New insights in hidden food allergies

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ABSTRACT

Food allergic reactions primarily occur after exposure to the offending food through ingestion, contact, or inhalation. However, it can occur covertly through hidden ways that are often missed, with undesirable consequences. Information has been accumulating over the years to indicate that food allergy (FA) may have been the problem in subjects who do not report an association to eating, touching, or smelling a food. Therefore, it would be prudent to explore the possibility of a hidden FA. The causative substance may be a food allergen or a nonfood allergen hidden in a previously tolerated food. Food allergens are commonly hidden in various medications, even in anti-allergy drugs. A blood product may passively transmit food allergens to a recipient who is sensitized or food-specific immunoglobulin E antibodies to a recipient who is nonatopic. It may also be excreted in breast milk, saliva, or semen. Transmission of the FA genetic trait can occur through transplantation of hematopoietic tissue. When the medical history and routine allergy evaluation do not point to the cause of an allergic reaction, it would be prudent to suspect hidden FA before labeling the reaction as idiopathic. A skillful detailed history taking, a cooperative patient, a careful reading of labels, and an interested allergist are needed for suspecting hidden FA and for planning an appropriate evaluation and verification of the offending allergen and, ultimately, optimal relief for the patient.

(J Food Allergy 5:19–24, 2023; doi: 10.2500/jfa.2023.5.230003)

The diagnosis of food allergy (FA) is usually considered when the reaction follows eating. In subjects who are highly sensitive, the reaction may also occur after touching[1] or smelling the food, particularly while being boiled, fried, or grilled.[2] However, severe FA has occurred in subjects who were not exposed to food through any of these three routes. This presentation addresses the hidden ways for food allergens in causing hypersensitivity reactions. Hidden exposures may occur in four main ways. First, the offending food allergen may be hidden in a previously tolerated food. Second, a nonfood offending allergen may be hidden in a previously tolerated food. Third, an offending food allergen may be hidden in a medical product. Fourth, passive transfer of the food allergen, of the food-specific immunoglobulin E (IgE) antibodies, or the FA genetic trait may occur.

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The author has no conflicts of interest to declare pertaining to this article
Presented at the Eastern Food Allergy & Comorbidity Conference, January 8, 2023, Palm Beach, Florida
Funding provided by the Eastern Food Allergy & Comorbidity Conference
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OFFENDING FOOD ALLERGENS HIDDEN IN TOLERATED FOODS

Offending food allergens that may be hidden in tolerated foods are listed in Table 1. Extrinsic contamination of a tolerated food by the offending allergen can be accidental or intentional.

Accidental contamination may occur at any stage during preparation of the food until its consumption. It can happen in the food industry, restaurants, home, or wherever food is being prepared or served. Indirect contamination can occur through the fingers of another person or through table utensils. In most instances, accidental contamination passes without being noticed. Food manufacturers may become aware of it if reactions are reported by multiple patients who were affected, which prompts constituent analysis of the implicated food by issuing a public "Allergy Alert," and withdrawal of the affected food batches from the market. Contamination in restaurants occurs from using shared utensils or from frying oils.

Intentional contamination is commonly practiced by adding "small" quantities of certain food ingredients to enhance taste, flavor, texture, or color. This is frequently done in the food industry, in restaurants, or at home. Psyllium-containing cereal products have provoked reactions in subjects who were sensitized through handling psyllium-containing laxatives.[3] Egg white allergens were detected in some processed meats.[4] It took many years for the U.S. Food and Drug Administration to require the food industry to provide safer labeling. In 2004, the Food Allergen Labeling and Consumer Protection Act required food manufacturers to list in plain common language the presence of any ingredient

Table 1 **Settings in which offending food allergens may be hidden in tolerated foods**

Extrinsic contamination
Food industry
Restaurants
Homes
Other (wherever food is handled)
Intrinsic contamination
Maternal food in breast milk
Fruit seeds in juice

Table 2 **Examples of food derivatives used on labels of commercial foods or medications**

