

Delayed-Onset Food Allergies

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In 1906, Clemens Von Pirquet, M.D., the noted Austrian pediatrician, coined the term allergy from the Greek “allos” (meaning changed or altered state) and “ergon” (meaning reaction or reactivity) to describe patients with excessive physiologic responses to substances in their environment.

Currently, 50 million Americans suffer from allergies on a yearly basis, with allergy ranking as the sixth leading cause of chronic disease and costing the U.S. health care system \$18 billion per year.¹ In fact, 16.7 million office visits to health care providers are attributed to allergic rhinitis alone.² At all ages, allergic rhinitis without asthma is reported by nearly 90 people of every 1000.³ In 1996, estimated U.S. health care expenditures attributable to sinusitis were more than \$5.8 billion.⁴ Two recent estimates of allergy prevalence in the United States were 9 and 16 percent,⁵ while the prevalence for specific allergic conditions, such as allergic rhinitis and atopic dermatitis, have increased over the last 15 years.^{6,7} What is even more alarming is the fact that these numbers continue to increase at a rapid rate. These statistics reflect the prevalence of clinically diagnosed, commonly established allergic conditions. Food allergy is one type of condition that is not always easy to recognize and, therefore, treat appropriately.

Food allergy is a complex of clinical syndromes resulting from sensitization to one or more foods whereby symptoms manifest locally in the gastrointestinal (GI) tract or elsewhere in the body as a result of immunologic reactions. Numerous food-based allergic syndromes with manifestations other than classical allergic symptoms are misdiagnosed and are, therefore, medically mismanaged. Delayed patterns of food allergy are not always clinically obvious and are generally unrecognized, because of the delay in symptom onset of hours to days.

The relative neglect of food as an allergenic factor in conventional medical practice has led to a gap in the management of patients with these allergies and a void in the understanding of the disease process involved. Because of this, food allergies other than type I, immediate-onset allergies are often unacknowledged in clinical medicine and research. Yet, food allergies that are attributable to type III, delayed-onset allergies have been implicated in numerous medical conditions, ranging from childhood hyperactivity to migraine headaches.

The concept of delayed-onset food allergies is not new. In the 1920s, reactions to food were linked, via experiments, to such physical symptoms as colitis, diarrhea, bladder pain, and Meniere’s syndrome.^{8,9} Other experiments were performed, demonstrating the ability of ingested food antigens to penetrate the GI barrier and become affixed to dermal mast cells.^{10,11} Food allergies other than type I were described in the 1930s, with reports of delayed symptoms of hours to days following the ingestion of suspect foods.¹²

A Review of Immunity and Allergy

The two types of acquired immunity, depending on the primary immune-cell response, are:

- (1) The *humoral* response primarily involves production of antibodies from B cells. Of the five major classes of immunoglobulin (Ig)—IgA, IgD, IgE, IgG, and IgM—IgE typically responds to parasitic infections and is the prime antibody that provokes immediate hypersensitivity allergic reactions (the majority of clinically diagnosed food allergies). IgA, IgD, IgG, and IgM antibodies are typically involved in longer-term immunologic processes; IgG is the largest portion of the 80 percent of total circulating antibodies (21). Of the five classes of immunoglobulins, IgG, IgM, and IgE are known to be involved in hypersensitivity reactions.
- (2) *Cell-mediated* immune responses typically involve destruction of infected cells by cytotoxic T cells or destruction of intracellular pathogens by macrophages activated by Th1 cells. Th1 and Th2 cells can also contribute to humoral immunity by inducing various subclasses of IgA, IgE, and IgG to react.

The mechanisms of immune-mediated tissue injury and disease fall into four major categories:

- (1) *Type I immediate hypersensitivity*—These IgE-mediated reactions (e.g., allergic rhinitis, asthma, anaphylaxis, in the clinical subgroups atopy and anaphylaxis) occur within minutes with late-phase inflammatory responses that may occur hours later. The reactions involve vasodilation, smooth-muscle contractions, and mucous-gland secretions.
- (2) *Type II antibody-mediated (cytotoxic) hypersensitivity*—These reactions (e.g., hemolytic anemia, Rh-factor hemolytic disease) involve specific reactions of IgG or IgM to cellular antigens and include activation of a complement cascade and cell destruction.

