

Food Allergy

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FOOD allergy is widely perceived by the public as a major health problem.¹ Although the true prevalence of food allergy is unknown, it is probably much less common than thought. Its prevalence among children has been variously estimated from 0.3% to 7.5%,² and it is believed that the incidence decreases with age. Acute allergic reactions to foods that are clearly IgE mediated can, however, develop in adults who previously tolerated foods with impunity.^{3,4} Clinically, food-induced reactions of the immediate-hypersensitivity type are well documented and include urticaria, angioedema, and anaphylaxis. Reactions to foods mediated through antigen-antibody-complex and delayed-hypersensitivity mechanisms remain to be implicated, except in gluten-induced enteropathy and severe milk- and soy-induced gastroenteropathies in infants and children.⁵

CLINICAL FEATURES

Immunologically mediated reactions to foods are expressed clinically by a diversity of signs and symptoms, ranging from abdominal pain to generalized anaphylaxis. These clinical expressions of food allergy are influenced by factors that include the age of the patient, the quality and quantity of food ingested, and the type and extent of associated medical problems. An allergic reaction limited to the gastrointestinal (GI) tract may be expressed as nausea and vomiting; an allergic reaction in the skin by urticaria, angioedema, or atopic eczema; and a reaction involving multiple organs by anaphylaxis.

The oropharynx and the GI tract are the initial sites of exposure to food anti-

gens. Edema and pruritus of the lips, oral mucosa, palate, and pharynx may occur as food contacts the mucosa. Such reactions are transient and are not always followed by other allergic manifestations. Entry of offending foods into the stomach and subsequently into the intestine may result in nausea, vomiting, cramping pain, abdominal distention, flatulence, and diarrhea. Occult fecal blood loss, malabsorption, protein-losing enteropathy, functional intestinal obstruction, and eosinophilic gastroenteritis also have been reported in association with GI tract allergic responses.

In addition to the GI system, food allergy also can be expressed in extraintestinal target tissues, particularly the skin and, less frequently, the respiratory tract.^{4,6,7} The basis of the preferential reactivity of one system over another is unknown. The skin is a common target organ in food allergy. Skin reactions are evidenced by acute urticaria, angioedema, or both and, much less frequently, by chronic urticaria. Exacerbations of atopic eczema, asthma, or rhinitis and asthma due to foods are known to occur in children. There is insufficient information about the importance of food allergy as a trigger for these conditions in adults. Behavioral disturbances and depression as manifestations of food allergy have never been demonstrated conclusively.⁸

Systemic anaphylaxis as a result of allergy to ingested foods usually occurs within the first hour after ingestion of the offending food. The first anaphylactic episode may be unexpected or may be forewarned by minor symptoms, such as abdominal discomfort or ur-

ticaria on previous exposure to the food. Systemic anaphylaxis involves multiple target organs, as evidenced by abdominal pain, nausea, emesis, diarrhea, dyspnea, cyanosis, chest pain, urticaria, angioedema, hypotension, and shock. Treatment of food-induced anaphylaxis should be immediate and should be continued until signs and symptoms abate.

PATHOPHYSIOLOGY

Food represents the largest antigenic challenge confronting the human immune system. For sensitization to occur, it is necessary for such antigens or fragments of antigens to have contact with immunologically competent cells. There is abundant evidence that intact macromolecules of sufficient size to be antigenic pass through the epithelium of the GI tract, interact with the mucosal immune system, and also gain access to the circulation.⁹⁻¹¹ A number of factors determine the molecular size of dietary breakdown products. Ingested food is acted on sequentially by stomach acid and pepsins, pancreatic secretions, and intestinal peptidases. The mucosal endothelial cells actively absorb amino acids, small peptides, and intact proteins and the cellular lysozymes further degrade the proteins and peptides. Antigenic proteins and peptides traversing through Peyer's patches or the mucosal endothelial cells elicit an immune response, leading to active secretion of specific antibodies (preponderantly IgA) into the gut, which form complexes with their respective antigens, limiting further absorption of those antigens. Abnormalities in any of these processes can lead to increased anti-

genemia, thereby exposing susceptible hosts to sensitization. Examples of such conditions include achlorhydria, mucosal injury secondary to gastroenteritis, selective IgA deficiency, and immaturity with relative IgA deficiency. Additional factors also influence sensitization. For example, individuals responding to food proteins with antigen-specific IgE are atopic and thus, in part, seem genetically predisposed to developing immediate reactions to foods.^{9,6,7}

