

Peanut Allergy

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ABSTRACT

Peanut allergies have become a major health concern in the United States. Peanuts are one of the most common causes of food allergies and along with tree nuts they account for most of the cases of fatal and near-fatal anaphylactic reactions to food. Not only is there a rise in the prevalence of peanut allergies in Westernized countries but also most patients with peanut allergies have lifelong clinical sensitivities to peanuts. Patient management involves strict avoidance, recognition of the early symptoms of anaphylaxis, and usage of an emergency treatment plan, including the self-administration of epinephrine in case of an accidental ingestion. Future treatment strategies may include recombinant peanut protein immunotherapy and anti-Immunoglobulin E therapy to modulate clinical reactivity to peanuts. This article reviews the current understanding of the clinical characteristics, pathogenesis, diagnosis, and management of the peanut allergy. (Allergy and Asthma Proc 24:259–264, 2003)

CASE REPORT

A 58-year-old man presented with a lifelong history of peanut allergy. Since the first peanut-induced hives occurred at 2 years of age, his reactions have become more severe. He had multiple accidental ingestions of peanuts resulting in four intensive care unit admissions, two of which required intubation. He had been evaluated 8 years ago with skin testing to peanuts, which provoked an anaphylactic reaction.

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His most recent anaphylactic reaction occurred at a friend's house. He had several bites of barbecue ribs after being reassured by the host that there were no peanuts contained in the sauce. Within several minutes, he developed total body pruritus, urticaria, throat tightness, and wheezing. He self-administered epinephrine but lost consciousness transiently and repeated another injection of epinephrine. He later learned that the chef had added one-half a teaspoon of peanut butter as a "secret ingredient" to thicken the barbecue sauce.

His past medical history included coronary artery disease, mild intermittent asthma with history of severe asthma as a child, seasonal allergic rhinitis, and a history of childhood eczema. He was on atenolol, albuterol as needed, and carried four self-injectable epinephrine pens at all times. Physical examination was unremarkable. Immunoassay by Pharmacia CAP (Pharmacia & Upjohn Diagnostics, Uppsala, Sweden) was 70.1 kilounits of allergen per liter (kU_A/L) for peanuts and 0.43–1.79 kU_A/L for walnuts, Brazil nuts, almonds, hazelnuts, pecans, and cashews.

The patient was diagnosed with a severe peanut allergy and was informed of the life-threatening risks associated with an accidental ingestion. He was educated on the strict avoidance of peanuts and tree nuts and the need to avoid all questionable foods in high-risk situations. The patient showed the proper usage of self-injectable epinephrine, understood the need to carry it at all times, and formulated an emergency treatment plan in case of an inadvertent exposure. In addition, he was counseled on future therapies for peanut allergy.

PREVALENCE

This case shows a patient with life-threatening allergic reactions to peanuts. Food allergies affect up to 8% of children <3 years of age as well as 2% of adults and account for ~30,000 anaphylactic reactions, 2000 hospitalizations, and 150 deaths annually in the United States.¹

Peanut and tree nut allergies affect ~1.1% of the general population or about 3 million Americans.² Peanuts are a common cause of food allergies³ and, along with tree nuts, are the major cause of fatal and near-fatal anaphylactic reactions to food.⁴

The prevalence of peanut allergies appear to be rising in the United States and other westernized countries.⁵ In a study of two sequential cohorts 6 years apart in the United Kingdom, sensitization to peanuts by skin testing increased from 1.1 to 3.3% and reported symptomatic reactions increased from 0.5 to 1.0%.⁶ In a cohort of American children referred for evaluation of food allergies over a 10 year period, peanut sensitization increased by 55% and symptomatic reactions increased by 95%.⁷

The increase in the prevalence of peanut allergies cannot be explained completely by the general increase in the prevalence of allergic diseases.³ One possible explanation for the rise in prevalence is the increase in the consumption of peanuts. As the vegetarian diet becomes more popular and as demand grows for quick nutritional foods, exposure to peanuts has increased in pregnant/nursing mothers and in infants.³ Consequently, virtually all children in the United States are exposed to peanuts by 2 years of age.⁸ Increased exposure translates into increased peanut sensitization in genetically predisposed children.

