The Pediatrician's Guide to Food Allergy

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Food allergy occurs in as many as 5% of infants less than 1 year old. Most food sensitivities disappear by age 3 to 4. Most immunologically mediated food allergy reactions are due to type I IgE mechanisms, with skin, gastrointestinal, and respiratory signs and symptoms the most common manifestations. Using the double-blind, placebo-controlled food challenge (DBPCFC) technique and atopic dermatitis as a model, the most common foods to which children are allergic are cow's milk, eggs, peanuts, wheat, fish, and soy proteins. Anaphylactic sensitivity in older children often involves crustacean seafoods (eg, shrimp), nuts, peanuts, fish, and eggs. Such sensitivities may be lifelong.

Infant colic is not due to allergy but may be improved with dietary manipulation. Food-induced diarrhea may be due to food intolerance or allergy. In severe milk-induced enterocolitis, casein-hydrolysate formula rather than soy formula is advised. Specific foods can exacerbate atopic dermatitis; their elimination from the diet will improve the condition. Gluten sensitivity is both a food intolerance and food allergy. A few cases of the attention deficit disorder can be improved with a diet absent of food dyes, particularly yellow #5. Although migraine headaches can be triggered by a number of factors, food allergy is not included. Pulmonary infiltrates due to cow's milk hyperimmune reactions (the Heiner syndrome) is thought to be a type III milk immune-complex reaction. In the infant, asthma and allergic rhinitis may be a manifestation of food allergy.

The diagnosis of food allergy depends upon the history, an IgE-mediated skin prick test or radioallergosorbent test, followed by dietary elimination, open challenge, or DBPCFC. In food anaphylaxis management, however, no food challenge is advised because of the risk. Some tests of unproved validity have been promoted in the diagnosis of food allergy.

The principal treatment, strict avoidance of a specific food, is sometimes difficult. Because anaphylaxis is a life-threatening risk, patients are advised always to have an aqueous epinephrine 1:1,000 self-injector unit available. Manipulation of the diet of the pregnant woman, nursing mother, and infant helps reduce the risk of allergy in the infant. Medications are of limited use in food allergy prevention, but specific drugs such as epinephrine and cortisone are helpful in treating allergic reactions. (Henry Ford Hosp Med J 1988;36:198-203)

The Definition

People often use the word "allergy" to describe the unpleasant and usually harmless effects resulting from exposure to something, almost anything (1). A better term is "adverse reaction." Medical professionals reserve the term allergy to refer to an adverse reaction caused by or affected by an immunologic event, especially a type I (Gell and Coombs') IgE-mediated one. Thus, allergy to cow's milk refers to an IgE-mediated reaction to a protein in the milk. All other adverse reactions to a food are called intolerances. The cause of these reactions may be known as in the reaction to the lactose sugar in cow's milk which occurs in patients lacking the enzyme lactase in their bowel wall, or unknown as is the case of infant colic apparently associated with the ingestion of cow's milk-base formula.

The Condition

While food intolerances are more common, food allergy does exist. Most true food allergy problems occur in early infancy. The exact incidence is unknown, but the mother perceives her child's adverse reaction. Studies of 473 unselected infants in Sweden and 501 successively born infants in the United States revealed the suspicion of an adverse reaction to a food in 20% and 28%, respectively (2,3). Most of the adverse reactions, such as a rash around the mouth or diarrhea, were caused by fruits. The organic acids in the fruits most likely caused the rash, and the fruit sugar caused the diarrhea. These food intolerances are usually diagnosed by diet elimination and challenge one month later. Reactions to other foods such as cow's milk and eggs, confirmed by either open challenge (5%) or double-blind, placebo-controlled food challenge (DBPCFC) (3%) are most likely food allergies (3,4).
The Foods

Most children who are allergic to foods are allergic to one or two foods at most, not multiple foods as is commonly assumed. The best model to study the relationship of foods to allergy has been atopic dermatitis. Utilizing the DBPCFC method, Sampson (5) not only proved specific food sensitivity in a group of patients but also related it to possible in-vivo (immediate reacting skin test) and in-vitro (radioallergosorbent test [RAST]) evidence of IgE food allergen specific antibodies. These methods can predict 90% those foods to which children become allergic. They are, in decreasing order: cow’s milk, eggs, peanuts, wheat, fish, and soy protein. Although unlikely, a child with sufficient exposure can become allergic to any other single food protein.

