Clinical Practice

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

Peanut Allergy

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A 19-year-old woman is brought to the emergency room because of the acute onset of dyspnea, wheezing, vomiting, and generalized flushing. She has well-controlled asthma as well as a history of atopic dermatitis as an infant and urticaria after ingesting peanut butter at the age of five years. According to friends she ate a chocolate-chip cookie from a vending machine in her college dormitory just before the symptoms developed. The list of ingredients on the cookie wrapper does not include peanuts. Nevertheless, how should this patient's condition be treated?

The Clinical Problem

In a patient with asthma, the acute onset of severe bronchospasm in the absence of earlier signs of asthma must always raise the suspicion of anaphylaxis. Food allergy affects about 6 to 8 percent of children younger than four years of age and about 2 percent of the U.S. population beyond the first decade of life.[1] Food allergy is the leading cause of anaphylaxis treated in hospital emergency departments in the United States and many westernized countries. Food allergy accounts for about 30,000 anaphylactic reactions, 2000 hospitalizations, and 200 deaths each year in the United States.[2] Allergies to peanuts and tree nuts account for the majority of fatal and near-fatal anaphylactic reactions.[3,4] A national survey indicated that about 1.1 percent of Americans, or 3 million people, are allergic to peanuts, tree nuts, or both.[5] Ironically, despite an increasing public awareness of food allergy, most patients are ill prepared to deal with anaphylactic reactions.[6] In a recent series, over 80 percent of patients who died from allergic reactions to food were not given appropriate information to avoid accidental food-induced reactions or self-injectable epinephrine to manage them.[4]

Food-induced anaphylaxis is primarily a clinical diagnosis and is often mistaken for severe status asthmaticus or an acute cardiovascular event. People who have life-threatening reactions usually have asthma and frequently have a history of atopy, including atopic dermatitis and food allergy as young children.[7] Symptoms may develop within minutes to a few hours after ingestion of the food, and in life-threatening cases, symptoms include severe bronchospasm. Although similar to anaphylaxis due to other causes, early symptoms of food-induced anaphylaxis often include oral pruritus and "tingling," pharyngeal pruritus and a sensation of tightening of the airways, colicky abdominal pain, nausea and vomiting, and cutaneous flushing, urticaria, and angioedema. Progressive respiratory symptoms, hypotension, and dysrhythmias typically develop in fatal and near-fatal cases. Obstructive laryngeal edema is uncommon, and cutaneous symptoms may be absent in severe cases. Surveys of fatal and near-fatal reactions suggest that a delay in the initiation of therapy such as injectable epinephrine is associated with a poorer prognosis, although about 10 percent of patients who receive epinephrine early still die.[3,4] Biphasic reactions have been noted in up to one third of patients with fatal or near-fatal reactions. These patients seem to have fully recovered when severe bronchospasm suddenly recurs; the recurrence is typically more refractory to standard therapy and often requires intubation and mechanical ventilation. The mechanism underlying this phenomenon is unknown, but it appears to be more common when therapy is initiated late and symptoms at presentation are more severe. Secondary pneumothoraxes are a fairly common consequence of the high airway pressures generally required to overcome the obstruction.

Although the relative epidemic of peanut allergy appears to be a phenomenon of the past two decades, peanuts were first cultivated in South America about 2000 to 3000 B.C., and the practice has spread throughout the world.[8] After the Civil War, peanuts became increasingly popular throughout the United States. America now ranks third only to China and India in peanut production, with over 40 percent of the U.S. peanut crop consumed as peanut butter. Whereas the per capita consumption of peanuts in China is similar to that of the United States,[9] peanut

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allergy is extremely rare in China.[10] In addition, the prevalence of peanut allergy appears to be rising in the United States and other westernized countries. In a population-based study of three-year-olds in the United Kingdom, the prevalence of sensitization to peanuts increased from 1.3 percent to 3.2 percent from 1989 to 1995.[11] In a cohort of American children referred for the evaluation of moderate-to-severe atopic dermatitis between 1990 and 1994, the prevalence of allergic reactivity to peanuts was nearly twice as high as that in a similar group evaluated between 1980 and 1984.[12] Data from the third National Health and Nutrition Examination Survey (collected from 1988 to 1994) indicated that about 6 percent of Americans have serologic evidence of sensitivity to peanuts (i.e., the presence of IgE antibodies specific for peanut proteins),[13] although the majority of these people will not have an allergic reaction when they eat peanuts.