Another explanation for the rise in the prevalence of peanut allergies may be related to the method whereby peanuts are prepared.³ Although peanut consumption in China is similar to that of the United States, peanut allergies are rare in China. Most peanuts consumed in the United States are dry roasted, whereas peanuts consumed in China are boiled or fried. The lower temperature required to boil or fry peanuts appears to reduce the allergenicity of peanut proteins compared with the high temperature of roasting, which increases the allergenicity.⁹

NATURAL HISTORY

Peanut allergy occurs early in life. The initial reaction to peanuts typically occurs at a median age of 14–24 months.^{10,11} In a cohort of 62 patients in the United Kingdom, peanuts accounted for all nut allergies in infants sensitized in the 1st year of life and 82% of nut allergies in children sensitized by 3 years of age.¹² Unlike milk and egg allergies, most patients who are allergic to peanuts do not outgrow their peanut sensitivities.³ Bock and Atkins¹³ followed 32 patients aged 2–14 years with confirmed peanut allergies by food challenge. Over the 7-year follow-up, none of the patients had outgrown their peanut allergy.

However, recent studies suggest that a small subset of patients may outgrow their peanut sensitivity. A study by Hourihane *et al.*¹⁴ found that 18% of young children with a history of mild reactions to peanuts had negative oral challenges. Skolnick *et al.*¹⁵ conducted a study of 233 patients with peanut allergies, and of those 233 patients, 85 patients with peanut-specific immunoglobulin E (PN-IgE) levels

<20 KU_A/L underwent oral challenge to peanuts. Forty-eight patients had negative challenge results, suggesting that approximately one-fifth of all patients (48 of the 233 patients) had lost their clinical sensitivities. Factors associated with loss of sensitivity were fewer signs of atopy at presentation,¹⁴ initial peanut-induced reactions limited to the skin,¹⁵ and PN-IgE levels <5 kU_A/L.¹⁵

For the majority of patients who continue to have clinical sensitivities to peanuts, reactions may become more severe with time.³ Up to one-third of patients with mild initial reactions may develop severe symptoms on subsequent exposures.¹⁶ Therefore, a mild reaction to peanuts does not translate into lifelong mild reactions.

PATHOGENESIS

The three major allergenic proteins in peanuts, Ara h 1, Ara h 2, and Ara h 3, are seed-storage glycoproteins that have molecular masses of 63.5, 17.5, and 60 kDa, respectively.⁸ These proteins share common characteristics with other allergenic food proteins: present in high concentrations, water soluble, and resistant to heat and digestion.¹⁷ Although peanuts belong to the legume family, <15% of the peanut-allergic patients react to other members of the legume family.¹⁸ Interestingly, although tree nuts belong to a different botanical family, 25–35% of patients who are allergic to peanuts have allergic reactions to tree nuts.³ The most common tree nuts that cause allergic reactions are Brazil nuts, almonds, and hazelnuts in one study¹² and walnuts, almonds, and pecans in another study.¹¹

Many studies have shown that 72–81% of peanut-allergic patients react to peanuts on their first known ingestion.^{11,16} This finding implies a high frequency of occult peanut sensitization. Because IgE antibodies do not cross the placenta, sensitization to peanut proteins must occur *in utero* or through the breast milk. In a case control study, Frank *et al.*¹⁹ found that mothers who consumed peanuts more than once a week during pregnancy were more likely to have peanut-allergic children than mothers who consumed peanuts less than once a week (odds ratio = 3.97). In a referral population of children who are allergic to peanuts, Sicherer *et al.*¹¹ found that 83% were breast-fed and >90% of the mothers had ingested peanuts during lactation. Moreover, major peanut allergens Ara h 1 and Ara h 2 could be detected in the breast milk of lactating women after maternal peanut ingestion.²⁰ Besides possible sensitization in utero or through the breast milk, observational evidence also linked the use of creams containing peanut oil on infants to increased risk of developing peanut allergies.²¹

Exposure to peanuts sensitizes the patient to develop IgE antibodies to the peanut proteins. The reason why some children develop sensitizing antibodies and others do not is not well understood. However, a genetic predisposition and exposure at an early age increase the risk of sensitization.¹

TABLE I

Diagnostic Decision Points that Are 95–100% Predictive of Clinical Reactivity to Peanuts

Authors	PN-IgE (kU _A /L)	Prick Wheal Diameter	PPV (%)	Sensitivity (%)	Specificity (%)
Sampson and Ho ²⁸	≥15		95	73	92
Sporik <i>et al.</i> ²⁹		≥8mm	100	55.1	100
Sampson ³⁰	≥14		100	57	100
Rancé <i>et al.</i> ³¹	≥57	≥16mm	100	27.8	100

PPV = Positive predictive value.

