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Soy Consumption and Allergies

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FOOD ALLERGIES: PREVALENCE, TYPES, AND DIAGNOSIS

By Carina Venter, PhD, RD

Introduction

Food allergies (FA) are commonly reported by children and adults. The true prevalence of FA is difficult to determine due to the heterogeneity of immunological presentations (symptoms) and foods involved. The diagnostic work-up also differs for each type of FA. No 2 studies of FA prevalence have used the same methodology. Food challenges or food reintroduction following a period of avoidance is the gold standard for the diagnosis of FA.[1] However, only a minority of studies reporting on FA prevalence have utilized this process as an outcome measure. A meta-analysis of 51 studies showed that self-reported FA varied between 3% and 35%, while confirmed FA ranged from 1% to 10.8% based on oral food challenges, including studies on both children and adults, across the world.[2] In addition to leading to incorrect prevalence rates, overreporting of FA has many negative effects on an individual and global level such as unnecessary dietary restrictions and labeling laws. Most importantly, however, overreporting of FA may cause some who are truly allergic to not be taken seriously.

Nomenclature

The National Institute of Allergy and Infectious Diseases defines a FA as "an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food."[1] This definition captures a range of food-related problems. If the production of immunoglobulin E (IgE) is involved, it is referred to as an IgE-mediated FA. An immune mediated reaction leading to an allergic reaction in the absence of IgE production is referred to as non-IgE-mediated FA. There are many diseases considered to be non-IgE-mediated gastrointestinal FA: food protein induced enterocolitis syndrome (FPIES), eosinophilic esophagitis (EoE), food protein induced allergic proctocolitis (FPAIP), food protein induced allergic enteropathy (FPIAE), and food protein induced dysmotility disorders (FPID) such as gastro-esophageal reflux disease (GERD) and constipation. Food-related symptoms that do not involve the immune system are referred to as food intolerances, e.g., lactose intolerance. There are currently no national or international allergy or gastrointestinal societies or associations that acknowledge or define the existence of food sensitivities—other than the reference to non-celiac gluten sensitivities.[3]

Prevalence

A systematic review by the University of Portsmouth in 2013 identified only 92 papers reporting on FA prevalence worldwide; and of these papers, food challenges were conducted in only 21.[4] This observation implies that prevalence is often based on self-report even though it is known that such figures are much higher than challenge-proven prevalence figures.[5]

IGE-MEDIATED FOOD ALLERGIES

Diagnosis of IgE-Mediated Food Allergies

IgE-mediated FA typically involve the production of IgE to a specific food and occur minutes to hours (usually 2 hours) after consuming a food. A clinical history is important to understand the symptoms reported, timing between food ingestion, and the development of symptoms, as well as the possible food/food allergen implicated.[6] Following this assessment, skin prick tests (SPT), specific IgE tests, and in some cases, component-resolved diagnostic tests (CRD) may be performed.[7] If there is agreement between the clinical history and the test result, a clinical diagnosis is made. The sensitivity is greater than 90% for skin testing and 70–90% for serum food-specific IgE measurement. For example, if the skin test for the specific test is negative, one can be about 70–90% certain the child does not have a food allergy. However, the specificity is less than 50% for both tests, meaning a positive skin or blood test indicates that the individual has less than a 50% chance of being truly allergic to the food.[8,9] Therefore, these tests cannot be used to make a diagnosis in the absence of a good clinical history.

In case of any disagreement between the patient history and test results, an unclear history, or when unequivocal diagnosis is required for research, either an open, single-blind, or double-blind, placebo-controlled food challenge may be performed. Challenge doses are usually based on the practical allergy (PRACTALL) guidelines[10] or can be performed according to infant food challenge guidance for peanut.[11]

Prevalence of IgE-Mediated Food Allergies

It is well-known that milk and egg allergy are most commonly seen in younger children. Peanut and tree nut allergies seem to occur later in childhood. Fish and shellfish allergies tend to develop in older children[12] and pollen-cross reactions

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are more often seen in teenagers and adults.[13-16] FA also differ among different populations being studied. Prevalence of common FA are different in different countries and age groups.[5,17-20]

The natural history of FA has been studied for only a few food allergens. Focusing on population based studies, Host et al.[21] and Venter et al.[5] reported remission rates of cow's milk allergy of 87% and 80% at 3 years, respectively. A more recent study from Europe reported that 66% of children developed tolerance to cow's milk between 2 and 3 years of age.[19] Data from 2 tertiary centers[22,23] confirm these tolerance rates, but 1 U.S. center showed lower tolerance rates of only 5% by 4 years.[24] Studies indicate that approximately 50% of egg-allergic children will be tolerant by the age of 3 years and 66% by the age of 5.[25,26] Recent data from the Europrevall study indicated that about 50% of those diagnosed with egg allergy by 2 years of age developed tolerance by 3 years.