Foods that need to be considered in older individuals, including adolescents, are those commonly associated with urticaria and systemic anaphylaxis (Table). These include crustaceans (shrimp, crab, lobster) and tree nuts (walnuts, cashews, Brazil nuts), as well as eggs, peanuts, and fish (6). Other foods to be considered in older patients are those associated with local anaphylaxis (isolated swelling and itching of the mouth) which is caused by a cross-reaction between the food and inhaled pollen sensitivity. These foods, usually melons (watermelon, cantaloupe) and bananas, cross react with ragweed pollen which is found only in North America (7). Less common in the United States is local anaphylaxis with carrots, parsnips, apples, potatoes, and hazelnuts (which is associated with birch pollen sensitivity) (8).

A new form of anaphylaxis is associated with exercise, particularly jogging. In some cases the urticaria or shock occurs only when the patient exercises after eating a particular food such as celery or shrimp (9).

The Natural History of Food Allergy

Most suspected and proved allergic reactions to food occur during the first year of life. In a prospective study of 501 children, Bock (10) found that only two of 15 cases of proved allergy (by DBPCFC) during the first year of life were still reactive at 13 to 24 months of age and that none of the 15 were reactive at 25 to 36 months of age. The mean age of initial onset of symptoms was six months, and the mean time until the food could be safely reintroduced was 14 months. The foods most likely to be eliminated from the diet because of an untoward reaction were eggs, cow’s milk, and soy protein. Bock (11) also found that seven of nine children who had had life-threatening anaphylaxis to cow’s milk, eggs, or soy within the first two years of life later tolerated either normal amounts (four patients) or small amounts of the food.

For many of these foods, such as cow’s milk and eggs, which had caused a reaction in early infancy but which were tolerated by age 3 or 4, Foucard (2) found that IgE evidence of sensitivity (skin-test positivity or in vitro IgE allergen specific antibody-RAST positivity) could still be demonstrated. Bock (10) showed that children who developed their food allergy after their third birthday were less likely to become tolerant to the food one to seven years later in contrast to those who had experienced the reaction before their third birthday. The foods most likely to continue to produce clinical reaction after accidental reexposure or challenge were peanuts, tree nuts, and fish. These sensitivities may be lifelong.

Clinical Reactions

Anaphylaxis

Anaphylaxis may be mild (urticaria) or severe (systemic anaphylaxis). Systemic symptoms include laryngeal edema, bronchial spasm (asthma-like symptoms), shock, and cardiovascular collapse. Urticaria, common in infants and children, is frequently associated with viral infection, medication, and food ingestion. The condition is usually not serious, frequently self-limited, and easily managed. When associated with systemic symptoms of anaphylaxis, however, urticaria is potentially life-threatening. Any food may be associated with urticaria/systemic anaphylaxis. Cow’s milk, cow’s milk-base formula, and eggs are most likely causes for the problem in infants, whereas peanuts, nuts, fish, and shrimp are more likely in older children.

Most skin reactions in early infancy such as simple urticaria and red rash around the mouth caused by fruits and juices are not due to IgE-mediated reactions to those foods but to the organic acids in them (especially citrus fruits and tomatoes (3). A rash immediately upon eating strawberries in older individuals is usually due to nonimmunologic release of histamine—not to allergy.

Colic

Colic is a common problem which occurs in approximately 20% of all infants whether breast- or formula-fed (12). While the exact etiology of colic is unknown, many theories have been proposed (13). Cow’s milk food allergy has been postulated as a cause of colic for over 25 years, but this has never been conclusively demonstrated. Although colic may disappear with no diet change, controlled studies have demonstrated that some infants are better when fed either a soy-base or a casein-hydrolysate formula (14).

Diarrhea

The most common cause of loose stools in infants secondary to food ingestion is sugar overload from ingesting fruit or fruit juice (2,3). Furthermore, some fruits contain sorbitol, a
crystalline alcohol formed from sugar, which is a laxative. Probably the second most common cause is lactose intolerance secondary to viral or bacterial enteritis. With the temporary loss of the capacity to digest lactose found in cow’s milk, the child develops diarrhea when given milk-based formula. Milk allergy is more common in the first year of life, and diarrhea is a common manifestation of allergy to this food protein (2,3). Diarrhea lasting over one month can be caused by either food allergy or food intolerance. Enterocolitis, the most serious food-induced diarrhea, is usually manifested by bloody diarrhea (15). This condition usually results from allergy to cow’s milk. Severely allergic infants and children may develop allergy to soy protein when they are fed a soy-base formula to treat the diarrhea induced by cow’s milk. For this reason, the Nutrition Committee of the American Academy of Pediatrics advises against the use of soy formula for children with milk allergy (16). Instead they recommend use of a casein-hydrolysate-base formula, such as Progestimil™ or Nutramigen™ (Mead Johnson Co, Evansville, IN), for children with gastrointestinal complaints.