There appears to be something unique about the peanut that is not shared by other members of the legume family or most other food proteins. The three major allergenic proteins in peanuts are Ara h 1, 2, and 3.[14] Although other legumes contain similar proteins and most patients with peanut allergy have IgE antibodies against these proteins, fewer than 15 percent of such patients react to other members of the legume family.[15] In addition, other legumes rarely provoke severe anaphylactic reactions or result in a lifelong allergy. However, in 25 to 35 percent of patients with peanut allergy, an allergic reaction to tree nuts (such as walnuts, cashews, and pistachios) will develop even though tree nuts are from a different botanical family.[16]

STRATEGIES AND EVIDENCE

Diagnosis

A physician who knows about food allergies should evaluate any person who is thought to have had an adverse reaction to peanuts. The evaluation should include a careful history-taking, skin-prick tests, radioallergosorbent tests, and possibly, an oral food challenge. Patients who have had unequivocal symptoms of allergy after the isolated ingestion of a peanut product (especially if they occur on more than one occasion) and who have evidence of peanut-specific IgE antibodies (a positive skin-prick test or radioallergosorbent test) do not usually need to undergo oral peanut challenges to establish the diagnosis. The use of a radioallergosorbent test to quantify the level of peanut-specific serum IgE antibodies can be diagnostic, since patients with peanut-specific serum IgE levels of at least 15 kU per liter have a likelihood of an allergic reaction of 95 percent or greater if they ingest peanuts.[17] In the absence of a conflicting history, these patients may be given a diagnosis of peanut allergy and do not need to undergo a food challenge. In persons who have peanut-specific serum IgE antibody levels of less than 15 kU per liter and no clear-cut history of peanut-induced symptoms, a physician-supervised food challenge is necessary to make a definitive diagnosis. The double-blind, placebo-controlled challenge is considered the gold standard for diagnosing food allergy, but less rigorous challenges are often adequate if they are performed by a physician with experience in food allergies and the treatment of anaphylaxis. Such challenges may lead to severe anaphylactic symptoms and so should be conducted only in a hospital setting by an experienced specialist.

Peanut allergy generally develops at an early age and, unlike many other food allergies in children, is often a lifelong disorder. In a registry of 4685 patients with peanut allergy, the first reaction to peanuts occurred at a median age of 14 months.[18] Infants who have peanut allergy tend to have more severe allergic reactions as they get older. However, recent studies suggest that about 20 percent of young infants who have allergic reactions to peanuts will outgrow their allergy, especially if they have low levels of peanut-specific serum IgE antibodies in infancy (less than 5 kU per liter).[19] Therefore, children with low levels of peanut-specific IgE antibodies should be reevaluated periodically to determine whether they have outgrown their allergy. A conversion of the skin-prick test from positive to negative generally indicates that a patient has outgrown his or her peanut allergy. However, skin-prick tests often remain positive for many years in children who have outgrown their peanut allergy and are therefore not as useful as the measurement of peanut-specific IgE antibodies for assessing clinical reactivity.

The diagnosis of an acute allergic reaction is based on clinical symptoms and a history of exposure to an allergen. Laboratory studies are not helpful in distinguishing food-induced anaphylaxis from severe asthma, since serum β-tryptase levels, a hallmark of mast-cell activation that is associated with anaphylactic reactions, usually remain normal in patients with food-induced anaphylaxis.[3,20]

Management

Currently, treatment of peanut allergy consists of teaching patients and their families how to avoid the accidental ingestion of peanuts, how to recognize early symptoms of an allergic reaction, and how to manage the early stages of an anaphylactic reaction (Table 1).[21] Patients must learn to check all food labels for the presence of peanuts and to avoid high-risk situations, such as foods served in buffets and ice-cream parlors and unlabeled candies and desserts. Although most patients with peanut allergy avoid ingesting pea-

TABLE 1. APPROACH TO PATIENTS WITH PEANUT ALLERGY.