In contrast, U.S. data indicate that only a small proportion (20%) of children with peanut allergy outgrow their allergy by adolescence or early adult life, and very occasionally a relapse may also occur.[27] Data from the U.K. showed that only 7% of peanut-allergic children became tolerant over the course of 7 years.[28] There are very limited data on the natural history of soy allergy. In the U.S., Savage et al.[29] reported that based on a retrospective review in a tertiary center, resolution of soy allergy predicted in 25% of children by 4 years, 45% by 6 years, and 69% by 10 years.

NON-IGE-MEDIATED FOOD ALLERGIES

Diagnosis of non-IgE-mediated FA is a clinical challenge. A thorough history is the cornerstone of diagnosing non-IgE-mediated FA and the foods implicated. The clinical history involves questions regarding typical characteristic signs and symptoms, followed by improvement of symptoms after withdrawal of the suspected trigger food(s). This diagnosis should ideally be followed by a food challenge or food reintroduction.

Food Protein Induced Enterocolitis Syndrome (FPIES)

FPIES can be characterized by acute (e.g., profuse vomiting 1–4 hours after eating the food) or chronic (e.g., persisting diarrhea with continued consumption of small amounts of the food) symptoms.[30] The true prevalence of FPIES is not known. Data for year 2011 from Israel indicate that .34% of infants developed FPIES to milk over the first 2 years of life.[31] Data from Australia indicated .0154% of new cases (age 0–2 years) per year to any food.[32] There is currently insufficient data to indicate if the prevalence or incidence of FPIES is increasing. Foods triggering FPIES also differ according to the country studied, as summarized by Venter and Groetch.[33] The main foods triggering FPIES in the U.S. are milk, rice, soy, and oats, whereas little FPIES to soy has been reported in Australia and Italy, and none was reported in Israel.[33] The main eliciting foods in the U.K. are cow's milk, fish, egg, soy, and wheat.[34] Food challenge protocols for FPIES are different than those for IgE-mediated FA and are suggested in the FPIES guidelines. SPT, specific IgE, and CRD play no role in the diagnosis of FPIES, but can be useful to diagnose atypical FPIES, often indicating more persistent disease. Only 2 small studies tested the ability of the atopy patch test (APT) to identify trigger foods in FPIES and showed contrasting results. Therefore, the FPIES guidelines made no recommendation regarding the use of this test.[35,36]

Eosinophilic Esophagitis (EoE)

EoE is defined as a clinicopathologic condition that is likely immune or antigen driven and characterized clinically by symptoms of esophageal dysfunction and histologically by 15 or more eosinophils per high-power field (eos/hpf).[37] EoE has an estimated prevalence of .057% in the U.S.[38] The dietary management of EoE comprises 3 phases. First is the elimination phase, during which potential trigger foods are removed followed by esophagogastroduodenoscopy (EGD) and biopsies to ascertain resolution. Second is the food reintroduction or challenge phase followed by an endoscopy. Last is the maintenance phase, where definite problematic foods remain out of the diet. SPT or IgE testing is not recommended to identify trigger foods in EoE due to non-IgE-mediated mechanisms driving EoE, but can be used to identify other co-existing FA or identify those sensitized to foods who may convert to clinical IgE-mediated FA after a period of avoidance. The APT has also been investigated to identify trigger foods in EoE, but data about efficacy are conflicting. Recent guidelines do not recommend the use of SPT, specific IgE testing, or APT for the initiation of elimination diet in EoE.[39] The ability of Immunoglobulin G4 (IgG4) to identify trigger foods in EoE is currently being investigated, particularly in relation to α-lactalbumin and β-lactoglobulin.[40] These proteins are the main proteins in milk, a major trigger of EoE. As IgG4 is usually a marker of tolerance, there is currently no explanation when IgG4 levels are raised in a food that is not tolerated by those with EoE. Other main foods triggering EoE have been summarized by Cianferoni et al.[41] and include egg, wheat, and soy in the U.S. and egg, wheat, and legumes in children in Spain.

