

Peanut-Induced Anaphylactic Reactions

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Key Words

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Abstract

Food allergies, particularly to peanuts, are a common cause of anaphylaxis. Approximately 125 people die each year in the USA secondary to food-induced anaphylaxis. Clinical anaphylaxis is a syndrome of diverse etiology and dramatic presentation of symptoms associated with the classic features of type I, IgE-mediated hypersensitivity [1]. Typically the term anaphylaxis connotes an immunologically-mediated event that occurs after exposure to certain foreign substances. This reaction results from the generation and release of a variety of potent biologically active mediators and their concerted effects on various target organs. Anaphylaxis is recognized by cutaneous, respiratory, cardiovascular, and gastrointestinal signs and symptoms occurring singly or in combination. This article focuses on allergic reactions to peanuts that manifest as signs and symptoms involving multiple target organs or the cardiovascular system alone.

Prevalence

The prevalence of anaphylaxis is unknown since unlike many disorders, there is no requirement to report such reactions to any national registry. In addition, it is likely that many cases are misdiagnosed. Also contributing to this lack of scientific data is the fact that many patients who experience a mild anaphylactic reaction recognize the causative relationship to a specific food and simply avoid that food rather than consult a physician. Sorensen et al. [2] reviewed all cases of anaphylactic shock occurring outside the hospital in the Thisted Hospital catchment area, in Denmark. Twenty cases of anaphylaxis were identified, or 3.2 cases per 100,000 inhabitants per year, and 5% were fatal. If similar rates occur in the USA about 8,300 cases of anaphylaxis could be anticipated each year, with about 415 deaths. As suggested above, these investigators found that 8 of the 20 cases (40%) had been given an incorrect *International Classification of Diseases* code at the time of discharge. In this series, drugs, food and insect stings accounted for virtually all of the anaphylactic reactions.

In a retrospective survey, Yocum and Khan [3] reviewed all cases of anaphylaxis treated in the Mayo Clinic Emergency Department (USA) over a 3.5-year period. Records were reviewed on all patients experiencing respiratory obstructive symptoms and/or cardiovascular symptoms plus evidence of allergic mediator release, e.g. urticaria. Overall, 179 patients were identified; 66% were female, 49% were atopic, and 37% had experienced an immediate reaction to the responsible allergen in the past. A probable cause was identified in 142 cases: food – 59 cases (33%), bee sting –

25 cases (14%), medications – 23 cases (13%), and exercise – 12 cases (7%). Allergic reactions to food were found to be the most common cause of anaphylactic reactions outside of the hospital, more frequent than reactions to bee sting and drugs combined. Again, extrapolating from the Sorensen data, this would suggest that there are about 2,500 food-induced anaphylactic reactions in the USA each year, with about 125 deaths. Peanuts and nuts were the most common foods causing serious anaphylactic reactions. In a separate study, Bock [4] surveyed 73 emergency departments in Colorado over a 2-year period and identified 25 cases of severe anaphylactic reactions to food with 1 death. From this data, it was concluded that at least 950 cases of severe food-induced anaphylaxis occur in the USA each year. However, the author cautioned that his survey was an underestimate of the problem since patients had been referred to him who were not included in the survey, and the proportion of reactions was higher in the rural emergency departments serving smaller populations than in the busier metropolitan departments. A 5-year survey of anaphylactic reactions treated at the Children's Hospital of Philadelphia also showed that food allergy was the most common cause of anaphylaxis outside of the hospital S.D. Dibs and M.D. Baker, presented at the Ambulatory Pediatrics Association, San Diego, Calif., 1995]. A recent survey of over 4,000 households with a validated survey instrument indicated that approximately 1.1% of the population in the USA had either peanut allergy or tree nut allergy (0.6% had peanut allergy) [5]. In this study, 81% of the respondents had respiratory tract or multisystem reactions. This data allows another estimate of the prevalence of food-induced anaphylaxis because of the percentage of individuals who experience systemic reactions after the ingestion of peanuts. Overall peanuts appear responsible for at least 25% of food-induced anaphylactic episodes.