Commercial soy formula, containing sucrose instead of lactose, is helpful for primary or secondary lactose intolerance (17). Some cases of prolonged diarrhea may be relieved by a special formula of soy protein and lactose (18). In children with intermittent loose stools separated by long intervals of normal bowel movements, allergy is highly unlikely.

**Eczema**

Eczema or atopic dermatitis occurs in 1% to 4.5% of American children (19). Food allergy is involved in the pathogenesis of this condition in some cases (5,19). Using the DBPCFC technique, specific foods have been shown to cause a flare-up in the rash, associated with the release of mediators such as histamine and accumulation of eosinophils in the skin. Positive IgE immediate reacting skin test reaction to the specific food or the presence of IgE food allergen antibodies (RAST) to DBPCFC correlated closely with the presenting clinical history of food sensitivity.

**Gluten sensitivity**

Gluten sensitivity enteropathy or celiac disease is a well-known reaction to gluten and is usually associated with wheat ingestion. The malabsorption which is the primary manifestation of the disease varies in degree depending on the extent of intestinal involvement. In classic celiac disease the damage is caused by the toxic effect of undigested gliadin on the epithelial cells of the small bowel. The reaction is probably a food intolerance which is influenced by immunologic events, probably cell-mediated sensitivity (Gell and Coombs’-type IV) (1,20).

**Hyperactivity**

The attention deficit disorder (ADD), first described by Kaufman in 1845, is a term used to describe a child who is difficult to discipline or who receives poor grades in school (21). This condition can occur with or without hyperactivity and has been estimated to involve between 5% and 10% of American school children. In 1973 Feingold (22) claimed that a diet free of food additives (especially food dyes) and natural salicylates would cure or improve this condition at least 50% of the time. The Feingold hypothesis was tested in several well designed clinical studies. In evaluating this theory, a National Institutes of Health Consensus Development Conference found that: 1) the Feingold diet may be helpful in a small number of younger children (preschool age) with the ADD, but not 50% as Feingold stated; and 2) the adverse effect on children with ADD was due to a drug-like action from food colors, particularly yellow #5, not allergy.

ADD is frequently misdiagnosed. Basing a diagnosis simply on the activity level of the child is risky since many children without this condition are very active at home and at school. Because allergy occurs in 20% of children and overactivity is also common, it is not unusual to find both conditions in the same child even though they are not directly related.

**Migraine**

Headaches are common among people from a variety of socioeconomic, cultural, geographic, and ethnic backgrounds (23). Migraine or “vascular” headaches were described over 25 centuries ago by Hypocrates. The migraine syndrome is a genetic disorder inherited as an autosomal dominant trait with greater penetrance in females, or is polygenic. The family history is positive in 65% to 90% of patients. The prevalence of migraine is 15% in adult men and 25% in adult women. By age 7, 1.5% of children have migraine headaches, and by age 15 the incidence increases to 5%.

Migraine attacks may be initiated by diverse factors including anxiety, stress, fatigue, excessive sleep, minor head trauma, exercise, travel, menses, illness, diet, hunger, odors, light, and medications. It has been suspected but not proved that naturally occurring or added chemical agents in foods, such as tyrosine (cheese and chocolate), histamine (red wine), and caffeine (coffee, cola), may trigger the migraine headaches (24).

A possible relationship between migraine and food allergy was proposed as early as 1913 but has remained unproved (25). This theory was recently examined in two separate studies by the DBPCFC technique (24,25). In an English study, Egger et al (24) evaluated 40 of 88 children with migraine in whom diet resulted in a decrease in headaches. Over 55 different dietary substances were identified as triggers. These included not only food “allergens” but also nonprotein foods and food additives such as tatarazine (yellow dye #5), benzoic acid (preservatives), and sugar. Of the 88 patients, 52% were shown to be allergic by having one or more positive immediate reacting allergy skin tests to common allergens. However, there was no difference between the allergic and nonallergic groups in response to the diet, and specific food allergy tests correlated with food challenge in only three of the 40 children (24).