Milk: casein, caseinate, whey, lactoglobulin, lactose, lactitol, lactis
Egg: albumin, ovalbumin, ovoglobulin, ovomucoid, ovomucin, ovovitellin, lysozyme, lecithin
Wheat: durum, semolina, triticum, triticale
Oat: avena
Corn: vegetable oil
Fish: gelatin, isinglass
Soybean: glycine, lecithin, vegetable oil
Peanut: arachis, vegetable oil
Almond: amygdalus, prunus
Brazil nut: bortholletia
Cashew: anacardium
Hazelnut: *Corylus*
Pecan: carya
Pistachio: pistacia
Walnut: juglons
Names of starches and their sources
Dextran: partially hydrolyzed corn or potato starch
Dextrin: hydrolysate of starch from corn, rice, tapioca, or wheat
Dextrose: powdered corn starch
Maltodextrin: starch from corn, potato, rice, or wheat
Pregelatinized starch: starch from corn potato, tapioca, or wheat
Starch glycolate: starch from corn, potato, rice, or wheat

of the eight most common food allergens: milk, egg, peanut, tree nuts, soybean, fish, shellfish, and wheat. Sesame was added to the list very recently (January 2023). Although this Act is commendable, it is far from providing optimal safety. Ideally all ingredients in a commercial food should be listed. Food labeling laws differ from one country to another.

Food labeling remains a significant problem by often being incomplete or incorrect, or by listing a large number of incorporated ingredients, which creates great difficulty in identifying the culprit, particularly when the added food ingredient is listed in terms that are not familiar to consumers (Table 2). Substituting ingredients by manufacturers can result in a reaction to a previously tolerated product. It is worth noting that the Food Allergen Labeling and Consumer Protection Act is voluntary labeling that lists such warnings as "may contain," "manufactured on shared equipment," and "processed in a facility that processes…" These individual "warnings" are determined by the manufacturer and do not indicate any level of risk.

Some labelings are meaningless to the consumer, *e.g.,* "natural and artificial flavors" or "starch." Packaged food labels may display symbols that consumers may not be familiar with, *e.g.,* "K" indicates a kosher food and "KD" indicates the presence of diary. However, inaccuracies may happen; some foods are labeled "K," yet the fine print of ingredients may include dairy products. The letter "U' inside a circle indicates that the Orthodox Union certified that the food's preparation was according to the Jewish dietary laws, *i.e.,* no dairy or pork; however, the presence of "D" next to the circle indicates the presence of dairy. The presence of "Parve" or "P" indicates the absence of dairy, meat, or fowl. A survey showed that consumers prefer having clearer, more specific, and consistent labeling on products.[5]

Intrinsic contamination can occur through mammary excretion of maternal diet allergens and may cause sensitization and provocation. Firer *et al.*[6] noted that infants who had minimal exposure to cow's milk developed more milk-specific IgE antibodies than infants who were milk fed. Such small quantities of food allergens can also provoke reactions exclusively in infants who were breast fed.[7] In five infants with allergy while being exclusively breast fed, the hidden responsible allergens were peanut, white egg and/or cow's milk.[8] The offending food may be identified by the mother if it was eaten infrequently, which facilitates the observation of a causal relationship with the infant's reaction.

Fruit-seed allergen should be among the suspects in subjects who react to commercial fruit juice but not upon eating the pulp.[9–11] Prick-by-prick skin testing results would be positive to the seed and not to the pulp.

NONFOOD ALLERGENS HIDDEN IN TOLERATED FOODS

Nonfood allergens that may be hidden in tolerated foods are listed in Table 3. When reactions occur after eating any of multiple different foods or a commercially prepared food but not when home prepared

Table 3 **Nonfood allergens that may be hidden in tolerated foods**

Additives
Spices
Medications
Natural rubber latex
Insects in grain or flour
Parasites (*Anisakis simplex* in seafood)

