now apparent that about 20% of children with peanut allergy may eventually develop tolerance. (63,102;103) The current approach to children with newly-diagnosed peanut allergy is to measure peanut-specific IgE levels annually and to perform an oral food challenge in patients 4 years of age or older if the peanut-specific IgE level decreases to < 2 kU/L. IgE levels < 2 kU/L are associated with a 50% rate of negative challenges. (62) Children who outgrow their sensitivity to peanut are then advised to consume peanut routinely and have epinephrine available until peanut has been tolerated for one year because up to 8% may develop a recurrence of their allergy. (104-106) Children > 5 years of age whose peanut-specific IgE level remains > 15 kU/L or who fail an oral challenge at a lower level are less likely to develop tolerance.

Favorable, but not conclusive, factors for outgrowing peanut allergy include the absence of atopic dermatitis or other food allergies, mild peanut-induced symptoms limited to the skin, and a small initial skin prick response (< 6 mm) or low (<10 kU/L) peanut-specific IgE level. In the future, patterns of epitope binding may be able to distinguish patients who are not likely to outgrow their allergy to peanut. (43)

An interesting and poorly understand observation of peanut allergic patients is their high likelihood of developing allergy to tree nuts (up to 50%), which are not botanically related, but not to other legumes (5%). (107) Due to the high rate of co-allergy and the risk of contamination with peanut protein, patients with peanut allergy are often counseled to also avoid eating tree nuts. Although allergy skin prick tests and food-specific IgE levels may indicate sensitization to different foods in the same botanical family (peanut and soybean), patients rarely have positive food challenges to related foods. (3,108) Therefore, they do not require strict avoidance of other legumes (green beans, green pea, lentils, etc) unless there is clinical evidence of allergy. Furthermore, screening for allergy to other legumes in the absence of clinical symptoms may not be particularly useful for peanut allergic patients because of the high rate of false positives due to allergen cross-reactivity. Clinical studies did not include large batteries of legumes, and it may be that particular types are more allergenic or cross-reactive. In more recent studies from Europe there appears a larger number of children with peanut allergy who also have clinical allergy to lupine. (109)

Given the rising prevalence of food allergy, interest in preventing its onset is increasing among parents and practitioners. Based on interpretations of existing studies for the primary prevention of food allergy in high-risk infants, the American Academy of Pediatrics (AAP)
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has encouraged exclusive breastfeeding for 4 to 6 months and supplementing with or weaning to an extensively hydrolyzed casein formula.

The most consistent benefit from prolonged breastfeeding and hypoallergenic diets in infancy is a decrease in infantile atopic dermatitis and cow’s milk allergy. (110,111) Maternal dietary interventions during the third trimester and lactation have not convincingly shown decreased cow’s milk allergy in infancy or decreased food allergy, atopic dermatitis, or asthma at older ages. (110,112) Furthermore, dietary manipulations after 4-6 months of age such as delaying introduction of egg, cow’s milk, peanut, and/or fish, are not likely to prevent or delay the development of atopy. However, the American Academy of Pediatrics currently advises high risk patients to delay introduction of peanuts beyond the third year of life. (48) It is likely these guidelines will be changed because of the lack of evidence in human studies that these recommendations are beneficial. In fact, others postulate that the lack of ingestion early in life may actually increase the possibility of becoming sensitized to peanuts. (22,113) There is the possibility that in children the introduction of small amounts of peanuts early in life may prevent sensitization, such that ingestion of Bamba (a peanut containing snack) may produce allergic tolerance to peanut proteins. (114) There are other observations suggesting that the prevalence of peanut allergy in infancy is low in populations that consume peanut containing snacks during the first year of life. (35,115) Further work is needed to define what role, if any, early peanut exposure plays in the development of allergy.

11. SUMMARY

The public’s awareness of peanut allergy has increased significantly over recent years. Children are experiencing allergic reactions to peanut at an earlier age. (17) These two observations seem difficult to reconcile because the obvious response to knowing about the high frequency of adverse reactions to a food would be to avoid it, especially in young children or those with a family history of allergy. Therefore, the earlier age of diagnosis may merely reflect recognition of adverse symptoms on the first ingestion rather than on subsequent ones. It is also possible that peanut protein has become more of a staple in our diets or is present in more processed foods, both of which would make it difficult to avoid. Even those with known allergy to foods have frequent accidental ingestions that may lead to life-threatening or fatal reactions. (9, 69,70) Regardless, avoidance of allergenic foods does not effectively prevent food allergy. Therefore, if food allergy cannot be prevented, and subsequent food-induced reactions are likely, efficacious, safe methods to modulate established immune responses to peanut are desirable.

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**Abbreviations:** Ara h : Arachis hypogaea, DBPCFC : placebo controlled food challenges, ELISA: enzyme-linked immunosorbent assays, FcεRI: high-affinity receptor for immunoglobulin E, HKE: heat-killed E. Coli, HKL: heat-killed Listeria, IFNγ: Interferon gamma, IL: Interleukin, MHC : Major Histocompatibility Complex , OIT: oral immunotherapy, RAST: radioallergosorbent tests, SLIT: Immunotherapy by the sublingual route, Th : T helper , TNF: tumor necrosis factor

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