



Food allergy: what it is and what it is not?

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Purpose of review

Food allergy is defined as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food. Food intolerance, certain gastrointestinal or systemic diseases are often confused with or mislabeled as food allergy because of symptomatic similarity and general improvement from food avoidance. The differences between these diseases are crucial.

Recent findings

Compared with many food-related diseases that are isolated to gastrointestinal organs, food allergy can affect not only local but the whole immune system and may lead to a life-threatening allergic reaction, known as anaphylaxis. In this review, the differentiation between food allergy, food intolerance, and other comparable diseases is discussed.

Summary

With recent medical advances reflecting on the importance of accurate diagnosis in food hypersensitivity, healthcare providers who are treating food hypersensitivity should familiarize with latest science progress, identify and treat active disease, and refer to appropriate specialists if needed.

Keywords

allergy, anaphylaxis, food allergy, food hypersensitivity, food intolerance

INTRODUCTION

Food allergy was defined by the Expert Panel of the National Institute of Allergy and Infectious Disease in 2010 as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food [1]. On the other hand, food intolerance, certain gastrointestinal or systemic diseases are often confused with or mislabeled as food allergy because of the similarity of gastrointestinal symptoms and general improvement from food avoidance. The differences between these disorders are crucial. Compared with many food-related diseases whose effects are localized to gastrointestinal organs, food allergy can affect not only local but the whole immune system, which may lead to a life-threatening allergic reaction, also known as anaphylaxis. In this review, the differentiation between food allergy, food intolerance, and other comparable diseases is discussed. Emerging studies and trials have also shed light on the importance of accurate diagnosis in food hypersensitivity.

CAUSE AND SUBCATEGORIZATION

The broad definition of food allergy reflects an adverse reaction resulting from a dysregulated immune system, whereas food intolerance is a problem with the digestion or absorption of, or tolerance

to certain food, chemicals, or ingredients such as lactose, fructose, and caffeine. There are two main types of allergic reactions to food, differentiated on whether the reaction is based on an immunoglobulin E (IgE)-mediated (immediate) or non-IgE-mediated (delayed) mechanism. However, food allergy, especially in the allergy and immunology field, is mostly restricted to the IgE-mediated (immediate) type of reaction. Following previous food-specific sensitization of mast cells and/or basophils, the reexposure of the food allergen cross-links with the IgE on these cells igniting a rapid release of preformed cytokines including histamines that trigger allergic symptoms. The onset of an IgE-mediated allergic reaction typically occurs within minutes to an hour postingestion and the severity can range from a local oropharyngeal reaction, that is, oral allergy syndrome, to a much more devastating outcome [2^{••}]. Anaphylaxis, the most severe form of food-related adverse reaction, results from a

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KEY POINTS

- The broad definition of food allergy is an adverse reaction resulting from a dysregulated immune system, whereas food intolerance is a problem with the digestion and absorption of, or intolerance to certain food, chemicals, or ingredients.
- The hallmarks of food allergy in terms of medical history are pruritus, multisystem involvement, and a low provoking dose.
- There are validated tests to evaluate food allergies through either skin or serum testing in addition to the gold standard double-blind, placebo-controlled oral challenge.
- Epinephrine, the most effective treatment for food-induced anaphylaxis but often underprescribed and underutilized, is the absolute first-line option treatment and should not be replaced by other adjunctive medications including antihistamines and glucocorticosteroids.
- As illustrated by recent promising approaches to food allergy prevention and novel treatments for food desensitization, healthcare providers who are treating food hypersensitivity should familiarize themselves with the latest progress in allergy science, identify and treat active disease, and refer to appropriate specialists if needed.