Fatal Food Anaphylaxis

The first of several reports on fatal food-induced anaphylaxis was in 1988 by Yunginger et al. [6] who reported 7 cases of fatal anaphylaxis evaluated during a 16-month period. In all but possibly 1 case, the victims unknowingly ingested a food which had provoked a previous allergic reaction. Similarly, 6 fatal and 7 near-fatal food-induced anaphylactic reactions in children (ages 2 to 17 years) were accumulated from three metropolitan areas over a 14-month period [7]. In these two studies, 7 of 13 food-related deaths were secondary to peanuts. Common risk factors were noted in these cases: all patients had asthma (although gener-

ally well controlled); all patients were unaware that they were ingesting the food allergen; all patients had experienced previous allergic reactions to the incriminated food, although in most cases symptoms had been much milder; and all patients had immediate symptoms with about half experiencing a quiescent period prior to a major respiratory collapse. In both series, no patient who died received adrenaline immediately, however, 3 patients with near-fatal reactions did receive adrenaline within 15 min of developing symptoms but still went on to develop respiratory collapse and hypotension requiring mechanical ventilation and vasopressor support for 12 h to 3 weeks. Interestingly, patients investigated with life-threatening food-induced anaphylaxis had no significant increase in serum tryptase, raising some questions about the exact mechanism of food-induced anaphylaxis [7].

Predisposing Factors

Several factors appear to predispose an individual to food-induced anaphylaxis including a personal history of atopy, family history of atopy, age, and dietary exposure. Atopic patients with asthma have an apparent increased risk of developing more severe food allergic reactions [7, 8]. In the reports of Yunginger et al. [6] and Sampson et al. [7], the majority of individuals were highly atopic, and all had histories of asthma. Although atopy reportedly does not predispose individuals to an increased risk of anaphylaxis [9], it does tend to predispose to more severe reactions. Individuals inherit the ability to produce antigen-specific IgE to food proteins, although there is no conclusive information that hypersensitivity to a specific food is inherited.

Age

Age may play a factor in predisposing an individual to food-induced anaphylaxis. The incidence of food allergy appears greatest in the first 2 years of life and decreases with age. Consequently, foods introduced during the first year (e.g. cow's milk, egg, soy, wheat, and in the USA, peanut (as peanut butter)) are more apt to induce hypersensitization. Allergic reactions to milk, egg, soybean, and wheat are generally 'outgrown' with age [10, 11]. While most food hypersensitivities are outgrown during childhood, food sensitivity to peanuts, tree nuts, fish, and shellfish often persist into adulthood [8, 12]. It is quite uncommon to find a patient that develops clinical tolerance to peanuts or tree nuts [13].

Dietary Factors

Dietary exposure can influence the occurrence of food-induced anaphylaxis in several ways. Different populations and nationalities may consume more of certain foods, and the increased exposure may result in increased prevalence of that specific food allergy. In the USA peanut is one of the most common food allergies [14, 15]. Americans ingest several tons of peanuts daily [12]. By contrast, in Scandinavia, where fish consumption is high, the incidence of allergic reactions to codfish is increased.

Foods

A large variety of foods have been reported to precipitate an anaphylactic reaction. The list of foods that potentially may induce an anaphylactic reaction is unlimited, and in theory, any food protein is capable of causing an anaphylactic reaction. Certain foods tend to be cited most frequently as the cause of anaphylaxis, although any food may be the cause. Foods most often responsible for anaphylactic reactions include peanuts (and to a lesser extent other legumes: soybeans, pinto beans, peas, green beans, garbanzo beans), fish (e.g. cod, whitefish), shellfish (shrimp, lobster, crab, scallops, oyster), tree nuts (hazelnuts, walnuts, cashew, almonds, pistachio), cow's milk, egg, fruits (banana, kiwi), seeds (cotton seed, sunflower seed), and cereals or grains (wheat, rice, rye, millet, buckwheat).