CLINICAL MANIFESTATIONS

Patients with allergic reactions to peanuts may present with a variety of symptoms. The early symptoms of anaphylaxis often include oral and pharyngeal pruritus, flushing, urticaria, nausea, vomiting, and chest tightness. Progressive symptoms of diffuse wheezing, hypotension, arrhythmia, and loss of consciousness may develop in fatal and near-fatal reactions.²² Many patients who are allergic to peanuts have severe symptoms on exposure. In a study involving 101 children, Sicherer *et al.*¹¹ found that 50% had two or more organ system involvement and that 20% required epinephrine treatment for their first reactions. In a larger study of 622 peanut-allergic patients, >50% had breathing difficulties or cardiovascular compromise.¹⁶ Furthermore, in a population-based study of 4374 households, many of the individuals surveyed had severe symptoms after peanut exposure: throat tightness (56%), dyspnea (43%), wheezing (36%), and loss of consciousness (4%).²

For those patients who are extremely sensitive to peanuts, exposure to minute quantities will induce an anaphylactic reaction. In a study of 26 patients with a history of peanut allergies, threshold doses needed to provoke allergic reactions ranged from 0.1 to 1000 mg of peanut protein (150 mg = 1 peanut).²³ Fifty percent of the study population had allergic reactions after ingestion of just 3 mg of peanut protein (1/50 of a peanut). The patients who had the most severe symptoms also were those individuals who reacted to the lower doses.

FATAL AND NEAR-FATAL ANAPHYLAXIS

Food-induced anaphylaxis is the leading cause of anaphylaxis in the United States.^{1,3} In a population-based study of Olmstead County, MN, the annual incidence rate of anaphylaxis to food is 7.6 cases per 100,000 person-years.²⁴ Extrapolating from this data would predict that food allergies causes ~30,000 anaphylactic reactions and 150 deaths every year in the United States. Yunginger *et al.*²⁵ and Sampson *et al.*²⁶ reported fatal and near-fatal anaphylactic reactions to food. Peanuts and tree nuts accounted for most of the reactions. Common characteristics of the victims included presence of atopy and multiple prior episodes of food-induced anaphylaxis. Risk factors contributing to the fatal reactions were concomitant asthma, denial of symp-

toms, and, most importantly, delay of the administration of epinephrine.

In a more recent study, Bock *et al.*⁴ analyzed 32 fatal anaphylactic reactions to food. Peanuts and tree nuts caused >90% of the deaths. All but one of the patients had a history of asthma, strongly implicating the association between fatal food-induced anaphylactic reactions and asthma. Although most patients were known to have food allergies before the fatal event, only 10% of the individuals had epinephrine available at the time of the reaction.

Biphasic reactions occur in about one-third of patients with anaphylaxis, and over 90% of delayed reactions occur within 4 hours after the initial symptoms.²⁶ Symptoms of the late reactions usually are more refractory to therapy and may require intubation and mechanical ventilation.³ The delayed reactions are more commonly observed in patients with severe symptoms at presentation and with late onset of treatment.

DIAGNOSIS AND LABORATORY EVALUATION

Evaluation of peanut allergies includes taking a thorough history, PN-IgE immunoassay, and skin-prick test.²² If the peanut-induced symptoms were severe, PN-IgE should be performed before determining the need for skin testing. The presence of PN-IgE and reactivity on skin-prick test provide evidence for peanut sensitization but do not establish the diagnosis of clinical reactivity.²² Double-blind, placebo-controlled food challenge (DBPCFC),²⁷ the gold standard in the diagnosis of food allergies, generally is reserved for patients with unclear *in vitro* diagnostic results or when identification of the food allergen is deemed to be lifesaving. Because DBPCFC is time-consuming, costly, and not without risk to the patient, many investigators have studied the usefulness of PN-IgE and the skin-prick test to predict clinical reactivity.

In four separate studies, investigators generated diagnostic decision points for PN-IgE and the skin-prick test that would yield high predictive values of clinical reactivity to peanuts.^{28–31} Any PN-IgE level or prick wheal diameter greater than the diagnostic decision point would obviate the need for oral challenge because clinical reactivity would be very likely. The results of the studies are summarized in Table I. Because sensitivity and specificity reflect inherent

properties of a test and predictive values depend on the prevalence of disease in the population under investigation, the decision points obtained from the four studies were different. Sampson²² recommended the stepwise approach in evaluating patients with suspected peanut allergy—perform skin testing to screen for the presence of peanut sensitivity and then measure the PN-IgE level to determine the likelihood of having clinical reactions. Taken together, the level of PN-IgE and the diameter of the prick wheal provide valuable information regarding the likelihood of clinical sensitivity to peanuts.