dramatic IgE-mediated response of generally two or more organ systems and can be fatal. Other cofactors, including concomitant alcohol, medication consumption, or exercise, can modulate the allergic reactions. For example, food-dependent exercise-induced anaphylaxis (FDEIA) is a unique food allergy subtype that requires both triggering food intake and exercise to induce the disease [3]. In this review, the term ‘food allergy’ is focused on and designated as a classic IgE-mediated immune hypersensitivity to a specific food allergen. Within this narrowed definition, the estimated prevalence of food allergy is about 15 million people in the United States, compromising around 4% in children and 1% in adults [2²²]. Among the culprits causing food allergy, eight food categories (eggs, fish, milk, peanuts, shellfish, soy, tree nuts, and wheat) contribute to more than 90% of food allergies in the United States [1]. Food allergy has become a significant health problem globally because of its potential mortality and increasing prevalence over the past two decades, for reasons that remain to be elucidated.

In contrast, the onset of non-IgE-mediated immune responses, such as celiac disease and food protein-induced enterocolitis syndrome (FPIES), may occur anywhere from several hours to days after

ingestion and these reactions could be cell mediated or involve multiple immunoglobulin subtypes [4]. Similarly, other subgroups of diseases, for example, eosinophilic esophagitis (EoE) and food-related atopic dermatitis, may involve mixed immunological features of both cellular and humoral pathways [4]. In each of these disorders, several immunological questions remain to be answered; ongoing bench researches and clinical studies aim to decode the complete pathophysiology of these diseases and explore novel pharmacological therapies. Both delayed and mixed type of diseases are usually not considered as ‘food allergy’ because of differences in phenotype and endotype from IgE-mediated reactions.

In the general population, food intolerance, despite its apparently high prevalence, is often considered as a neglected disease category. There are a couple of explanations for this. First, the term food intolerance is poorly defined and oftentimes confused with other diseases such as food allergy, irritable bowel syndrome (IBS), or even gastroesophageal reflux disease (GERD). Second, there is a lack of consensus on how to test for and thus define and diagnose food intolerance. Third, because of uncertainty with respect to diagnostic methods, there are difficulties in identifying and classifying various subgroups within food intolerance, which further impedes active research and patient management. So far, the best studied and known diseases in food intolerance are lactose and fructose intolerance. Lactose is the major disaccharide in mammalian milk that can only be absorbed after it is broken down into its constituent monosaccharides, glucose and galactose, by a β -galactosidase enzyme in the small intestine. As the intestinal brush border concentration of this enzyme declines after infancy, the intrinsic downregulation of lactase activity in certain ethnic groups causes lactose malabsorption and subsequent bacterial fermentation of the unabsorbed disaccharide results in symptoms. Fructose intolerance, however, reflects a limited absorptive capacity for a monosaccharide, fructose, in the healthy population. Owing to symptom overlaps with food allergy and lack of diagnostic testing, the exact prevalence of food intolerance in the general is hard to measure. Despite these epidemiologic difficulties, it is estimated that individual food intolerances are more prevalent in the general population than all food allergies combined. For example, lactose and fructose intolerance are estimated to affect 65 and 40% of the general population, respectively [5,6]. With the exception of well-defined entities such as lactose and fructose intolerance, the very existence of other purported examples of food intolerance, such as non-celiac gluten sensitivity, monosodium glutamate intolerance, and histamine intolerance continues