Other Non-IgE-Mediated Food Allergies

Other forms of non-IgE-mediated FA include a range of gut and skin related symptoms. The prevalence of these other non-IgE-mediated FA are unclear, although milk is considered the main food allergen implicated. IgE testing is not recommended for other forms of non-IgE-mediated FA unless other co-existing allergic diseases are being considered.[42] International guidelines do not recommend APT as a routine test for the diagnosis of non-IgE-mediated allergies.[1,43] As with FPIES and EoE, suspected foods should be excluded and if symptoms improve, a clinical diagnosis can be made. However, reintroduction of food allergens with reoccurrence of symptoms is the preferred option to diagnose these non-IgE-mediated FA.[44,45] Routine endoscopies are not recommended. Testing for IgG and IgG4 is also not recommended.[42]

Food Sensitivities

"Food sensitivities" is not an official term acknowledged by allergy associations/societies and symptoms such as headaches, chronic abdominal pain, and chronic behavioral symptoms are unlikely to represent FA.[46] Yet, many commercial entities market products such as IgG/IgG4 testing, applied kinesiology, electrodermal testing, antigen leukocyte antibody testing, provocation-neutralization testing, and hair analysis for the diagnosis of food sensitivities. The use of these unproven tests has been discouraged by the Canadian Society of Allergy and Clinical Immunology, the American Academy

of Allergy, Asthma and Immunology, National Institute of Allergy and Infectious Diseases, and various allergy experts.[1,47-49]

These tests can artificially inflate reported prevalence rates of adverse reactions to foods and lead to unnecessary dietary avoidance and delayed introduction of food allergens in young infants. One test of particular concern in the U.S. is the LEAP Mediator Release Test (MRT). The manufacturers of this test classify adverse food reactions as FA, food-induced autoimmune disease, and food sensitivities. They claim that food sensitivities affect up to 30–40% of the population, without substantial evidence. The MRT measures volumetric changes in mediators (cytokines, leukotrienes, prostaglandins, etc.) released from various cells (lymphocytes, eosinophils, monocytes, neutrophils) in both the innate and adaptative immune system. This test causes confusion as IgG[50] and IgA[51] (adaptive immune system) have been associated with tolerance development rather than adverse food reactions in numerous citations. There is also currently no evidence that the adaptive immune system can launch adverse reactions to repeated exposure of food allergens, i.e., the adaptative immune system is non-specific as claimed by the manufacturers.[52]

Currently, only 1 study has evaluated the LEAP MRT. In 2004 at the meeting of the American College of Gastroenterology (ACG), Williams[53] reported improvements in patients with diarrhea prominent IBS. Within 1 month of avoiding foods identified by LEAP MRT, patients reported a decrease in diarrhea, less systemic symptoms, and an increase in their well-being. However, this study involved only 10 adults and was never published in full manuscript form.

Summary

In summary, FA is often reported, but there is a large discrepancy between reported and diagnosed FA. This discrepancy may be due to confusion in nomenclature and the differences in study methodologies. In children, the prevalence of FA depends on the food studied and the country involved. It is unclear if FA are increasing due to a lack of data studying the same food in the same population, using similar methodologies. A large number of foods are reported to cause symptoms of FA. Only 8 foods (e.g., milk, egg, peanut) form the core components of FA. If secondary food allergens (e.g., apple cross-reaction with birch pollen) are taken into account, the number/range of foods triggering allergic reactions increases dramatically. The number of foods triggering adverse reactions becomes even more inflated when foods identified by unvalidated tests are taken into account.

Registered dietitian nutritionists working in the field of FA should be aware of the nutritional pitfalls of unnecessary food avoidance. Overreporting of adverse reactions to food are a common occurrence, often driven by unvalidated tests. Foods should only be excluded from an individual's diet if advised by a physician (e.g., allergist, immunologist, gastroenterologist) with experience in FA.

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PREVALENCE OF SOY ALLERGY

By Mark Messina, PhD, MS

Soy protein is widely used by the food industry for its functional benefits such as enhancing moisture retention. For this reason, considerable diligence is required by those who are allergic to soy protein because it is present in many commonly consumed foods. Fortunately, this diligence is required by relatively few individuals as overall, surveys indicate that the prevalence of soy allergy is lowest among the Big 8 food allergens.