Patient education
Avoidance of peanut proteins
Recognition of early signs of anaphylaxis
Early treatment of allergic symptoms (anaphylaxis) with injectable epinephrine (EpiPen Autoinjector) and oral liquid diphenhydramine (the most easily absorbed form)
Treatment of acute reaction*
By patient and family members
Injection of epinephrine, depending on patient's history and symptoms
Administration of oral liquid diphenhydramine (1 mg/kg of body weight; maximum, 75 mg)
Transport to emergency facility
By emergency personnel
Administration of supplemental oxygen and airway management
Administration of intramuscular epinephrine (0.01 ml of a 1:1000 dilution/kg every 10 to 20 minutes as needed; maximum, 0.3 to 0.5 ml) or intravenous epinephrine in patients with severe hypotension (0.5 to 5 μg/min to maintain blood pressure)
Administration of intravenous fluids
Administration of oral, intramuscular, or intravenous H_1-receptor antagonist (e.g., diphenhydramine, 1 mg/kg; maximum, 75 mg)
Treatment with oral prednisone (1 to 2 mg/kg; maximum, 75 mg) or intravenous methylprednisolone (2 mg/kg; maximum, 250 mg)
Administration of nebulized albuterol (1.25 to 2.5 mg every 20 minutes as needed or continuously with monitoring)
Use of H_2-receptor antagonist (e.g., for adults: 4 to 5 mg of ranitidine/kg orally; maximum, 300 mg; 50 mg intramuscularly or intravenously every 6 to 8 hr; for children: 1.5 mg/kg intramuscularly or intravenously; maximum, 50 mg)
Follow-up
Treatment with oral H_1-receptor antagonist for 3 days: cetirizine (patients weighing less than 30 kg, 5 mg/day; patients weighing at least 30 kg, 10 mg/day), fexofenadine (patients younger than 12 years of age, 30 mg twice a day; patients at least 12 years of age, 60 mg twice a day), or loratadine (patients younger than 6 years of age, 5 mg/day; patients at least 6 years of age, 10 mg/day)
Treatment with oral prednisone (1 mg/kg/day; maximum, 75 mg) for 3 days
Referral for evaluation by allergist if patient has not previously been evaluated

*Treatment varies depending on the patient's symptoms.

nut oil, highly processed oils — acid-extracted, heat-distilled oils — do not contain peanut protein and can be safely consumed by such patients.[22] However, cold-pressed or extruded peanut oils contain peanut protein and many induce allergic reactions.

Although considerable educational material is available through organizations such as the Food Allergy and Anaphylaxis Network (telephone number, 1-800-929-4040; Web site, http://www. foodallergy.org), inadvertent exposure as a result of peanut contamination of equipment used in the manufacture of various products, inadequate food labeling, cross-contamination of food during cooking in restaurants (e.g., the use of the same pan to cook foods containing peanuts and foods without peanuts),[23] and unanticipated exposures (e.g., the inhalation of peanut dust in airplanes[24]) result in an allergic reaction every three to five years in the average patient with peanut allergy.[16] Consequently, such patients must be given a written emergency plan (one is available at the Food Allergy and Anaphylaxis Network Web site) and appropriate doses of liquid diphenhydramine and self-injectable epinephrine (e.g., EpiPen Autoinjector, Dey, Napa, Calif.) so that therapy can be initiated in case they accidentally eat peanuts. Patients who have an allergic reaction to peanuts that requires the use of epinephrine should always go to a local emergency room for follow-up in case they have persistent refractory symptoms or a biphasic response.

Patients who have an anaphylactic reaction to peanuts should be treated aggressively with intramuscular epinephrine[25]; oral, intramuscular, or intravenous histamine H_1- and H_2-receptor antagonists; oxygen; inhaled albuterol; and systemic corticosteroids. Because over 90 percent of biphasic responses occur within four hours after the initial reaction, patients should be observed for at least four hours before being discharged from the emergency department.[3] The administration of corticosteroids does not appear to reduce the risk of a biphasic response. A subsequent three-day course of oral prednisone (1 mg per kilogram of body weight per day; maximum, 75 mg per

day) and an antihistamine is often recommended, although there are no studies demonstrating that this practice decreases the risk of recurrent symptoms.

AREAS OF UNCERTAINTY

Cause of the Increasing Prevalence of Peanut Allergy

The cause of the rising prevalence of peanut allergy and the reasons this increase appears to be confined to westernized countries remain uncertain. In addition to theories regarding the general increase in the prevalence of allergic disease worldwide over the past several decades,[26] a number of factors have been suggested to account for the apparent increase in prevalence. The growing demand for highly nutritional, "quick-energy" foods has made the peanut a staple of the American diet. Breast-feeding is increasingly common, and peanut products have increasingly been promoted as excellent nutritional sources for pregnant and lactating women. In one registry of patients with peanut allergy, about 85 percent had been breast-fed and more than 70 percent had had their first allergic reaction after their first apparent contact with peanuts. Since reactions require previous exposure for sensitization and since IgE antibodies do not cross the placenta, these findings suggest that peanut protein was encountered in utero or through breast milk.[24,27] In a French study of 54 infants who were less than 11 days of age and 71 who were 17 days to 4 months of age, 8 percent had a positive skin-prick test for peanuts.[10] Another study found that mothers of children with peanut allergy ate more peanuts during pregnancy, but not during lactation, than mothers of children with an allergy to milk or eggs.[28]

Given the immaturity of the immune system at birth, food allergies are more likely to develop during the first few years of life.[1] The majority of American children are exposed to peanuts (e.g., peanut butter) in the first year of life, and virtually all have been exposed by their second birthday.[29] In countries where peanut butter is rarely eaten, such as Denmark and Norway, peanut allergy is much less common.