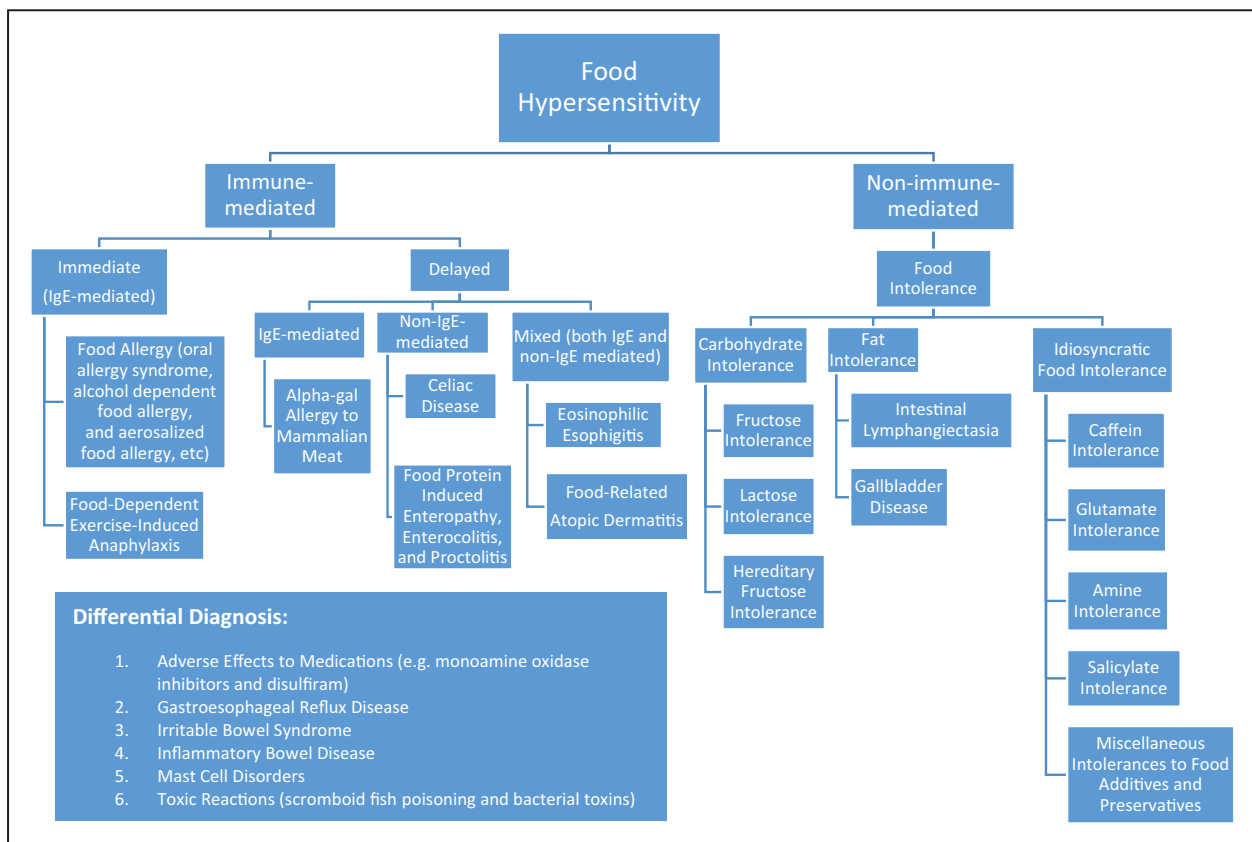


FIGURE 1. A schematic classification of food hypersensitivity along with a differential diagnosis.

to be highly debatable. However, this should not preclude physicians and scientists from continuously exploring any opportunity that can help and improve outcomes for our patients.

A schematic classification of both food allergy and intolerance is summarized in Fig. 1 along with various differential diagnoses such as IBS, GERD, toxic reactions (scombroid fish poisoning and bacterial toxins), inflammatory bowel diseases, and adverse effects of medications (e.g., tyramine intolerance with monoamine oxidase inhibitor and alcohol intolerance with disulfiram), and so on. These diseases, unlike very specific food allergies or intolerances usually involve relatively nonspecific reactions to certain foods, chemicals, or ingredients. Some notable and recent research findings have considerably advanced our understanding of the basis for some reactions to food. For example, α -gal allergy, also known as mammalian meat allergy, is an IgE-mediated allergic reaction to galactose- α -1,3-galactose (often medically abbreviated as α -gal) [7]. It is the first known carbohydrate to cause an allergic reaction, unlike the vast majority of food allergy culprits which are glycoproteins. Studies have shown that the original sensitization of α -gal, comes not from food, but from specific tick bites. Subsequently, cross-reactivity between α -gal and α -gal-containing