- (3) *Type III immune complex-mediated hypersensitivity*—These reactions (e.g., serum sickness, Arthus reactions) involve IgG or IgM forming complexes with allergens to activate a complement, resulting in a rise in inflammatory mediators.
- (4) *Type IV T-cell-mediated hypersensitivity (delayed hypersensitivity)*—These reactions (e.g., contact dermatitis, tuberculin reactions) are mediated by T-helper lymphocytes, not by antibodies and occur when contact with an allergen leads to dermal inflammation, with a latency period of 1–2 days after contact.

The Complex Roles of Immunoglobulins

Food allergies, including immediate hypersensitivity reactions involving IgE and other, delayed hypersensitivity reactions involving other immunoglobulins, contribute to immune-mediated tissue injury and disease.

IgE antibodies are thought to trigger allergic reactions when crosslinking occurs on GI mast cells, resulting in a cascade of histamines and leukotrienes. Histamine-receptor activation is one possible mechanism for underlying cellular pathways that cause the barrier function of the intestinal epithelium to break down.¹³ The onslaught of previously mentioned inflammatory allergic molecules and their alteration of intestinal permeability permit food macromolecules to pass through the mucosal serosa. Once food antigens are in circulation, they may predispose other organs and systems of the body to allergic reactions.

In addition, IgG antibodies have been shown, experimentally, to increase the permeability of the intestinal wall.¹⁴ Intestinal permeability has been indicated as a precipitating factor in allergic diseases, such as chronic urticaria.¹⁵

The majority of food allergies are IgE-mediated and the amount of evidence on this immunoglobulin as a *marker* for food allergy is extremely large and is increasingly more common. However, the significance of food-specific serum IgG4 antibody in *food allergy is unclear* although concomitant elevations of both IgE and IgG are found in various food allergies.¹⁶ This does not imply, necessarily, that these IgG levels are *causing* the allergy symptoms but rather that IgG is somehow involved in the allergy process.

Although IgGs are present in the food allergy reaction, it is unknown if these antibodies are *contributing* to the allergic process and concomitant symptomatology or if they provide a type of blocking mechanism *against* IgE antibodies involved in the allergic process.

For example, two common food allergens, peanut and ovalbumin, elicit specific IgG antibody responses that are measured using enzyme-linked immunosorbent assays (ELISAs) as well as testing for IgE responses.¹⁷ It has been suggested, however, that IgG is responsible for long-term reactivity to allergens because of the extended life of IgG antibodies in the serum. IgE has a half-life of only 1–2 days (in circulation) while mast cell-committed

IgE has an approximate half-life of 14 days. Alternatively, IgG has a half-life of approximately 21 days in circulation, with a half-life on bound mast cells of 2–3 months.¹⁸ The conventional radioallergosorbent test (RAST) and skin testing of food allergies are not wholly adequate for diagnosing an IgG-related allergy because these tests mainly reveal the presence of IgE-related allergies.

The Etiology of Food Allergies

The GI tract plays a pivotal role in the mucosal immune response. While permitting the absorption of nutrients from the intestinal lumen to the systemic circulation, the GI tract also protects the body against invasion from microbes and other antigens by inducing an immune response. Dysfunctioning of oral tolerance—the decrease or downregulation of the immune response, allowing benign antigenic substances access to the systemic circulation without the initiation of an immune response—can lead to the development of food allergen reactivity.¹⁹

Some scientists say that this dysfunction may be caused by exposure to high doses of antigens, which override the protective mechanisms,

but other scientists question if this is, indeed, a matter of dysfunction, suggesting instead that the body might normally react to high levels of exposure to antigens. Allergic reactivity to food is the result of both IgE and non-IgE-mediated mechanisms. Non-IgE-mediated allergic responses tend to involve a T-cell-mediated delayed hypersensitivity reaction, with released cytokines determining the immune response.