The majority of allergic reactions to foods are IgE-mediated, mast cell-dependent, immediate-hypersensitivity reactions. Such reactions have been transferred passively by intracutaneous injection of sera from allergic subjects into normal recipients, followed by oral challenge with the corresponding antigen.⁹ Mast cells in the GI tract mucosa reside primarily in the lamina propria, although occasionally mast cells are seen within the epithelial layer. Additional mast cells are seen in the submucosa near small blood and lymphatic vessels.¹² Human mucosal mast cells have been reported to degranulate in vitro in an IgE-dependent reaction.¹⁸ Food antigen-specific, IgE-mediated, mast cell-dependent reactions have been reported in vivo after passive sensitization of nonhuman primate ileum and colonic mucosa. Local reactions could be induced after such passive sensitization by either ingestion or direct application of the antigen.

Mast cell degranulation results in the release of preformed mediators such as histamine, chemotactic factors, exoglycosidases, tryptic enzymes, heparin, and the generation of secondary mediators, including prostaglandins and leukotrienes. The immediate consequences of the release of these mediators from mucosal and submucosal mast cells include a local change in vasopermeability, stimulation of mucus production, increased muscle contraction, stimulation of pain fibers, and recruitment of inflammatory cells.¹² Studies suggest that when ingested food antigens encounter these IgE-coated mast cells, degranulation occurs, leading to increased goblet cell activity and increased mucus secretion, edema of mucosal epithelial cell villi, increased protein loss from the gut, and increased absorption of foreign antigens.^{9,10} Intestinal biopsies performed in humans before and after food challenge have disclosed findings consistent with a similar course of events. Local intestinal anaphylaxis has been shown to facilitate the passage of macromolecules through the GI tract barrier so that they may then be distributed to other target organs, initiating degranulation of mast

cells at those sites. Such degranulation may be accompanied by an increase in plasma histamine.^{4,14}

While immediate hypersensitivity reactions can explain many reactions to foods, there is evidence that antigen-antibody complex-mediated mechanisms are also involved in milk- and soy-induced gastroenteropathies. IgG and IgM antibodies to food determinants have been demonstrated both in GI tract secretions and serum.¹⁵ Interaction of food antigen with such specific antibodies may lead to complement activation. Complement deposition has been demonstrated in GI tract tissues. Complement activation within the bowel wall could be expected to lead to mast cell degranulation through generation of C3a and C5a anaphylatoxins.

Two observations suggest that delayed hypersensitivity reactions to ingestants can occur. Oral hyposensitization against poison ivy (*Rhus dermatitis*) has led to inflammatory stomatitis, pruritus ani, and exacerbations at healed skin sites. A similar picture is observed three days after eating the inedible portion of ginkgo tree fruit. Cytotoxic-type hypersensitivity reactions have not been documented in food allergy.

DIAGNOSTIC TECHNIQUES

The diagnosis of food allergy starts with a careful history. The use of skin and radioallergosorbent tests (RAST) assist in the clinical diagnosis. Confirmation of the diagnosis, when required and when judged safe, can, however, only be obtained by double-blind or single-blind, placebo-controlled oral challenge with suspected foods.

History

A medical history should be obtained from each subject, including detailed accounts of the suspected reactions to food. Inquiry should be made as to the existence of other atopic diseases including atopic dermatitis, asthma, and allergic rhinitis and to the agents that incite these problems. The presence of one or more of these would increase the likelihood that the putative adverse reaction occurred due to an allergic reaction rather than some other mechanism. Suspected foods are identified primarily by the ingestion in some temporal proximity to the reaction and are more likely to be identified if consumed infrequently. Interestingly, only a few of the hundreds of different foods consumed cause the majority of hypersensitivity responses. Food antigens causing allergic reactions tend to be glycoproteins with a molecular weight between 20 000