products such as the chemotherapy drug cetuximab or mammalian meats leads to an α -gal immediate or delayed allergic reaction, respectively [8]. Other advances in this field include the identification of mast cell disorders (including mastocytosis and monoclonal or idiopathic mast cell activation syndrome) and evidence for a role for intolerance to fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) in IBS [9]. Although a comprehensive discussion regarding α -gal allergy, mast cell disorders, low FODMAP diet, and other non-IgE-mediated food hypersensitivity is beyond the scope of this review, it is recommended that the physician seeing patients with food allergy and/or intolerance should familiarize himself or herself with the latest developments in relevant science, be able to identify and treat real disease, and refer to appropriate specialist, if needed.

MEDICAL HISTORY

Even though the differentiation between food allergy, intolerance, and other diseases may be achieved solely by diagnostic testing, there can be false-positive and negative results. A diagnosis of any disease that is based on medical history and confirmed by testing, including food allergy and intolerance, is the ideal.

Most instances of food allergy can be identified and differentiated from food intolerance on the basis of history alone. For instance, food allergy, because of its immunologic nature, often leads to symptoms outside of the gastrointestinal system. Depending on the different organs involved and the intensity of activation of the immune cascade, symptoms can range from a perioral or oropharyngeal tingling sensation and pruritus, urticaria and angioedema, nasal rhinorrhea and congestion, conjunctival pruritus and erythema to more dangerous signs such as dyspnea and wheezing from lower airway bronchoconstriction, hypotension and syncope from cardiovascular involvement, and dizziness and seizure from neurological system involvement. Pruritus, that is, itchiness, is commonly a true allergy regardless of body location. Other important clues are the timeline of the reaction and dose of the allergen to which the patient has been exposed. The majority of food allergies are immediate responses and symptoms happen and progress within minutes to an hour after ingestion, although, rarely, the onset can be delayed for up to 4 h or even 6 h especially in instances of FDEIA and α -gal allergy [3,7]. With regard to the dosage required to trigger an allergic or intolerant reaction, the medical literature often states that food allergy is a dose 'independent,' whereas food intolerance occurs in a dose 'dependent' fashion. This is a misnomer because there is always a threshold level to trigger a reaction. Food allergy is labeled as dose independent because of its very low triggering threshold which makes it appear that there is no correlation to the amount ingested. Accordingly, the lowest eliciting dose known for peanut allergy can be as minute as 0.1 mg of peanut protein (approximately 0.03–0.04% of a single peanut kernel) [10]. Food allergic reactions to aerosolized forms of food-specific allergens have also been reported [11[■]]. Therefore, a report of a very low triggering dosage tends to favor a food allergy instead of intolerance or other diseases. The hallmarks of food allergy in terms of medical history are pruritus, multisystem involvement, and a low provoking dose. With respect to symptom reproducibility, gastrointestinal manifestations, and response to a nonspecific treatment, overlaps may occur between food allergy and other diseases. For food intolerance, patient self-reporting of tolerance to lactose-free milk or fructose-free products are valuable clues to the diagnosis and definitive testing may not be required.

DIAGNOSIS

Objective and validated tests for food intolerance are scant, and include hydrogen breath testing for lactose and fructose intolerance and direct oral challenge for all other chemical or specific

