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What Is Food Allergy?

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Introduction

Food allergic reactions are due to an immune response to specific food components, allergens, that are commonly glycoproteins or other proteins or, rarely, carbohydrates. The most frequent allergic reactions are immediate hypersensitivity reactions mediated by antibodies (IgE) to food allergens. These antibodies circulate in the blood and are unique in that they can attach to mast cells in the skin, respiratory tract, and gastrointestinal tract, as well as to basophils in the circulation. Mast cells and basophils contain histamine and other substances that produce the signs and symptoms of an allergic reaction: itching, hives, swelling, wheezing, throat constriction, nausea, vomiting, diarrhea, dizziness, loss of consciousness, and, potentially, death from shock (anaphylaxis). When a food allergen interacts with IgE specific to that allergen, the antibodies can trigger a biochemical process in the mast cells and basophils resulting in the release of histamine and other inflammatory substances. These processes occur rapidly, within minutes; thus, the term “immediate hypersensitivity.” In addition to the immediate reaction, some people may also have a so-called “late-phase” reaction that occurs 4 to 6 hours after exposure to the allergen. Other immunologic reactions to foods can occur, such as celiac disease (gluten-sensitivity) and other gastrointestinal diseases that have a delayed onset. Because IgE-mediated allergic reactions can be potentially fatal, this review will focus on these reactions.

Although mechanisms are not completely understood, genetics plays a significant role in the development of food allergy. Children of parents who have allergic diseases (hay fever, asthma, eczema) are at risk for food allergy. More than 10 genes have been linked to food sensitivity in at least one study population (*Hong X, 2012*). Exposure to several environmental conditions including tobacco smoke, microbes, timing of food introduction, and exposure to specific foods are also factors affecting allergic reactions. For example, peanut is a common food allergen in the U.S. whereas codfish is common in Scandinavia. Cod was found to be the most common allergen in North African children whereas peanut allergy was most common in central African children (*Cheikh R, 2013*).

In the U.S., eight foods are the most frequent causes of food allergy: peanut, shellfish, tree nuts, milk, egg, wheat, soy, and finfish. The prevalence of food allergy in the U.S. is approximately 1–2% of adults and 4–6% of children, and about 2.5% overall (*Liu AH, 2010*). The percentage of children with food allergies appears to vary depending on the geographic area in which they reside in the U.S. A survey of >38,000 children from all 50 states demonstrated an increased odds for food allergy at southern and middle latitudes compared to more northern states. However there were exceptions, with some northern states having an apparently higher prevalence than some southern states. Prevalence rates did vary significantly with population density: 9.8% of children in urban centers compared to 6.2% of children in rural areas were reported to be allergic to one or more foods. Reasons for these urban–rural differences are not clear. It has been suggested that more pollutants in the urban environment may have a role in increasing allergic reactions or that exposure to some microbes more common in the rural environment may be protective (*Gupta RS, 2012*).

Data compiled by CDC from NHIS (National Health Interview Surveys) demonstrate a significant linear increase in food allergy among U.S. children aged 0 to 17 years, from 3.4% in 1997–1999 to 5.1% in 2009–2011. There was also a significant trend by poverty status, with a higher percentage of children in higher income households reported to have allergic reactions to foods than children in homes with incomes below the poverty level (*Jackson KD, 2013*). Interestingly, the estimated number of emergency room visits for food allergic reactions in adults declined over the period 2001–2009, from 147,000 visits to 97,000, although there was an estimated increase from 77,000 to 92,000 for visits by allergic children (<18 years) (*Clark S, 2013*).

Reasons for the increasing frequency of food allergy, reported in many developed countries in recent decades, are not well understood. One proposed explanation is the “hygiene hypothesis.” As food and water supplies have become safer in terms of infectious agents (especially parasites) and children are routinely vaccinated against many diseases, their immune systems have been deprived of the stimulation necessary to prevent allergic sensitization to what are ordinarily harmless substances (e.g., foods, pollens). Exposure early in life to farm environments, pets, and some crowded living conditions appears to protect children from development of allergic reactions.

A revised version of the hygiene hypothesis proposes that a balance of microbial signals is necessary for proper development of the immune system. Our commensal microbiome in the intestine is comprised of about 10^{14} bacteria, with an estimated 1,500 different species. Fecal microbiota in food-allergic children have been shown to differ from the fecal microbiota of non-allergic children; lifestyle changes in developed nations, such as diet, frequency of breast feeding, and antibiotic use, as well as increased sanitation, may have altered the proportions of different microbial species in the intestine. These changes may alter the risk for food allergies and susceptibility to some diseases and infections (*Feehley T, 2012*).

Can the introduction of novel foods into the U.S. diet lead to new food allergies?

Virtually any food can be an allergen and well over 200 sources of food allergens have been identified to date. With increased globalization of markets, new foods have become more available worldwide. Introduction of novel foods into the U.S. diet over recent years has led to case reports of allergic reactions. An example of such a new, potentially allergenic food is quinoa, a South American crop with protein-rich seeds that is eaten as a substitute for other grains. A case of quinoa allergy was recently documented in Missouri (*Hong J, 2013*). Other foods not commonly eaten in the U.S., including amaranth (Rajgira) grain (*Kasera R, 2013*) and insects (*Belluco S, 2013*), have caused allergic reactions in some people. Additional reports of new food allergic reactions are likely to appear in the future as novel foods continue to be introduced into the diet.