Another important observation from the studies is that although the PN-IgE level and the prick wheal diameter may predict the likelihood of clinical reactivity, they do not correlate with the severity of the peanut-induced reactions.²⁸ Patients with PN-IgE levels above the diagnostic decision point may only develop hives and those with low PN-IgE levels may have anaphylactic reactions after ingestion of peanuts.

In acute reactions to peanuts, laboratory evaluation may not be helpful in the diagnosis of anaphylaxis. Serum β -tryptase, a marker of mast cell activation, usually is normal in patients who have an anaphylactic reaction to food.²⁶ Therefore, clinical diagnosis and history of ingestion remain the most important determinants for diagnosis of acute peanut-induced anaphylaxis.³

MANAGEMENT

The diagnosis and management of peanut allergies carry great emotional and medical significance for patients and their families.⁵ All patients with nut allergies should be referred to a specialist for proper evaluation and management. The general management of peanut allergy is based on three approaches: strict avoidance of peanuts, prompt recognition of allergic reactions, and rapid initiation of treatment for anaphylaxis.³

Avoidance

Avoidance is critical for patients who are allergic to peanuts. Parents of children who are allergic to peanuts must always check product labels for food ingredients that may contain peanuts. If there is any doubt regarding the content, that food should be avoided. “High-risk” foods are unlabeled ice creams, cookies, and candies. Similarly, high-risk locations where accidental peanut ingestion is more likely to be encountered include eating at buffets and restaurants (cross-contamination of food during cooking), friends’ houses, and ice cream parlors (use of secret ingredients), as well as day care centers and school cafeterias (food sharing).²² Schools and day care centers need to provide a safe environment with strict rules prohibiting the sharing of food among children.

Regarding the prophylactic avoidance of peanuts, the Department of Health in the United Kingdom recommends that in families with a history of atopy, women who are

pregnant, and nursing mothers should avoid eating peanuts and should avoid giving peanuts to their infants during the first 3 years of life.³² Children who are allergic milk or eggs during the 1st year of life should avoid peanuts because up to one-third of these children will develop other food allergies.³ Similarly, children <5 years of age who are allergic to peanuts should avoid tree nuts because up to one-third of these patients will develop tree nut allergies.¹² Regarding the avoidance of soy, there is no current evidence to recommend the avoidance of soy in peanut-allergic, soy-tolerant patients.⁸

Recognition of Anaphylaxis

Given the wide and frequently hidden use of peanuts in food, avoidance can be difficult. It has been estimated that the average patient with an allergy to peanuts will have an allergic reaction from accidental ingestion of peanuts every 3–5 years.¹¹ Patients and their families should be educated regarding the recognition of the early symptoms of anaphylaxis. Those patients with a history of severe symptoms should be encouraged to wear Medic Alert bracelets so that prompt recognition and treatment can be given if reactions occur outside the home.

Emergency Treatment Plan

All patients with an allergy to peanuts should be given an emergency treatment plan that may include liquid diphenhydramine and self-injectable epinephrine with instructions to call emergency medical personnel in case of an accidental ingestion. In a recent series of patients who received epinephrine for food-induced reactions, only one-third of the patients correctly demonstrated the use of the device.³³ Therefore, patient education on the proper administration of epinephrine is very important.

The definitive emergency treatment for anaphylaxis is the early administration of epinephrine, and all patients at risk for experiencing anaphylaxis need to carry self-injectable epinephrine. Furthermore, patients should be educated that diphenhydramine is not a substitute for epinephrine. If clinically indicated, epinephrine may be judiciously repeated every 5 minutes for both children and adults.³⁴ Failure to recognize the symptoms of anaphylaxis and failure to administer epinephrine immediately after the onset of anaphylaxis increase the risk of a fatal outcome.^{25,26}

Patients who have severe reactions requiring the self-administration of epinephrine should call emergency response services and should be transferred to the local emergency department for further evaluation and observation for biphasic reactions. Patients with anaphylaxis should be treated aggressively with intramuscular epinephrine,³⁵ H_1 and H_2 receptor antagonist, oxygen, nebulized albuterol, and systemic corticosteroids as appropriate. Corticosteroids may not reduce the risk of a biphasic response.³ Patients should remain under medical supervision for at least 4 hours to monitor for delayed reactions. On discharge from the

emergency department, a short course of oral prednisone and an antihistamine often are recommended, although there is no literature showing the effects of such an approach.³

NOVEL THERAPIES

Until recently, the management of food allergies consists of avoidance and treatment of symptoms. Despite strict avoidance, an average patient who is allergic to peanuts will still have an allergic reaction from inadvertent exposure every 3–5 years.¹¹ Immunotherapy using peanut extract was studied as a method to modify clinical sensitivity.^{36,37} Although some patients were able to tolerate higher doses of peanuts on oral challenge, repeated systemic reactions to immunotherapy occurred in most patients, even during maintenance injections. Because of the unfavorable benefit-to-risk ratio, new treatment strategies for peanut allergy are necessary.