and 40 000 daltons.¹⁶ These proteins, although generally heat and enzyme resistant, may be altered in some instances by food preparation. Thus, such factors as whether the food was raw, cooked, or otherwise processed may be of importance. A suspected food may fail to lead consistently to an allergic reaction. Reasons for this inconsistency include the amount consumed, the presence of other simultaneously ingested foods that may delay digestion, the state of the food, and the possibility that medications such as antihistamines may have altered the reactions. Table 6-1 contains a list of foods most commonly implicated in double-blind, placebo-controlled oral food challenges as causing immediate allergic reactions. While it is commonly believed that tomatoes and citrus fruits are frequent causes of such reactions, there is no evidence to support this from controlled studies. Moreover, the hives, which may be observed after ingestion of strawberries, have never been shown to have an IgE-mediated basis.

Foods may be contaminated by a wide variety of substances that lead to reactions that may be confused with food allergy (Table 6-2).¹⁷ Milk from cattle has been, and occasionally still is, contaminated with bacitracin, penicillin, and tetracycline that are employed to treat bovine diseases, although there are regulations to prevent such contamination. The yellow dye, tartrazine, can cause non-IgE-mediated hypersensitivity reactions in a small percentage of persons who may also be sensitive to aspirin.¹⁸ Monosodium glutamate in sufficient quantity may provoke the "Chinese restaurant syndrome," consisting of burning sensations, chest and facial flushing and pain, and pulsatile headache occurring approximately 20 minutes after ingestion.¹⁹ Bacteria and bacterial toxins may cause both GI tract and systemic symptoms, which may be confused with food allergy. A diagnosis of poisoning must also not be overlooked in the emergency department when a patient presents with a "food reaction." Scombroid poisoning, due to the ingestion of tuna and related fish containing high levels of histamine and saurine, resembles food allergy and can be confirmed by finding high levels of histamine in the implicated fish.²⁰

Intrinsic properties of certain foods lead to problems resembling food allergy. Prunes, soybeans, other beans, and onions can cause gastroenteric symptoms by irritation or pharmacologic activity. Vasoactive amines (epinephrine, norepinephrine, tyramine, dopamine, histamine, and 5-hydroxytryptamine) are found in bananas

Table 6-1.—Foods Most Commonly Implicated as Causing Immediate Hypersensitivity Reactions

Egg
Milk
Tree nuts
Peanuts
Whitefish
Crustacea

Table 6-2.—Differential Diagnosis of Food Allergy

Gastrointestinal tract disorders
Structural abnormalities
Hiatal hernia
Pyloric stenosis
Tracheoesophageal fistula
Enzyme deficiencies (primary vs secondary)
Disaccharidase deficiency (lactase, sucrase-isomaltase, and glucose-galactose)
Galactosemia
Phenylketonuria
Malignancy
Others
Pancreatic insufficiency (cystic fibrosis)
Gallbladder disease
Peptic ulcer disease
Contaminants and additives
Flavorings and preservatives
Sulfiting agents
Monosodium glutamate
Nitrites/nitrates
Aspartame, benzoates, butylated hydroxytoluene, and butylated hydroxyanisole
Dyes
Tartrazine
Toxins
Bacterial (*Clostridium botulinum* and *Staphylococcus aureus*)
Fungal (aflatoxins, trichothecenes, and ergot)
Seafood associated
Scombroid poisoning (tuna and mackerel)
Ciguatera poisoning (grouper and snapper, barracuda)
Saxitoxin (shellfish)
Infectious organisms
Bacteria (*Salmonella*, *Shigella*, *Escherichia coli*, *Yersinia*, and *Campylobacter*)
Parasites (*Giardia* and *Trichinella*)
Virus (hepatitis, rotavirus and enterovirus)
Accidental contaminants
Heavy metals (mercury and copper)
Pesticides
Antibiotics (penicillin)
Pharmacologic agents
Caffeine (coffee, tea, soft drinks, and cocoa)
Theobromine (chocolate, tea)
Histamine (fish, beer, wine, chocolate, and sauerkraut)
Tyramine (cheeses, pickled herring, avocado, orange, banana, and tomato)
Tryptamine (tomato and blue plum)
Serotonin (banana, tomato, plum, avocado, and pineapple juice)
Phenylethylamine (chocolate)
Glycosidal alkaloid solanine (potatoes)
Alcohol
Psychological reactions