In studying 43 adult migraine patients, Mansfield et al (25) found that food allergy skin tests identified significant numbers of patients who improved with food elimination (11 of 16 in the positive skin test group versus two of 27 in the negative skin test group). In seven patients the specific migraine-provoking food was confirmed by DBPCFC. In two of these cases, a rise in the plasma histamine correlated with the headache. This finding has
Respiratory allergies

Rhinitis and asthma secondary to food allergy are usually a problem only in children (6). In Bock's (3) survey of 501 unslected infants over the first year of life, nasal congestion, rhinorrhea, coughing, and wheezing due to food ingestion ranked third to gastrointestinal and cutaneous signs and symptoms. DBPCFC confirmed one case of allergic nasal congestion. This technique has also confirmed asthma as a manifestation of food allergy in older children (28). When Sampson and Albergo (29) used DBPCFC in 132 cases presenting chiefly with atopic dermatitis, 85% of the positive challenges were associated with a skin rash flare. However, only 28% of these patients manifested a skin rash as the only symptom of the food allergy reaction. Of the total group who reacted, 57% developed gastrointestinal complaints (nausea, abdominal pain, vomiting, and diarrhea), and 36% of the positive challenge cases developed respiratory symptoms with or without rash or gastrointestinal symptoms. Respiratory symptoms that occurred with challenge included nasal congestion, rhinorrhea, sneezing, stridor, and wheezing.

The Diagnosis

Most true food allergy reactions in children resemble allergic reactions from other substances, eg, drugs, pollens, cats. Systemic anaphylaxis, urticaria, and atopic dermatitis as well as both upper and lower respiratory allergic symptoms are easily identifiable. More difficult to associate with food allergy are gastrointestinal complaints in which food intolerances (such as lactose) must be considered along with nondiet-related conditions. Those complaints that do not resemble the signs and symptoms of allergic reaction are usually not caused by food allergy. Problems such as hyperkinesis, behavioral abnormalities, and migraine headache are included in this category. The history of a relationship between a specific food reaction and the allergic signs and symptoms is usually reliable in cases of acute urticaria, systemic anaphylaxis, and respiratory allergic reactions. Usually the manifestation of allergy occurs within minutes to hours of exposure. Foods such as eggs and cow's milk in infants or peanuts, fish, shrimp, and nuts in older children are most often implicated. With atopic dermatitis or gastrointestinal complaints, however, the history of specific food sensitivity is often unreliable (5,19).

Sampson and Albergo (29) found that the most reliable predictors of specific food sensitivity in atopic dermatitis were the immediate-reacting IgE prick skin test (ST) or the in vitro food allergen specific RAST. In most cases, using the atopic dermatitis model and the DBPCFC endpoint, five foods were involved—cow's milk, eggs, peanuts, wheat, and soy beans. If the ST was 2+ or greater with these foods, the likelihood of the DBPCFC being positive was about 50%. If the RAST to any of these foods was positive, the likelihood of a positive challenge was between 40% and 50%. With other foods the likelihood of a positive DBPCFC was less. These studies show that an individual child can have IgE antibodies to a food but be able to tolerate the food in the diet.

When foods have been identified to which the patient may be allergic, specific challenge is necessary to confirm a specific sensitivity (30). Except in the case of anaphylaxis, such a challenge can be open or the DBPCFC method can be utilized (30).

In the case of systemic anaphylaxis, there is usually enough circulating food-specific IgE available to produce a positive in vitro RAST, especially if the investigation is done within a relatively short time of the reaction. Therefore, skin testing may be avoided. If a positive food RAST is found, a presumptive diagnosis of food anaphylaxis is made and no challenge is advised. If the history is suggestive of a food allergy, skin tests to foods are positive, and systemic anaphylaxis is not involved, the patient is given a diet containing nonallergic foods for two weeks (31). This is followed by open challenge over three to five days with specific foods. Those foods that are tolerated are added to the basic diet, and the child is challenged with additional foods. One may not assume that children who are allergic cannot tolerate a given food simply because of a history or a positive skin test. Allergy diets are not intended to be therapeutic but rather diagnostic.