Serum analysis of patients with immediate-type food allergy symptoms have revealed a significant correlation between titers of antiallergen antibodies of both isotypes, indicating that immune stimulation from allergenic foods is not limited only to IgE but also affects IgG-producing antibody systems as well.²⁰

GI symptoms in food allergy have been explained by alterations in transport across the intestinal wall (increased secretory and/or decreased absorptive functions), increased permeability, and motility of the intestine.²¹ In addition, repeated intestinal infections, coupled with reduced secretory IgA levels, can alter intestinal permeability and result in increased food antigen access to the systemic circulation. Such an increased antigenic load, combined with a patient's allergic predisposition, may foster immunologic responses to food proteins.

It is commonly acknowledged that food comprises the largest pool of antigenic challenges to the immune system.²² Food allergy is, indeed, an important and common health issue that warrants the need to identify and characterize the sensitizing potential of food proteins. Current approaches to identify food allergy include consideration of amino-acid sequence homology with known human allergens, sequence homology with human cell-surface antigens (as is the case with numerous cereal grains and connective-tissue antigens), serologic crossreactivity with

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known allergens, and quantifying resistance to proteolytic digestion. Although these concepts do not explain the ability of a protein to cause allergic sensitization, they do provide information regarding the pathogenesis of allergy.

What does explain the increasing incidence of allergic symptoms? A primary cause may be repetitive consumption of high doses of similar foods on a long-term basis, along with ingesting food additives, such as preservatives, coloring, flavor-enhancing agents, and antibiotics.²³ In addition, it has been speculated that infrequent food rotation predisposes patients toward developing hypersensitivities. Coupled with inadequate digestion of proteins into requisite amino acids, dipeptides, and short-chain polypeptides, partial proteins are able to retain their antigenic properties thereby provoking the immune system once they are allowed into systemic circulation.

Food Allergies and Illnesses

Food allergies cause a number of conditions that have often been attributed to other causes. These conditions include asthma, eczema, urticaria, migraine headaches, and irritable bowel syndrome (IBS).

Asthma

Atopy is a major predisposing factor for asthma and environmental allergens are a causal factor for producing asthma. Food allergy is frequently underestimated in association with asthma, despite having been shown to trigger or exacerbate broncho-obstruction in 2–8.5 percent of children with asthma.²⁴ Sensitization of food can occur early in life, involving a T-cell response of the Th2 phenotype in addition to the commonly cited IgE-mediated hypersensitivity. Diagnosis of asthma-associated food aller-

Allergy Detection Tests

The enzyme linked immunosorbent assay (ELISA)

The ELISA is a useful and powerful method for estimating ng/mL to pg/mL ordered materials in the solution, such as serum, urine, and culture supernatants (i.e., any cell-derived material that is used in the test, depending on the ELISA that is being run). This is the most reliable test for detecting antibodies and is commonly used in diagnostic testing for allergies. Antibodies to various antigens are detected easily by this test. Extracted and purified antigens are fixed to a surface to which the patient's serum is added. After washing and centrifugation, adherent immunoglobulin is then detected when a second antibody couple to an enzyme is added to the original surface. The last stage of the test involves adding the enzyme's substrate, causing a color reaction that is then measured by a spectrophotometer. This test is also performed by placing the antibody on the plate surface. ELISA assays are very sensitive and can measure IgA, IgE, IgG, and IgG4 antibodies, yielding disclosure of both immediate and long-term hypersensitivity reactions.

The radioallergosorbent test (RAST)

For the RAST, possible allergens are affixed to a plate that is then saturated with a sample of serum from the patient. If the patient's serum contains an antibody that is specific to an affixed antigen, it will link to the antigen. Next, a small amount of radioactive, polyclonal antireagenic antibody is then added to the plate. Following a reaction and washing period, residual radiation is measured to determine what percentage of the radioactive antibody is bound to the linked antigen-antibody complex. Higher amounts of radioactive bonding equate to a greater amount of reactive antibody that is specific to tested allergens in the patient's serum. The RAST primarily measures IgE-mediated allergies, that is, immediate hypersensitivity. Being that a growing body of evidence cites IgG in food allergies, the RAST may not detect all food allergen reactions accurately.

The radioallergosorbent procedure (RASP)

The RASP is similar in nature to RAST, but follows a different protocol. The RASP is a mild variant of the RAST that identifies IgG results in a meaningful and reproducible way. The RASP also has greater sensitivity and specificity for detecting food allergens than the RAST, which may be the result of ability of this test to detect IgG complexes in addition to IgE.