The potency of particular foods to induce an anaphylactic reaction appears to vary and is also dependent upon the sensitivity of the individual. In general, it appears that for some foods such as peanuts, microgram quantities may be sufficient to induce a reaction. In oral food challenge studies where food-allergic patients are challenged on a regular basis (e.g. annually) over a period of years, patients who eventually become tolerant to a food often appear to tolerate more of the antigen in successive years. For example, the initial challenge may be positive after 500 mg of the food and then in the subsequent challenge 1 year later the patient may tolerate 5 g of the food. The next challenge the following year may reveal that the patient is no longer sensitive to that food.

Prior exposure and sensitization to food allergens theoretically must precede the initial anaphylactic reaction. However, there are patients who have had an anaphylactic reaction after the first known exposure to a food substance. In a recent study of patients with either peanut and/or tree nut allergy, almost 75% of the patients who were allergic to peanuts had a clinical reaction on their first known exposure

[16]. Several possibilities may account for this apparent paradox: most often, infants are sensitized to foods passed in maternal breast milk during lactation; sensitization may occur following an unknown exposure to a food antigen (e.g. milk formula given during the night in the newborn nursery, food given by another caregiver (e.g. babysitter or grandparent), or food contained in another product which was not suspected of containing the antigen in question), and sensitization may occur because of cross-sensitization to a similar allergen (e.g. kiwi or banana allergy in a latex-sensitive individual [17]). There has also been recent data suggesting that sensitization may occur in utero [18].

Peanut Allergens

Immediate hypersensitivity reactions to foods are mediated through the interaction of IgE to a specific food protein. While specific IgE-binding epitopes from the major allergens of cow's milk [19], codfish [20], hazel nut [21], soybeans [22], and shrimp [23] have been elucidated, there have been few, if any, common characteristics found in these binding sites. We have determined the linear epitopes of the three major peanut allergens by synthesizing overlapping peptides that represent the entire allergen and then using pooled serum IgE from a peanut-sensitive patient pool to identify IgE-binding regions. As an initial screen, each peptide was 15 amino acids long and was offset from the previous peptide by 8 amino acids. In this manner the entire length of each allergen could be studied in large overlapping fragments. These peptides were then probed with a pool of serum from 15 patients with documented peanut hypersensitivity or serum from a representative control patient. Serum from control patients did not recognize any of the synthesized peptides. In contrast, there were 12, 3, and 4 IgE-binding regions along the entire length of the Ara h 1, Ara h 2, and Ara h 3 allergens, respectively, that were recognized by this population of patients with peanut hypersensitivity [24–26].

In order to determine the exact amino acid sequence of the IgE-binding regions, small peptides (either 10 or 15 amino acids long offset by 2 amino acids) representing the larger IgE-binding regions were synthesized. In this manner it was possible to identify individual IgE-binding epitopes within the larger IgE-binding regions. There were 23, 10, and 4 IgE-binding epitopes identified in this manner for the Ara h 1, Ara h 2, and Ara h 3 allergens, respectively. The size of the epitopes ranged from 6 to 15 amino acids in length. There was no obvious amino acid sequence motif shared by all the epitopes.

In an effort to determine which, if any, of the epitopes was immunodominant, each set of epitopes was probed individually with serum IgE from 10 different patients. Five patients were randomly selected from the pool of 15 patients used to identify the common epitopes, and 5 patients were selected from outside this pool. All of the patient sera recognized multiple epitopes with 4, 3, and 1 epitopes being identified as immunodominant for Ara h 1, Ara h 2, and Ara h 3, respectively.