(especially the peel), tomatoes, avocados, cheeses, pineapples, and wines. Sulfiting agents used to preserve fresh fruit, shrimp, and vegetables and found in wine, beer, and Mexican food can exacerbate asthma in some individuals.²¹

Several GI tract diseases are associated with acute symptoms after food ingestion. Examples include hiatal hernia, gastric and duodenal ulcers, and cholelithiasis. Gastroesophageal reflux may cause bronchial irritation, chronic cough, and wheezing in young children

and infants. Disaccharidase deficiencies may also cause acute symptoms on feeding of the offending sugar and, thus, may be confused with food allergy.

Laboratory Tests

Both in vivo and in vitro diagnostic procedures can be used to assist in making or ruling out a clinical diagnosis of food allergy. These include non-specific tests such as blood eosinophil counts, stool examinations for pH, reducing substances, blood, mucus, and parasites and specific tests designed to detect IgE antibodies to food. The latter techniques use water-soluble extracts of foods, which, unfortunately, are poorly standardized.

Skin Testing.—Skin testing with food extracts is usually done by the prick or scratch methods. If the recipient has IgE antibody to the food antigen, local wheal-and-flare reactions typical of immediate hypersensitivity are produced. Individuals may have positive skin test results in the absence of clinical food allergy (false-positive results). However, allergic reactions to foods are infrequent in the face of negative skin test results (false-negative results).^{3,5,7,22} Thus, prick skin testing seems best used to exclude the possibility that certain foods are capable of causing IgE antibody-mediated immediate hypersensitivity in given individuals. Intradermal testing is generally avoided because of a greater danger of systemic reactions as well as local, non-specific irritant reactions. Results of skin testing with selected food extracts including tree nuts, egg, milk, peanuts, crustacea, and fish correlate fairly reliably with allergic manifestations. However, patients should not be advised that they are allergic to certain foods solely on the basis of positive skin test results. Because of the risk of anaphylaxis, skin testing with food extracts should only be performed by a physician experienced in the procedure. The back provides quite sensitive areas for scratch- or puncture-type skin tests. Skin testing on the forearm, however, has the advantage of allowing application of a tourniquet should a systemic reaction occur. Application of a tourniquet delays the systemic adsorption of antigen from the skin test site while treatment is instituted for anaphylaxis.

RAST.—The RAST is used to demonstrate the presence of serum IgE antibody to a specific antigen. This test seems generally less sensitive than the puncture (prick) test.²³ Other disadvantages to the RAST include cost, the availability of RASTs for only a limited number of foods, and the delay in obtaining results. A positive RAST result

alone is no more diagnostic of food allergy than a positive skin test result. The RAST may be useful in the evaluation of certain cases of eczema, where extensive skin lesions interfere with skin testing, in the evaluation of patients with dermatographism, and in some cases of suspected food-induced anaphylaxis.

Controversial Techniques.—The procedures of cytotoxic testing, provocative subcutaneous testing, and provocative sublingual testing have been used by some in efforts to diagnose food sensitivity. In large, well-designed, controlled studies, both cytotoxic and sublingual testing have been shown to be of no diagnostic value. A 1981 position statement issued by the American Academy of Allergy reported the efficacy of all three techniques to be unproved, and held that their use should be limited to well-controlled clinical studies.²⁴

Controlled Oral Food Challenge

Double- or single-blind, placebo-controlled oral food challenge is at present the only definitive procedure for the diagnosis of food intolerance. However, this test need not and should not be used if there is a clear history of major allergic symptoms following ingestion of a specific food, such as swelling of the lips, tongue, face, or entire body, hoarseness, hypotension, or other symptoms of systemic anaphylaxis. Furthermore, no food challenge is without risk of side effects, and the patient must be made aware of these dangers. Therefore, such procedures should be done only under the supervision of a qualified physician, and are often, but not necessarily, done in a hospital setting.