Skin tests

Epicutaneous or cutaneous allergen testing produces a localized pruritic wheal and erythema that is maximal at 15–20 minutes postintroduction. It is used most commonly for diagnosing of allergic respiratory diseases in patients with symptoms of pruritis, congestion, sneezing, and chronic coughs with wheezing. Skin testing for allergy is appropriate only if a patient has symptoms that are consistent with IgE-mediated allergy within 2 hours of eating a suspected food.

The elimination-challenge diet

Oral provocation with suspected allergenic foods administered in a double-blinded, placebo-controlled test is widely considered to be the definitive test for food allergy. This type of testing is not performed in patients with suspected food-induced anaphylaxis. Testing via this method will reveal immediate hypersensitivity to foods that cause symptomology. However, the relationship between certain foods ingested and resulting symptoms is not entirely clear-cut. In such cases, patients are placed on limited diets that involve the removal of commonly allergenic foods (e.g., foods with corn, wheat, soy, and dairy products) and the addition of hypoallergenic foods or foods that are rarely consumed by patients.

Patients are maintained on the diet for several weeks, on the theory that that allergy symptoms that have been caused by previously removed allergenic foods will be reduced or removed and that reintroduction of such foods at a later date will cause significant clinical symptoms that are reportable by patients. This type of testing for food allergies is advisable because singular tests are unable to identify specific triggers for patients who experience a wide array of symptoms (such as nausea, abdominal pain, vomiting, cramping, and diarrhea), which may be the result of various mediators of allergy, such as mast cells, eosinophils, IgE, and IL-4.³² To achieve specificity, however, more testing may be required.

gy is important for children with respiratory symptoms, especially when asthma symptoms begin early on in life and when they are associated with other manifestations of food allergies. Elimination of food allergens early in infancy have resulted in improved clinical asthma manifestations as well as exerting a protective effect on the progression of allergic tendencies later in life, as evidenced by decreased production of both total and specific IgE.²⁵

Eczema

Atopic disease prevalence is increasing worldwide. Atopic eczema affects nearly 18 percent of infants in the first 2 years of life. It has been widely speculated that food allergies are the main cause of atopy. Strong associations between atopic eczema and IgE-mediated allergies to milk, eggs, and peanuts have been demonstrated. However, nearly two thirds of patients with food allergies display no IgE sensitization to the instigating food proteins and symptoms either returned or were exacerbated upon administration of food-challenge tests.²⁶ These patients with allergic reactions to the ingestion of specific foods did not display sensitized IgE to the foods, yet still had allergic reactions when the foods were reintroduced in their diets. Thus, such patients can be said to be allergic to the foods with no identifiable IgE antibodies, in essence, having “hidden food allergies.”

Urticaria

In one study, patients with chronic idiopathic urticaria were placed on oligoantigenic and histamine-free diets for 21 days followed by systematic food reintroduction over the next 70 days. These patients developed histamine levels that diminished to control levels as well as experiencing significant reductions of symptoms during the test phase, indicating that histamine plays a large role in chronic idiopathic urticaria.²⁷ Another study of patients with chronic urticaria suggested that the symptoms of a group of patients with chronic urticaria indicated intestinal permeability, which was concordant with joint complaints, high titers of IgG, and the absence of specific IgE.¹⁵

Migraine Headaches

The link between food allergy and migraine has long been dismissed by many general practitioners, who do not tend to treat their patients' migraine headaches as having food-allergy based etiologies, however various foods have been cited as causative agents including citrus fruits, tea, coffee, pork, chocolate, milk, nuts, vegetables, and cola drinks.²⁸ In general, higher IgE incidence is no greater among people with migraine headaches than among the general population. However, this does not rule food allergy out as a cause of migraine headaches. This, however does not rule food allergy in either because there are various causes of migraines that are more appropriately labeled as food sensitivities to tyramine, phenylalanine, phenolic flavonoids, alcohol, caffeine. In addition, food additives, such as sodium nitrate, monosodium glutamate, and aspartame, are thought to induce migraine headaches by modifying vascular tone. Each patient must be individually assessed for various causes and relationships to foods prior to establishing an allergic causation of the headaches.