Our work on the IgE-binding sites of Ara h 1, 2, and 3 indicates that there are no common amino acid sequence motifs shared by these epitopes. However, we have determined that in the IgE-binding epitopes of these allergens the hydrophobic amino acid residues appear to play a critical role in IgE binding. This was determined by synthesizing each of the allergen epitopes either as a 10 or 15 amino acid long peptide with alanine residues being substituted one at a time for each of the amino acids in the epitope. These peptides were then probed with serum IgE from 15 patients with documented peanut hypersensitivity. Results from these experiments indicated that each epitope could be mutated to a non-IgE-binding site by the alteration of a single amino acid. In addition, each epitope had more than one amino acid, when changed to alanine, that resulted in loss of IgE recognition. The observation that alteration of a single amino acid leads to the loss of IgE binding in a population of peanut-sensitive individuals is significant because it suggests that while each patient may display a polyclonal IgE reaction to a particular allergen [25, 27], IgE from different patients that recognize the same epitope must interact with that epitope in a similar fashion. Besides finding that many epitopes in each of the different peanut allergens contained more than one residue critical for IgE binding, it was also determined that more than one residue type (ala or met) could be substituted at certain positions in an epitope with similar results. This information may allow for the design of a hypoallergenic protein that would be effective at blunting allergic reactions for a population of peanut-sensitive individuals. Furthermore, a peanut where the IgE-binding epitopes of the major allergens have been removed may prevent the development of peanut hypersensitivity in genetically predisposed individuals.

The characteristics that have been attributed to allergenic proteins include their abundance in the food source, their resistance to food processing, and their stability to digestion by the gastrointestinal tract [28–30]. The major allergens of foods and in particular the Ara h 1 peanut allergen have been shown to survive intact most food-processing methods and to be stable to digestion in *in vitro* systems designed to mimic the gastrointestinal tract. Our observa-

tions on the tertiary structure of the Ara h 1 monomer and the determination that this protein readily forms a trimeric complex may help to determine why this protein is allergenic. While there are numerous protease digestion sites throughout the length of this protein, the structure may be so compact that potential cleavage sites are inaccessible until the protein is denatured. A homology-based model of Ara h 1 tertiary structure was generated to determine the location of the epitopes on this relatively large allergenic molecule. The tertiary structure of the molecule consists of two sets of opposing antiparallel β -sheets in Swiss roll topology joined by an interdomain linker. The terminal regions of the molecule consist of α -helical bundles containing three helices each. Interestingly, even though the IgE-binding epitopes are scattered along the entire length of the Ara h 1 linear sequence, the tertiary structure of this molecule shows that the IgE-binding epitopes are clustered primarily on the α -helical bundles [31]. The physical properties of the Ara h 1 molecule and the other peanut allergens may help to explain the extreme allergenicity exhibited by peanut proteins.

The only therapeutic option currently available for the prevention of a peanut hypersensitivity reaction is food avoidance. Unfortunately, for a ubiquitous food such as peanut, the possibility of an inadvertent ingestion is great. Interestingly, most of the peanut allergens identified to date, including Ara h 1, 2, and 3, have sequence homology with proteins in other plants. This information may help to begin to explain the cross-reacting IgE antibodies to other legumes that are found in the sera of patients that manifest clinical symptoms to only one member of the legume family [32]. Certainly, the elucidation of the position of the Ara h 1 binding epitopes clustered on the surface of the molecule may enable us to understand why these regions elicit the clinical symptoms associated with peanut hypersensitivity. Perhaps the presentation of multiple, clustered epitopes to mast cells results in a more efficient and dramatic release of mediators that result in the more severe clinical symptoms observed in patients with peanut hypersensitivity. Current work is exploring this possibility by comparing the IgE-binding epitopes and tertiary structures of other legume allergens.

Taken in total these studies suggest that an altered Ara h 1, 2, or 3 gene could be developed to replace its allergenic homologue in the peanut genome, thus blunting allergic reactions in sensitive individuals who inadvertently ingest this food. Since these gene products are abundant and integral seed storage proteins, it would be necessary for the altered protein to retain as much of its native function, properties, and three-dimensional structure as possible. The information

gained from these studies on the peanut allergens indicates that development of hypoallergenic seed storage proteins may be feasible. Additionally, a less allergenic peanut protein with the immunodominant IgE epitopes mutated, may prove to be beneficial in feeding the at-risk group of atopic individuals rather than the current peanut protein as we know it. However, the effect of altering critical amino acids within each of the IgE-binding epitopes has on the properties of the seed storage proteins is currently unknown. Given the widespread use of peanuts in consumer foods and the potential risk this poses to individuals genetically predisposed to developing peanut allergy and to the health of individuals already peanut sensitive, this approach is currently being explored in our laboratories.