Since 2004, the U.S. Food Allergy Labeling Consumer Protection Act has mandated that the label of a food that contains an ingredient that is protein or is a derived protein from a "major food allergen" must include language noting the allergen included. The 8 foods classified as major allergens are thought to be responsible for 90% of the food-related allergic reactions among Americans.

When the Big 8 was established, relatively little prevalence data were available. However, as discussed below, over the past 10 years large surveys have provided considerable insight into the prevalence of food allergies among Canadian and U.S. children and adults.

The first report in the scientific literature of soy allergy dates to 1934, although in this case the allergic response was the result of airborne transfer of soy allergens among workers in a plant that milled soybeans.[1] More than 30 potential soybean allergen sequences have been identified; 16 of which have been confirmed with some data to support sensitization and elicitation.[2] However, IgE binding assays using immunoglobulins from soybean sensitive individuals reveal that about ⅔ of the total allergenic response is caused by 1 allergen, P34 (Gly m Bd 30K).[3-5]

The amount of soy protein required to elicit allergic responses in soy-sensitive individuals is generally much higher than for other food allergens.[6] In fact, it may be more than an order of magnitude higher than observed for peanut allergy.[7-9] Highly refined soybean oil is exempt from labeling because any residual trace amounts of protein that might be in soybean oil have been shown not to cause reactions in soy protein-sensitive individuals.[10]

Allergic reactions to soy are generally considered to be more moderate in comparison to other food allergens, although some cases of anaphylaxis have been reported in the literature. In 1999, Foucard et al.[11] concluded that soy allergy has probably been underestimated as a cause of food anaphylaxis. This conclusion was based on a review of medical records of all fatal and life-threatening reactions sent to them by physicians in Sweden over a 3-year period. It was determined that 4 individuals suffered fatal allergic reactions in response to soy protein. However, 1 year later, Sicherer et al.[12] suggested that these reactions were not caused by soy, per se, but instead because the soy-containing foods consumed were contaminated with trace quantities of peanut protein, lupine, or some other allergen. They noted that if these reactions were due to soy protein, Foucard et al.[11] would have identified more fatal soy-allergic reactions in a single country than have been reported in the rest of the world.

Generating accurate prevalence data is challenging because for the most part it relies on self-reported data, that is, survey respondents report whether they are allergic to specific foods. In some cases, respondents also indicate whether their allergy was diagnosed by a physician, although the method of physician diagnosis is not necessarily reported. It is generally recognized that self-reported data overestimate prevalence when compared to more rigorous diagnostic methods.[13] In some cases, surveys can partially control for this discrepancy by assessing whether the report of allergy is consistent with patient history.

Self-Reported Prevalence of Food Allergy Reported by U.S. and Canadian Adults for Major Food Allergens (percent of population)

Food	U.S.-NHANES[18]	U.S.-FDA[19]		NIAID Adults[14]	Canada (SCAAALAR)[20]
		Self-report (SR)	SR-doctor diagnosed		
Years data collected	2007–2010	2010		2015–2016	2008–2009
Sample size	20,686	4,568		40,443	7,469
Any food	9.72	9.8	4.6	10.8	8.34
Milk/dairy	2.64	4.1	2.0	1.9	1.89
Shellfish	2.04	3.6	1.6	2.9	1.91
Fish	0.46	1.7	0.8	0.9	0.60
Tree nuts	0.87	1.3	0.7	1.2	1.07
Wheat/gluten	0.63	1.3	0.9	0.8	0.86
Egg	0.51	1.0	0.5	0.8	0.67
Peanuts	0.89	0.9	0.6	1.8	0.78
Soy	0.35	0.1	0.1	0.6	0.16
Sesame	NA	NA	NA	0.2	0.07

Despite the limitations, recent North American surveys provide considerable insight into the prevalence of soy allergy. As shown in the table, among U.S. and Canadian adults, surveys consistently show that the prevalence of soy allergy is lower than the prevalence of the other 7 foods in the Big 8. For example, the prevalence of milk/dairy allergy is between about 3 and 41 times greater than the prevalence of soy allergy. Estimates of the prevalence of soy allergy range from 1 to 6 per 1,000 adults.