Irritable Bowel Syndrome

Allergic reactions in the gut have an estimated prevalence of approximately 1–2 percent in adults. Clinical symptoms include abdominal pain, nausea, vomiting, cramping, and diarrhea. Intestinal mast cells and intestinal eosinophils have been shown to be involved in the pathogenesis of food-allergy-related enteropathy. In addition to classical IgE-dependent degranulation, other agonists such as interleukin (IL)-4, have been demonstrated to activate mast cells.²⁹ Because low-grade mucosal inflammation predominates in IBS, undiagnosed food allergies may play a role in the promotion and perpetuation of the low-grade inflammatory process.³⁰ Food products have variously been reported as causing, perpetuating, or being used to treat IBS and many patients with IBS report histories of food intolerance concomitant with IBS symptoms.³¹ Given the high prevalence of gluten-enteropathy (approximately 1:200 patients) and the overlap between symptoms of celiac disease and IBS, many gastroenterologists believe that every patient with IBS-like symptoms should be tested for this (e.g., with antitransglutaminase IgA titers).

Other Physical Manifestations

Numerous additional conditions and symptoms have been empirically attributed to food allergies and sensitivities, including:

- *Dermatologic conditions*—acne, unexplained pruritis, and rashes
- *Musculoskeletal conditions*—bursitis, joint pain, and low-back pain
- *Immunologic conditions*—chronic infections
- *Genitourinary conditions*—enuresis and chronic cystitis
- *Gastrointestinal conditions*—Apthous ulcers, chronic diarrhea, ulcers, gastritis, and colitis
- *Respiratory conditions*—coughing
- *Cardiovascular conditions*—dysrhythmia, edema and syncope
- *Head, eyes, ears, nose, and throat (collectively, HEENT)*—headaches, sinusitis, palate pruritis, postnasal dripping, and “black circles around the eyes.”

Identifying Food Allergens

For determining the food antigens to which a patient is susceptible, food allergy tests are performed to determine a patient's allergies sensitively and specifically. Modern serum testing, used with detailed history taking and analysis of a patient's symptomatology, can expedite a diagnosis of food allergy. This approach is helpful because symptoms of such allergies are typically quite difficult to isolate and explain via food ingestion-related causes and effects, because of the delayed reactions that are typically involved.

Laboratory and challenge tests can provide reliable information to help identify both suspected and unsuspected food allergens. Although standard laboratory tests, such as the RAST and ELISA are simple for a patient, tests that entail challenging a patient with antigenic foods, either orally or dermally, are much more difficult and may not provide adequate specificity to identify offending food allergens.

For example, two common offenders, wheat and soy, are so prevalent in foods (under different names), that, in recalcitrant cases, it is necessary to utilize laboratory tests to identify other reac-

tive—or possibly reactive—foods. This is especially true because some patients have allergies to food other than the most common culprits that might not be removed in elimination diets. See box entitled Allergy Detection Tests for more information about the different tests that are available, how they are performed, and their utility.

The Alternative Approach

In general, alternative medical practitioners do not attempt to suppress allergy symptoms. An M.D. might attempt to achieve suppression by downregulating the body's response to the antigen protein that is being treated by the body as a foreign substance. Instead, allergic reactions—watery eyes, mucus production, sneezing, coughing, and other symptoms—are considered to be protective warning signs that allergens have invaded the body. Thus, patients are encouraged to take supplements, such as methylsulfonylmethane, quercetin, vitamin C, and others, to support the body's ability to deal with the allergens.

Conclusions

The diagnosis of food allergens requires extensive detective work. Detecting delayed-onset food allergies is becoming more acceptable among physicians because conventional food allergy testing does not completely uncover food allergy reactions other than immediate-onset IgE- and IgG-mediated symptoms.

Although cutaneous testing remains the "gold standard" in allergy diagnosis, according to the majority of allergists, some allergists do believe that this method of testing is indeed inaccurate and outdated. However, it is still not easy to find allergists who are willing to explore the possibility of food allergies with etiologies other than IgE or those allergies that have already been researched and localized to the gut (e.g., IBS, urticaria, Crown's disease), in addition to pursuing links among other body symptoms and food allergy.

While an array of testing possibilities exist, much work is needed in order to elicit fully the far-reaching effects of delayed food-allergy reactions. □

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