Diagnosis

Because of its abrupt and dramatic nature, the diagnosis of systemic anaphylaxis is generally readily apparent. In many cases where a food is implicated, the inciting food is obvious from the temporal relationship between the ingestion and the onset of symptoms. The initial step in determining the cause of an episode of anaphylaxis is a very careful history, especially when the cause of the episode is not straightforward. Specific questions to address include the type and quantity of food eaten, the last time the food was ingested, the time frame between ingestion and the development of symptoms, the nature of the food (cooked or uncooked), other times when similar symptoms occurred (and if the food in question was eaten on those occasions), and whether any other precipitating factors appear to be involved, e.g. exercise.

Basically, any food may precipitate an anaphylactic reaction, but there are a few specific foods which appear to be most often implicated in the etiology of food-induced anaphylactic reactions: peanuts, tree nuts, fish, and shellfish. In cases where the etiology of the anaphylactic reaction is not apparent, a dietary history should review all ingredients of the suspected meal including any possible concealed ingredients or food additives. The food provoking the reaction may be merely a contaminant (knowingly or unknowingly) in the meal. For example, peanuts or peanut butter are frequently added to cookies, candies, pastries, or sauces such as chili, spaghetti, and barbecue sauces. Chinese restaurants frequently use peanut butter to hold together the overlapping ends of an egg roll, pressed or 'extruded' peanut oil in their cooking, and the same wok to cook a variety of different meals resulting in residual contaminant carry-over. Another infrequent (but not rare) cause of food contamination

occurs during the manufacturing process. This contamination may happen with scraps of candy that are 'reworked' into the next batch of candy or in processing plants where there is a production change from one product to the next. As an example, a reaction to almond butter by a peanut-allergic patient started an investigation that determined that 10% of the almond butter produced in that plant was contaminated with peanut butter. This occurred after a production change in the manufacturing process from peanut butter to almond butter.

Laboratory evaluation

The laboratory evaluation of patients with an anaphylactic reaction should be directed at identifying specific IgE antibodies to the food in question. IgE antibody can be recognized *in vivo* by prick or puncture skin testing. Although not absolutely proven in patients with anaphylaxis, a negative prick/puncture skin test is an excellent predictor for a negative IgE-mediated food reaction to the suspected food. In contrast, a positive prick skin test does not necessarily mean that the food is the inciting agent, but in patients with classic histories of anaphylaxis to ingestion of an isolated food and a positive prick/puncture skin test to that food, this laboratory test appears to be a good positive predictor of allergic reactivity.

There may be some limitations to skin testing which need to be recognized. There is speculation that skin testing shortly after the occurrence of anaphylaxis may fail to yield a positive response owing to temporary anergy. Although not demonstrated in food allergy, this phenomenon has been demonstrated in Hymenoptera sensitivity following an insect sting [33]. Possible causes of false-negative prick skin tests include: (1) improper skin test technique, (2) concomitant use of antihistamines, or (3) the use of food extracts with reduced or inadequate allergenic potential. With some foods, the processing of the food for commercial extracts may diminish antigenicity [34]. This is especially true for some fruits and vegetables. However, if there is a high index of suspicion that a food may have precipitated an anaphylactic reaction even though the prick skin test is negative, the patient should be tested with the natural food utilizing the 'prick-plus-prick' method to ensure an absence of detectable specific IgE antibody [35]. Some caution should be exercised in doing this procedure since the amount of antigen on the prick device will not be controlled, and appropriate negative controls also should be performed.

Appropriate skin testing is indicated in each patient, although *in vitro* measurement of food-specific IgE may be

evaluated initially. In many patients with anaphylaxis, limited prick skin testing is necessary to confirm the etiology of the anaphylactic reaction. In cases of idiopathic anaphylaxis, more extensive prick testing may be helpful for diagnosis [36]. The clinician must decide how many skin tests are practical and justified, taking into account the anticipated low yield of positive results in idiopathic anaphylaxis and the value of discovering an etiology in this serious disorder.