The prevalence of food allergy is greater among children than adults, although recent data indicate that food allergies often begin in adulthood.[14] As in adults, soy allergy prevalence among children is the lowest among the Big 8. Children tend to outgrow their allergies, although the rate and extent to which this outcome occurs

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varies.[15] Estimates in the literature suggest 70% of children outgrow their soy allergy by age 10.[15,16]

Finally, concerns about soy allergy appear to be 1 reason many products targeting flexitarians and vegetarians are now made with pea protein rather than soy protein. Although pea protein has not been studied as extensively, it does cause allergic reactions. In fact, concentrating the protein—as is the case for pea protein isolate and pea protein concentrate—may lead to enhanced allergenicity.[17] Canadian researchers recently described 6 cases of severe allergic reactions to foods containing concentrated sources of pea protein.[17]

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HIGHLY REFINED SOYBEAN OIL DOES NOT ELICIT ALLERGIC REACTIONS IN SOY PROTEIN-SENSITIVE INDIVIDUALS

By Mark Messina, PhD, MS

The U.S. Food Allergen Labeling & Consumer Protection Act (FALCPA) mandates labeling of all ingredients derived from commonly allergenic foods. In the U.S., 8 foods, commonly referred to as the Big 8, have been identified as the most frequent human food allergens; accounting for 90% of food allergic reactions among Americans. These foods are milk, eggs, fish, crustacea, wheat, peanuts, tree nuts, and soy.[1,2] However, the prevalence of allergy for each of these foods varies markedly. North American surveys published over the past 10 years show that among the Big 8, the prevalence of soy allergy is lower than the prevalence of the other 7 foods.[3-6]

Importantly, the FALCPA exempts highly refined oils from these labeling provisions. Soybean oil is viewed similarly in Europe, where soy protein is classified as one of the 14 most common foods that induce allergic reactions.[7] The reason for these exceptions is that highly refined soybean, as well as peanut and sunflower seed, oils have been clinically documented to be safe for consumption by individuals allergic to the source food.[8-11] For example, Taylor et al.[12] tested the ability of a mixture of 4 soybean oils with the highest protein level from a group of 30 highly refined oils obtained from 30 different worldwide processors in a group of 28 soy protein-allergic individuals. Study participants consumed increasing doses of 1, 5, and 10g soybean oil (test material) and canola oil (control material) in a double-blind placebo-controlled food challenge. No untoward reactions were encountered to either soybean or canola oils.

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The process of commercially refining soybean oil involves extraction with hot solvents, bleaching, and deodorization, which serve to eliminate almost all soy protein (and thus allergens) from the oil.[13] It is, however, difficult to quantify the protein content of oil. Attempts to do so indicate that crude oils contain about 100–300mg/kg, whereas fully refined oils contain at least 100 times less.[13] This difference explains the lack of reaction observed in response to ingesting highly refined oils, unlike ingesting unrefined or partially refined culinary oils, which have been found to elicit allergic reactions in sensitized individuals.[14] While highly refined soybean oil does contain residual soy protein, the residue levels are extremely low—too low to elicit an allergic response in nearly all cases.[13,15–17] Analytical data from Rigby et al.[18] on cumulative threshold doses for soy protein suggest that even the most sensitive individuals would need to consume at least 50g of highly refined oil to experience subjective symptoms.[18]

There have been a few cases where soybean oil elicited an allergic response, but these cases followed intravenous infusion of an emulsion containing soybean oil, which seems far removed from typical consumption.[16,19,20] There is also 1 unusual case of a possible soy oil-induced allergy after an infant was fed exclusively on an amino acid-based formula containing a soybean oil-based component.[21] The circumstances of exposure in this exceptional case are unusual and the association with the soybean oil component of the formula was somewhat speculative.

In contrast to highly refined soybean oil, lecithin derived from soybeans does require labeling (a few exemptions have been granted) even though nearly all the protein is removed in the soy lecithin manufacturing process. According to Steve L. Taylor, PhD, and Joe L. Baumert, PhD, Food Allergy Research and Resource Program, University of Nebraska, soy lecithin does not contain sufficient soy protein residues to provoke allergic reactions in the majority of soy-allergic consumers.[22] On the other hand, these authors note there is "the possibility that some of the more sensitive soybean-allergic consumers might react to ingestion of soybean lecithin." More research on the allergenicity of soy lecithin is warranted.

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