Food challenge may be performed in an open, single-blind, or double-blind manner. In an open food challenge, both the patient and the physician are aware that a specific food is being administered. In a single-blind food challenge, only the patient is unaware of what food is being given. In a double-blind food challenge, the patient remains unaware of whether a specific food or a placebo is being given. A "neutral" observer such as a physician or nurse is also unaware of what is being administered. Results are scored by the patient and the medical observer. Double-blind challenge has the advantage of objectivity. Food challenge is most reliable when the resulting symptoms, such as erythema, urticaria, rhinitis, vomiting, diarrhea, or asthma, can be observed directly in such a controlled situation. During challenge procedures, the patient should remain on a limited diet, using foods

known not to cause symptoms. The amount of food administered as a test dose is governed by the apparent degree of suspected hypersensitivity, ranging from 10 mg when the history suggests that small amounts of foods provoke symptoms to 8 g when only large amounts of foods lead to difficulty. Suspected foods may be administered by masking within other foods, by placement within opaque gelatin capsules, or by insertion via a nasogastric tube. A single gelatin capsule holds from 400 to 600 mg of dried food. It must be remembered in calculating equivalent doses of dried foods that water content varies widely. Eleven grams of dried milk is equivalent to $\frac{1}{2}$ cup (4 oz) in the liquid state. At times, challenge must be performed with, for example, raw fruits or vegetables since cooked or dried foods result in destruction of relevant allergens. The patient should be observed for a period exceeding the time determined in the history to have elapsed between food ingestion and symptoms. If no symptoms are produced by the test dose, the challenge should be repeated using increasingly larger doses (twofold to tenfold increments) until the amount of food ingested exceeds the amount that, by history, elicited the alleged reaction or until approximately 8 g of lyophilized dehydrated food is reached. If 8 g is tolerated, the food in its natural form and usual amount can be administered to the patient. If no reaction ensues, the food can be added to the diet after the patient is informed that no reaction was induced by it. This procedure is repeated until all incriminated foods have been examined.

A single unequivocally positive reaction, such as hives or asthma, to a food tested in a double-blind, placebo-controlled food challenge may be taken as evidence of an acute adverse reaction to that food. However, in chronic disorders where wheezing or hives occur several times a week, two to three sets of positive challenges along with an equivalent number of negative placebo challenges are necessary to establish an association. If placebo challenges are frequently positive, no association between the food and symptoms can be made. In cases of subjective complaints, however, a statistically significant number of positive test responses to a suspected food, along with an equivalent number of totally negative placebo test results, also are necessary to substantiate diagnosis. Acceptance of a positive test result does not prove that an immunologic mechanism is responsible. Adverse reactions may also be due to conditions such as disaccharidase deficiency.

Elimination Diets

Although much more tedious than in-hospital, placebo-controlled oral challenges, this approach has been used as an outpatient diagnostic aid for many years. The principle is somewhat the same, ie, if the offending food is removed from the diet of the affected individual, the food-induced illness will resolve. The likelihood of establishing a diagnosis using elimination diets is greater when fewer foods are responsible for the symptoms. Such diets are often not necessary in the diagnosis of food-induced anaphylaxis where the offending foods may be obvious. In cases of anaphylaxis where the offending food is not well delineated, no encouragement should be given to the patient to eat foods suspected of causing the anaphylactic reaction. Elimination diets followed by return of suspected foods to the diet should be applied only in situations where symptoms are not life threatening, such as chronic hives or rhinitis. The need for extreme caution in reintroducing suspect foods on an outpatient basis is demonstrated by the precipitation of anaphylaxis in four of 80 patients with eczema during challenge procedures.²⁶ It should be remembered that changing the type and amount of foods may also alter symptoms of such diseases as disaccharidase deficiency, gluten-sensitive enteropathy, and cystic fibrosis.

It is useful for the patient to remain on his or her usual diet for approximately ten to 14 days before any special diet is initiated. During that time, the patient should record the type and amount of foods ingested and the occurrence and character of adverse reactions. This record is useful in searching for suspected foods and in establishing baseline symptoms against which the success or failure of elimination diets may be measured. The elicitation of symptoms may be too infrequent to appreciate a change in their occurrence during the period of an elimination diet if symptoms fail to occur within this period. If one to several foods are prime suspects as the cause of symptoms, the initial elimination diet can consist simply of removing these foods. Care must be taken that suspected foods are not inadvertently consumed while hidden in other foods. For example, eggs are commonly found in such food mixtures as mayonnaise, salad dressings, and ice cream.