One novel approach uses recombinant peanut protein immunotherapy where amino acids within the peanut IgE epitopes are modified to prevent the binding of PN-IgE antibodies.³⁸ Because the T-cell epitopes differ from IgE-binding epitopes, IgE binding can be eliminated while T-cell proliferation and tolerance can still be induced. In a study by Li *et al.*,³⁹ the recombinant peanut protein in combination with bacteria adjuvant markedly reduced the sensitivity to peanuts without triggering IgE-mediated reactions in a murine model of peanut anaphylaxis.

In another approach, Li *et al.*⁴⁰ described a mixture of traditional Chinese medicine that blocked the allergic reaction in a murine model of peanut anaphylaxis. The herbal formula completely blocked peanut-induced anaphylactic reactions, reduced PN-IgE levels, and decreased peanut-induced lymphocyte proliferation. The investigators reported no adverse effects on the liver and kidneys and no overall immune suppression.

Most recently, Leung *et al.*⁴¹ studied the effect of humanized monoclonal antibody to IgE TNX-901 on the non-specific modulation of clinical sensitivity to peanuts. TNX-901 is specific for the Cε3 domain of IgE that is responsible for the binding of IgE to the IgE receptor on mast cells and basophils. TNX-901 does not bind to cell-bound IgE, and the biologically inert IgE-TNX-901 complex does not activate the complement system.⁴² Eighty-four patients who were allergic to peanuts confirmed by DBPCFC were randomly assigned to receive subcutaneous injections of TNX-901 or placebo every 4 weeks for a total of four doses. All patients underwent repeat oral challenge within 4 weeks of the last dose. In a dose-dependent manner, the average threshold of sensitivity increased from less than one peanut to almost nine peanuts in the highest dose group. TNX-901 has few side effects and is a promising new treatment for patients with severe reactions to peanuts.

CASE DISCUSSION

The case vignette shows a patient with severe anaphylactic reactions to peanuts. This patient has many of the common characteristics of peanut allergy. His peanut allergy developed early in childhood, and he has a history of atopy. His clinical sensitivity to peanuts did not resolve but worsened over time. Despite careful avoidance, the patient still has multiple accidental exposures to peanuts, requiring self-administration of epinephrine.

The patient's allergy to peanuts is particularly difficult to manage given his history of coronary artery disease and his use of atenolol. Not only are patients on β -blockers more likely to experience paradoxical bradycardia with anaphylaxis, but they also are more likely to have the actions of epinephrine impeded by the β -blockade.³⁴ Furthermore, both the symptoms of anaphylaxis and the effects of epinephrine cause an immense amount of stress on the patient's heart and increase his risk for a cardiac event. Future therapy with anti-IgE would benefit him by increasing his threshold of clinical reactivity to peanuts.

For patients on β -blocker therapy, if anaphylaxis is not being adequately treated with epinephrine, glucagon at 20–30 $\mu\text{g/kg}$ (maximum 1 mg) can be administered intravenously over 5 minutes followed by an infusion of 5–15 $\mu\text{g/minute}$.³⁴ Because glucagon may cause nausea and vomiting, aspiration precautions should be observed.

SUMMARY

Peanut allergies have become a major health concern in the United States. The rising prevalence, lifelong sensitivity in most patients, and, sometimes, severe clinical symptomatology make peanut allergies an important entity to manage. Despite an increasing public awareness of food allergies, many patients with food allergies are poorly prepared to treat anaphylactic reactions. In families with a history of atopy, women who are pregnant and nursing mothers should avoid eating peanuts and should avoid giving peanuts to their children during the first 3 years of life. Patients who are allergic to peanuts need to be educated regarding strict avoidance, early recognition of the symptoms of anaphylaxis, and the prompt administration of epinephrine. Through the improved knowledge of IgE-mediated allergic diseases, future treatments of peanut allergy will be aimed at modifying the immune response and clinical reactivity to peanuts.

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