ingredient intolerance. In contrast, there are validated tests to evaluate food allergies through either skin or serum testing in addition to the gold standard – a double-blind, placebo-controlled oral challenge. The goal of either the skin or serum testing is to evaluate for the presence of food allergen-specific IgE antibodies. Both have a high sensitivity (fewer false-negative results) but only moderate specificity (more false-positive results). The possibility of a false-positive result by either testing can be up to 50%, which means that a single individual has an up to 50% chance that his/her skin or serum tests will prove positive results for specific foods that he/she can consume without having any reactions or symptoms [12[■]]. With regard to skin tests, the skin prick method is preferred over intradermal testing because of the higher rate of false-positive tests associated with the latter. The pathophysiology and clinical significance by which some people with food allergen-specific-IgE antibodies can tolerate that food, so-called sensitized nonreactive phenotype of food allergy, remains uncertain [11[■]]. Owing to the aforementioned limitations, testing in food allergy must always be selected and interpreted in the context of medical history. Furthermore, both the degree of reaction in skin testing and level of food-specific IgE in serum testing do not correlate with the severity of a previous reaction nor predict the magnitude of a future reaction [12[■]]. An allergist/immunologist is a physician specially trained to diagnose, manage, and treat allergies and, therefore, is experienced with performing the testing, interpreting the results, and treating any adverse events that may happen during the testing.

For non-IgE-mediated immunologic food hypersensitivities and other masquerading diseases, there are certain tests or procedures to help validating the diagnosis. Such diagnostic modalities include, but are not limited to, serum IgA and IgG for tissue transglutaminase and deamidated gliadin peptide and genetic human leukocyte antigen testing for celiac disease; esophagogastroduodenoscopy with biopsy for EoE; tryptase level and KIT gene mutation analysis for mast cell disorders. There may also be some value in evaluating food-specific IgE levels in mixed immunological type of food hypersensitivity. For example, the presence of food-specific IgE antibodies are indicative of a prolonged disease course in FPIES, whereas skin and serum testing combined with food avoidance could confirm the diagnosis of food-related atopic dermatitis [13,14].

MANAGEMENT

Conventional approaches to the treatment of food allergy and intolerance are based on the strict

elimination of specific foods. Accordingly, an appropriate diagnosis is imperative to rule out nonspecific food-related diseases and lead to proper tests identifying the food responsible for either allergy or intolerance. Additionally, it is of equal importance to differentiate food allergy from intolerance and to determine the underlying immune mechanism. Comorbidities, complication rates, and prognosis vary among each disease and the degree of difficulty in terms of avoidance is substantially different between triggering foods. Either abstaining from common foods such as egg, milk, soy, and wheat or commonly occurring chemicals and ingredients can significantly affect a patient's nutritional status and quality of life. Because food allergy and intolerance are frequent clinical diagnoses, healthcare providers who are actively treating these diseases should know how to manage and/or refer to a specialist, if needed.

Importantly, life-saving treatments of food allergy should be emphasized as fatal reactions may occur. Epinephrine, the most effective treatment for food-induced anaphylaxis, is often underprescribed and underutilized by physicians and patients. Delays in the administration of epinephrine have been shown to correlate with severe and even biphasic reactions [15]. It is paramount to initiate epinephrine treatment and not to substitute it with other adjunctive medications including antihistamines and glucocorticosteroids. The patient should be trained on how to use epinephrine auto-injectors if there is clinical necessity.

For all other diseases other than food allergy, there may be unique managements in addition to traditional food avoidance. Examples would be enzyme replacement for lactose intolerance, swallowed glucocorticosteroids for EoE, and a low FOD-MAP diet for IBS. These tailored therapies once again reinforce the importance of precise diagnosis.

CONCLUSION

Even with the medical breakthroughs in food hypersensitivity, physicians and researchers are still struggling to find a succinct explanation for common questions asked by our patients, such as 'why am I only reacting to this food?; how long will I be reactive?; what will happen if I accidentally eat the food next time?' The answer to the most fundamental question for, namely, what is food allergy and what is not, as this review article is entitled, will not have a fixed but rather a continuously evolving answer. However, this does not prohibit physicians and scientists from deciphering this conundrum. As recent promising evidence for food allergy prevention and novel emerging treatments for food desensitization including sublingual, oral, and epicutaneous

immunotherapies have been demonstrated, there will be even more ways to take advantage of that knowledge and completely change our understanding of food allergy, intolerance, and other diseases in the future [16].

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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