Table 4 **Medical products that may contain food allergens**

Oral medications
Injectables
Dermatologic topical
Nasal drops
Respiratory inhalers
Suppositories
Dental preparations

and a routine evaluation for FA is negative, the culprit can be a hidden nonfood allergen. A large variety of additives[12] and spices[13] are being added to foods and can cause allergic reactions. Identification of the offending culprit can be difficult and time consuming. It requires skillful history taking, a very cooperative patient, complete food labeling, and tactfully obtaining detailed information from the food source. The difficulty is compounded by the lack of reliable skin testing extracts or blood tests for additives or spices. Reasonable diagnostic approaches have been published.[12,13] One of my patients was a teenager who had recurrent acute urticaria after some meals without pointing to any specific food and her evaluation for FA was negative. In subsequent visits, she suspected ice cream. Realizing that acetyl salicylic acid is often added as an acidifier in some food products, including ice cream, challenging her with 100 mg of aspirin induced lip angioedema and generalized giant urticaria within minutes.

Chemicals may be added to commercial foods to prevent spoilage, most commonly nitrites, nitrates, benzoate, and sulfites. Polyethylene glycols and polysorbates are incorporated in many foods[14] The addition of antibiotics to consumable food is illegal and has caused allergic reactions in some subjects after consuming an antibiotic-contaminated food (*e.g.*, milk, cheese, chicken, beef). Handling food with natural rubber latex gloves can provoke reactions in subjects who are highly sensitive.[15]

Insects (*Dermatophagoides* or *Liposcelis bostryochophilia*) can infest grains or flour and cause severe reactions in patients with respiratory allergy to these insects.[16,17] *Anisakis simplex*, a nematode that infests sea mammals is seemingly common in Japan and Spain; its larvae use several seafood species as intermediate host. The larvae protein is heat stable and can sensitize and provoke allergic reactions in consumers of the infested seafood.[18]

FOOD ALLERGENS IN MEDICAL PRODUCTS

Medical products that may contain food allergens are listed in Table 4. Food proteins are commonly incorporated as inactive ingredients in medications, yet rarely are thought of as a possible culprit in reactions related to drugs. Solid oral medications were reported to contain lactose (derived from bovine milk) in 44.8%, corn starch in 36.5%, and gelatin (fish or cattle derived) in 16.9%.[19] Lactose is declared on the label of several asthma medications in inhalers or tablets in small quantities that do not affect subjects who are lactose intolerant and can be tolerated by most patients with milk allergy but may provoke reactions in patients who are exquisitely sensitive. Several antihistamine preparations contain lactose, gelatin, cinnamon, cocoa butter, or starch (of corn, potato, rice, or wheat), any of which was reported to provoke allergic reactions.[20] Similarly, some corticosteroid preparations contained minute quantities of food proteins that triggered acute systemic reactions.[21] A particular injectable corticosteroid preparation (methylprednisolone) contained milk protein in one of its marketed concentrations but not in another, although by the same manufacturer and with the same trade name.[22]

Reactions have been reported to egg-derived lysozyme in a nasal drops preparations[23] or in vaginal suppositories.[24] Anaphylaxis occurred during artificial insemination with the husband's sperms that were suspended in a medium that contained bovine serum albumen.[25] Egg- or soybean-derived lecithin is present in propofol and has provoked reactions in subjects allergic to the respective food.[26] Certain vaccines contain food protein (egg, milk, or gelatin) in very minute quantities that rarely caused reactions in the respective subjects who are allergic. Current Corona COVID-19 vaccines do not contain food proteins. Some reactions to dermatologic preparations or cosmetics were actually caused by a food ingredient derived from milk, egg, wheat, oat, sesame, or peanut.[27] In Lithuania, a survey of 276 skin care products that were being marketed for children revealed that 39% of product labels listed at least one food allergen.[28] In the 156 products that declared food allergens, almond was in 41.7%, wheat in 22.4%, soy in 15.4%, oat in 10.3%, sesame in 8.3%, milk in 1.3%, and peanut in 0.6%.

PASSIVE TRANSFER OF FA

Routes of passive transfers of FA are listed in Table 5. FA has occurred through passive transfer of the food

Table 5 **Passive transfers of food allergy**

Transfer of	Route
Food allergen	Transplacental, transmammary, saliva, blood-products infusion
Food-specific immunoglobulin E antibodies	Blood-products infusion
Atopic genetic trait	Bone marrow or stem cell transplantation, liver transplantation

allergen to a patient already food sensitized or of food-specific IgE antibodies to a person who is nonatopic. Transmission of the food-specific atopic genetic trait has also been reported.