Differences in the way peanuts are prepared may also contribute to the increasing prevalence of peanut allergy as well as to variations in the rates of peanut allergy among countries. Most peanuts in the United States are dry-roasted, including peanuts that are made into peanut butter, whereas peanuts in China are typically boiled or fried. The higher temperatures required for dry-roasting increase the allergenicity of the three major peanut proteins more than do the lower temperatures used for boiling or frying.[9] Although genetics plays a part in the development of peanut allergy,[30] the prevalence of peanut allergy is similar among the children of Chinese immigrants to the United States and the children of native-born Americans.

Therapy for Peanut Allergy

Unlike traditional immunotherapy for allergic reactions to inhalants and bee stings, injections of peanut extracts have an unacceptable risk–benefit ratio.[31] However, novel therapeutic agents are being investigated for the treatment of peanut allergy.[32] One approach being evaluated in phase 1 and 2 trials is monthly injections of humanized recombinant anti-IgE antibodies, which may reduce the levels of IgE bound to mast cells and basophils sufficiently to prevent the activation of allergic responses, at least to small amounts of peanut protein. Another approach uses engineered (mutant) recombinant peanut proteins, in which substitutions of critical amino acids within the IgE-binding epitopes prevent the activation of IgE-mediated reactions, for traditional desensitizing immunotherapy. Both engineered recombinant proteins and a series of overlapping peptides comprising T-cell epitopes of peanut reversed sensitivity to peanuts in a murine model of peanut-induced anaphylaxis without triggering IgE-mediated acute reactions.[32] However, the clinical usefulness of these approaches has not been established.

GUIDELINES

Both the American Academy of Asthma, Allergy and Immunology and the American Academy of Pediatrics have published guidelines on the management of food-induced anaphylaxis.[33,34] Patients, as well as the parents and caregivers of children with peanut allergy, must be educated to avoid accidentally ingesting peanuts, learn to recognize early signs of an allergic reaction, and learn to medicate themselves as soon as symptoms develop. All patients with peanut allergy should be given a written emergency plan and adequate doses of liquid diphenhydramine and self-injectable epinephrine for use in case they accidentally ingest peanuts. School and day-care personnel must also be educated to provide a safe environment for children with peanut allergy[35] and to recognize and treat food-induced reactions. In the event of an allergic reaction to peanuts, especially if epinephrine is used, patients should be taken to the nearest emergency room where they can be treated further and observed for at least four hours.

Whether peanut allergy can be prevented remains in question. Nonetheless, the Department of Health in the United Kingdom (and many allergists in the United States) recommend that mothers from "high-risk" families (those with a history of atopy) avoid eating peanuts during pregnancy and lactation and that they not give their infants peanut products for the first three years of life.[36]

CONCLUSIONS AND RECOMMENDATIONS

Food allergy — and peanut allergy in particular — has become a major health concern in the United States and many other westernized countries. Pending further information, it is probably wise to encourage mothers from families with a history of atopy to avoid eating peanuts during pregnancy and lactation and to avoid introducing peanut proteins to their offspring for the first three years of life. Children in whom an allergy to milk or eggs develops during the first year of life should also avoid peanuts, since other food allergies will develop in about one third of them. Any person suspected of having had an allergic reaction to peanuts should be evaluated by a specialist knowledgeable in this area. Since about one third of patients with peanut allergy are also allergic to at least one tree nut,[16] patients who have had an anaphylactic reaction to peanuts should be evaluated for nut allergy. Children younger than five years of age who are allergic to peanuts should avoid all nuts because of the risk of developing new nut sensitivities and the difficulty children in this age group have accurately identifying peanut-containing products. Physicians must teach their patients appropriate avoidance strategies and to recognize early signs of an allergic reaction and provide them with emergency plans and appropriate medications in case of an accidental peanut ingestion. Child-care facilities and schools must develop appropriate plans to protect children with peanut allergy and initiate treatment in case of an accidental ingestion. Restaurants and other public eating establishments and airlines need to be more cognizant of the needs of people with peanut allergy. Mandatory food-labeling laws and manufacturing practices should be enacted to prevent the inadvertent ingestion of mislabeled or contaminated products.[37]

If an accidental ingestion occurs, as apparently occurred in the patient described in the clinical vignette, intramuscular epinephrine and liquid diphenhydramine should be given immediately (Table 1). The patient should be brought to an emergency department as quickly as possible and treated with epinephrine, antihistamines, supplemental oxygen, intravenous fluids, nebulized albuterol, and corticosteroids, as appropriate. Because of the risk of a biphasic reaction, the patient should be observed for at least four hours before being discharged and should then be given a short course of prednisone and an antihistamine.

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