Initiation of a severely limited diet is warranted if removal of one or several foods from the diet is not successful in eliminating symptoms or if multiple food sensitivities are suspected. Severe elimination diets, especially in children,

can be used for only one to two weeks. More prolonged diets can lead to severe malnutrition. Extensive elimination diets include the following: for infants younger than 3 months of age, milk substitute alone (casein hydrolysates, such as Nutramigen or Pregestimil); for those 3 to 6 months, milk substitute and rice cereal; for those 6 months to 2 years, milk substitute with vitamin supplement, rice cereal, applesauce, pears, carrots, squash, and lamb; and for older children and adults, lamb and rice. Caution must be taken to instruct the patient to take nothing by mouth but the foods on the diet and water. Oral medications including aspirin, vitamins, and laxatives must be avoided when possible. Continuation of symptoms while following restricted diets indicates that symptoms are not due to foods or other avoided substances. The unlikely possibility that individual foods on the restricted diets are causing symptoms may be eliminated by substituting other foods known not to correlate with symptoms. However, if symptoms resolve on the restricted diet, resumption of a normal diet should be accompanied by a return of symptoms; and subsequent resumption of the restricted diet should alleviate these symptoms. Such cycling must reproducibly eliminate or provoke symptoms to allow the conclusion that symptoms may be secondary to foods. If a relationship to diet is established, foods eliminated but not clearly implicated in causing symptoms should be returned to the diet individually at intervals of three to four days. Foods returned to the diet without induction of symptoms may remain in the diet. Foods provoking symptoms should be removed until the procedure is completed. If resumption of symptoms is associated with the introduction of specific foods, then this cause-and-effect relationship must be verified by disappearance of symptoms on elimination of that food. Although the procedure described may seem more applicable to outpatient evaluation, this procedure is unblinded and, therefore, is subject to biased interpretation by the patient and the physician. Psychogenic factors cannot be excluded and misdiagnoses could reinforce aberrant behavior. Consequently, single- or double-blind, placebo-controlled oral food challenge under direct medical supervision is necessary to diagnose food hypersensitivity accurately.

PREVENTION AND TREATMENT

Although the relative merits of avoiding highly allergenic foods during pregnancy and breast-feeding are uncertain, there is a convincing rationale for this

practice, particularly in families where one or both parents have atopic disease.²⁶ It is known that food antigens can cross the placenta and that they are also secreted into breast milk. Similarly, there is a sound rationale for avoiding exposure of immature or inflamed gastric mucosa to such foods. Thus, if the ideal infant food, breast milk, cannot be given, artificial feeding should consist of casein hydrolysate formulas (eg, Nutramigen and Pregestimil) rather than soy formulas if (1) one is dealing with an infant with atopic allergy, (2) one is dealing with an infant from a family with a high incidence of atopic disease, or (3) one is considering the type of formula to use for an infant recovering from a bout of acute gastroenteritis.

The only specific treatment of food allergy is avoidance. In those cases where the allergen is a common hidden ingredient of prepared foods and the reaction may be life threatening, it is necessary for the patient to have, and to be prepared to use, epinephrine.²⁷ Such individuals should wear a bracelet or a similar article identifying their sensitivities and reactions. Less severe symptoms following inadvertent ingestion can be controlled by administration of an antihistamine. Prednisone has been used successfully in treating eosinophilic gastroenteritis, which in some instances is associated with food allergy.²⁸

CONCLUSIONS

To diagnose food allergy, it is first necessary to exclude the possibility that

one of a number of other causes might be responsible for the signs and symptoms observed. Once this is accomplished, an attempt should be made to identify potential foods responsible for eliciting symptoms by history and prick or scratch skin testing with food extracts. Double- or single-blind, physician-supervised oral food challenge should be employed when the diagnosis is uncertain or the particular food or foods causing symptoms are unclear, as this is presently the only unequivocal way of documenting a specific food allergy. In some instances where such challenges are not possible, an elimination diet carried out at home may lead to a clinical diagnosis of food allergy. The basic treatment for food allergy is avoidance.

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