Transplacental transfer of food allergens is supported by clinical observations and by experimental findings. In clinical practice, parents often report allergic reactions in the infant to the very first postnatal exposure of a certain formula or a baby food, which suggests a prenatal sensitization. Food-specific IgE, which does not cross the placenta from the mother's circulation, has been detected in the umbilical cord.[29] A relationship has been reported between food sensitization in young infants and the maternal intake of the respective food during pregnancy.[30] An *ex vivo* experiment demonstrated the passage of food protein through the placenta from the maternal side to the infant's side.[31,32] In a case report on a 2-hour old newborn,[33] the first dose (3 mL) of a milk formula caused a severe reaction 4 hours later; the baby had a very high total IgE level, of 29 IU/mL, and of milk-specific IgE class 4.

Transmammary transmission of food protein has been referred to above. Experimentally, when the ingestion of 50 g of peanut by 23 lactating mothers, the allergen was detected in breast milk in about half of them (11).[34] It was detected within 1 hour in 8 (73%), 2 hours in 2, and 6 hours in 1; it cleared by 3 hours in 9 (82%), by 6 hours in 1, and > 8 hours in 1.[34]

With regard to the transplacental and transmammary food allergen transfer, the pediatrics and allergy societies guidelines consider the studies did not provide evidence strong enough to recommend dietary restrictions during pregnancy or lactation to prevent FA in infants.[35]

Saliva can transmit food allergens that can provoke a reaction through kissing. The food allergen may remain in the oral cavity even after tooth brushing.[36] A man with peanut allergy developed a reaction after a kiss by his girlfriend who 2 hours earlier ate peanuts then brushed her teeth well, rinsed mouth, and chewed gum.[37] This suggests that the food allergen after systemic absorption may be excreted in allergenic quantities in the saliva.[38]

Semen may transmit food allergens and provoke a local or systemic reaction on vaginal mucosal contact of the woman who was allergic.[39] Such a route is markedly missed because is difficult to suspect by the patient or to explore by the physician, particularly with the involvement of embarrassment.

Blood products can transmit FA in two ways. A subject who is sensitized or allergic and receives a blood product from a donor who is not allergic whose circulation contains the offending food allergen.[40] Alternatively, food-specific IgE antibodies in blood from a donor who is allergic can cause transient passive sensitization in the recipient who would react on exposure to the specific food for a period of weeks or months.[41] Skin and/or specific IgE testing would be initially positive but, after a few weeks, turns negative and the subject resumes eating that food without any symptoms.

Genetic transmission of the FA-specific trait can occur through bone marrow or stem cell transplantation to a recipient who is nonatopic.[42,43] Liver transplantation (a hematopoietic organ) may transfer either the FA genetic trait or of sensitized mature lymphocytes.[44]

GUIDELINE FOR HIDDEN FA INVESTIGATION

Hidden FA is probably much more common than being currently realized, estimated at 22% of all FA reactions.[44] When routine history taking and allergy evaluation do not point to a cause of an allergic reaction, it would be prudent to explore the possibility of a hidden food allergen.

A skillful history should include all ingredients of the suspected food, the source, where was the food consumed, and any other consumed food or medications around the time of that meal. In addition to a careful reading of labels, tactful contact with the food's source may be needed. Information on the circumstances at the time of the reaction may reveal the involvement of cofactors.[45,46] An interested allergist and a cooperative patient are needed to suspect a hidden food allergen, in planning to identify the culprit, and the provision of personalized dietary management. Skin-prick testing with the suspected food as a whole and its individual ingredients might be rewarding but of very low reliability for hot spices or synthetic additives. Well-designed blind, titrated challenge tests would verify the culprit. Suggested titrated challenge doses of common additives and spices have been published.[12,13] The concentration of a constituent allergen

in the suspected food should not decide on its role without verification.[47,48]

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