How much exposure to a food allergen is needed to cause an allergic reaction?

One important concern for both allergic individuals and food processors is that ingestion of very small quantities of a food to which a person is sensitized can cause a severe and potentially fatal reaction. The amount probably varies from food to food and individual sensitivity also differs. Thus, it is difficult to determine a "threshold dose" (i.e., the smallest dose capable of producing a reaction in the most sensitive individual). As little as 100 micrograms of peanut can produce subjective symptoms (e.g., itching, tongue tingling, for example). As little as 1 milligram of peanut may produce objective signs, such as vomiting or hives (*Blom WM, 2013; Taylor SL, 2010*). Because assay methods for detecting food allergens in processed foods can detect levels in the mg/kg (ppm) range, concerns about labeling arise when these extremely low levels are found. Do they pose a risk to the food-allergic consumer?

Can food processing reduce food-allergic reactions?

Food allergen proteins are frequently stable (retain their IgE antibody binding activity) after heating, enzymatic digestion, and at low pH. However, several recent reports suggest that heating may reduce the allergenicity of certain hazelnut and almond proteins (*Masthoff LJ, 2013*), and some cooking methods lessen the allergenicity of hen egg allergens (*Liu XY, 2013*). Lye peeling can reduce allergens in peach nectar, and soaking and blanching may reduce peanut allergenicity (*Sathe SK, 2009*). On the other hand, boiling, frying, and roasting decreased the solubility of some major peanut allergenic proteins and IgE-binding to the insoluble proteins increased (*Schmitt DA, 2010*). Enzymatic degradation of proteins may lessen their allergenicity, depending on the extent of hydrolysis of the allergen (*Cabanillas B, 2010*). Further processing can affect the results of food allergen assay methods (ELISAs, liquid chromatograph–mass spectrometry) (*Hebling CM, 2013*; *Cabanillas B, 2010*). Lastly, carefully performed equipment cleansing procedures may significantly reduce allergens in foods as well as the risks of cross-contamination (*Wang X, 2010*).

Detection methods for allergens in processed foods

Methods for detecting allergens in foods have been commercially available for several years. However, no "gold standard" assay currently exists. These assays are largely enzyme-linked immunoassays (ELISAs) that employ polyclonal antibodies to food protein allergens. Lower limit of detection is about 2.5 mg/kg. A recent review of these assays has been published (*Schubert-Ullrich P, 2009*). Some regulatory agencies (Japan) have set an arbitrary level of 10 mg of the allergic proteins/g of food as a level that requires labeling (*Sakai S, 2013*). However, some analytical methods can be unreliable in processed foods due to chemical changes in the allergenic proteins that occur during processing (*Cucu T, 2013; Iqbal A, 2013)*. In addition, the matrix in which the allergenic protein is incorporated can affect the effectiveness of extraction methods needed to prepare food samples for allergen assays.

Monoclonal antibody-based ELISAs have also been developed (*Peng J, 2013*). Monoclonal antibody-based assays have the advantage of providing an unending supply of a uniform reagent in contrast to polyclonal antibody-based assays; but monoclonal antibody-based ELISAs have the same limitations as polyclonal antibody-based assays.

Newer methods using polymerase chain reaction (PCR) techniques have been reported for detection of hazelnut (*López-Calleja IM, 2013*) and salmon (*Ishizaki S, 2012*), for example. PCR methods can detect extremely low levels of allergens (0.02 kg/ml DNA). Such assays may well be too sensitive because these levels may not pose a clinically significant risk to food-allergic consumers. Additional newer methods that employ chromatographic techniques combined with mass spectrometry are being studied. As with ELISAs, PCR, and other assays, allergen detection can be affected in comparable ways by food processing.

To address the concerns of food safety by food-allergic consumers, the food industry, and regulatory agencies a recent symposium at the American Chemical Society was held that examined the "state of the art," new developments, and challenges for the detection and quantification of allergenic proteins in processed foods (*Ross MM, 2013*). It is hoped that with continued research, problems such as extractability of protein allergens and matrix effects can be overcome.

SUMMARY

Food allergy, particularly those reactions due to IgE-mediated sensitivity, is an important issue for the food industry because of the risk of severe and potentially fatal reactions. Food allergy, although not extremely common (1–2% of U.S. adults, 4–6% of U.S. children), appears to be increasing in numbers of people affected and possibly in the severity of the reactions.

Globalization has led to the introduction of new foods in the U.S. diet, some of which may prove to be allergenic. Because small quantities of allergenic proteins can cause reactions, efforts to establish "threshold doses" have been difficult and the level may vary from food to food and person to person. Methods to detect allergenic proteins in food are commercially available and in use by the food industry and regulatory agencies, although limitations exist. Newer approaches are being investigated. Processing methods may reduce the levels of allergens in some foods, but allergenic proteins are frequently resistant to degeneration by low pH, heating, and enzymatic hydrolysis. Efforts to reduce the production of allergenic proteins in plant foods by genetic engineering are being explored. For the food-allergic consumer, industry efforts to avoid cross-contaminations in processed foods and proper labeling of products can reduce the risk of reactions.

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