A negative food allergy ST or RAST in a suspected food-allergic patient is perhaps of greater value, for when these are negative the DBPCFC will almost always be negative also (29). Other immunologic tests, such as cow's milk serum precipitans, are occasionally helpful. However, some food allergy tests of unproved validity have been promoted. These include the cytotoxic food test, the provocation and food neutralization test, and in vitro assays for IgG food antibodies (32). The latter test deserves special mention, since it is gaining in popularity. All normal individuals make IgG antibodies to the food they ingest. Patients with IgA deficiency and with the Heiner syndrome (cow's milk antibodies) make more than the usual amount of IgM and IgG food antibodies. Except in these cases, there is no correlation between the level of IgG food antibodies and clinical allergy.
Management of Food Allergies

When food allergy is diagnosed, specific food avoidance is the only preventive treatment advised. The natural history of food sensitivity must be considered in infants. Allergies to cow’s milk and eggs are usually self-limited, and these foods are tolerated when the child is a few years of age. Bock (30) recommends open challenge at six-month intervals. For an infant below age 1, food rechallenge should be postponed until the child is 2 or 3 years old. Some indication of decreasing immune sensitivity may be obtained by serial IgE food RAST assays.

A special problem exists for the patient who is egg allergic and who requires the measles, mumps, and rubella (MMR) vaccination at 15 months of age. Herman et al (33) found that the vaccine contained enough egg protein to stimulate an allergic reaction in a few infants. These infants can be safely skin tested to the MMR vaccine, and if positive, can be quickly “desensitized” and safely immunized.

When cow’s milk or cow’s milk base-formula induces severe enterocolitis, avoidance of soy protein as well as milk protein is advised because of the risk of sensitization to soy (15,16). A casein-hydrolysate formula is preferred. In prolonged infant diarrhea, the specific sugar in the formula is also important (17,18). In the Heiner syndrome, cow’s milk protein avoidance is essential for the affected infant (26). For unknown reasons this condition usually disappears in time (24).

A diagnosis of potentially life-threatening food anaphylaxis usually requires specific food avoidance for an indefinite period. This course is also essential in cases of other proven IgE anaphylactic sensitivity, eg, penicillin or hymenoptera. Although the incidence of allergic anaphylactic reaction decreases with age, the sensitivity may be lifelong in some patients.

Fish sensitivity is of worldwide concern. The risk of reaction exists not only with ingestion or skin contact but even when the patient is simply near the fish. Fish protein is aerosolized, and the odor of a fish market and the steam from cooking fish constitute a significant risk to these patients (34). Potent food allergens such as cow’s milk and eggs can initiate an anaphylactic reaction in previously sensitized nursing infants if the mother ingests the food and transmits the allergen via breast milk.

In the United States, peanut anaphylaxis is a concern. The risk in this generally long-lasting sensitivity is that increasingly peanuts are added to a wide variety of cooked and prepared foods—bakery products, salads, candy, artificial cashew nuts, even chili. For the sensitive patient, eating such prepared foods can be life-threatening.

Anaphylactically sensitive patients are advised to carry injectable aqueous epinephrine in the event of a food allergy exposure. The most convenient device available is a self-injecting unit, Epi Pen® (0.03 mL) or Epi Pen Jr® (0.15 mL) (Center Laboratory, Port Washington, NY). One of these self-injector units should be kept in the house, one in the car, and one on the person. If anaphylaxis occurs, the self-injector device can be jammed into the thigh and the spring-loaded needle will penetrate clothing. A dose of 1:1,000 aqueous epinephrine is injected, and the patient should be taken to the nearest hospital emergency room (35).

Preventive manipulation of the diet of infants, pregnant women, and nursing mothers has been studied for 60 years. Evaluation of conflicting results indicates that breast-feeding for six months with delayed introduction of solid foods reduces the risk of atopic dermatitis and food allergy in infants from allergic families (36). However, alteration in both the child’s and the mother’s diet is difficult to achieve.

The use of medications to treat food allergy is limited to epinephrine for acute anaphylaxis, bronchial dilators to treat asthma, H1 antihistamines to treat urticaria and rhino-conjunctivitis, and corticosteroids to treat severe gastroenteritis and life-threatening anaphylaxis (35,37). Sodium chromoglycate which prevents local mast cell degranulation has been proposed as a preventive oral agent for gastrointestinal food allergy. Although several European and United States investigators reported encouraging results with this drug, only one group used the DBPCFC method to define a study population of food-sensitive patients. In this study of children allergic to eggs, oral chromoglycate was not effective in preventing food allergy signs and symptoms.

H2 antihistamines have been advocated to treat chronic urticaria and when combined with H1 antihistamines suggested as preventive agents before exposure to foods known to produce symptoms. Ketotifin, a drug not yet released in the United States, has also been shown to be a preventive medication for patients with either food allergy or food intolerance.

References

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