Some individuals will perform intradermal skin tests following negative prick/puncture skin tests, but the diagnostic significance of a positive intradermal test following a negative prick/puncture test is dubious, and probably of no clinical benefit [37]. Anaphylactic reactions have been documented following intradermal skin tests to foods [38], so extra caution should be exercised if intradermal tests are performed. In reality there is no indication for an intradermal skin test to foods to be performed.

In cases where extreme hypersensitivity is suspected, alternative approaches may be warranted including the further dilution of the food extract prior to prick skin testing or the use of a food-specific in vitro test, e.g. radioallergosorbent test; RAST. Overall, the RAST is considered less sensitive and specific than the prick skin test. In high-quality laboratories a 3+ to 4+ RAST (on a 1+ to 4+ Phadebas RAST scale) probably has a similar positive predictive accuracy as prick skin test 3 mm greater than the negative control [39]. The new CAP-FEIA™ appears to be slightly more sensitive than the standard RAST and has improved predictive values [40].

Massive activation of mast cells during anaphylaxis results in a dramatic rise in plasma histamine and somewhat later a rise in plasma or serum tryptase [41–43]. Plasma histamine rises over the first several minutes of a reaction, generally remains elevated for a brief period of time, requires special collection techniques, and will break down unless the plasma sample is frozen immediately. Consequently, measurement of plasma histamine to document anaphylaxis is impractical except in research situations. Whether measurement of urinary methylhistamine will be useful in the documentation of anaphylaxis remains to be demonstrated. Serum tryptase rises over the first hour and may remain elevated for many hours. It is fairly stable at room temperature and can be obtained from postmortem specimens. Tryptase has been shown to be markedly elevated in most cases of bee sting or drug-induced anaphylaxis [42, 43]. Unfortunately, tryptase is frequently not elevated in food-induced anaphylaxis [7]. The reason for this is not clear, but suggests that other cells, such as basophils or monocytes/macrophages may be more important in food-induced anaphylaxis.

Double-blind placebo-controlled food challenges are contraindicated in patients with an unequivocal history of anaphylaxis following the isolated ingestion of a food to which they have evidence of significant IgE antibodies. However if several foods were ingested and the patient has positive skin tests to several foods, it is essential that the responsible food be identified. Patients have been reported who experienced repeated anaphylactic reactions because physicians incorrectly assumed that they had identified the responsible food [7]. Young children who experience anaphylactic reactions to foods other than peanuts, tree nuts, fish and shellfish may eventually outgrow their clinical reactivity, so an oral challenge may be warranted following an extended period of food elimination with no history of reactions to accidental ingestions.

Long-Term Management

The life-threatening nature of anaphylaxis makes prevention the cornerstone of therapy. If the causative food allergen is not clearly delineated, an evaluation to determine the etiology should be promptly initiated so that a lethal recurrence can be prevented, as discussed above. The central focus of prevention of food-induced anaphylaxis requires the appropriate identification and complete dietary avoidance of the specific food allergen. Certain factors place some individuals at increased risk for more severe anaphylactic reactions: (1) history of a previous anaphylactic reaction, (2) history of asthma, especially if poorly controlled, (3) allergy to peanuts, nuts, fish, and shellfish, (4) patients on β -blockers or ACE inhibitors, and (5) possibly being female. An educational process is imperative to ensure the patient and family understands how to avoid all forms of the food allergen and the potential severity of a reaction if the food is inadvertently ingested. The *Food Allergy Network* is a nonprofit organization in Fairfax, Virginia, USA. (Tel. +1 800 929 4040) which can assist in providing patients information about food allergen avoidance and which has several programs for schools and parents of children with food allergies and anaphylaxis.

It is not uncommon for patients experiencing a previous food-allergic reaction to subsequently demonstrate some instinctive avoidance measure. This may be typified by extreme dislike for the taste or even smell of the offending food. A very proactive role is required for the sensitized person to completely avoid a food that has caused a previous anaphylactic reaction. For many this may even require total removal of the food from the household. Educational measures must be directed at the patient, his/her family, and

school personnel and other caretakers or fellow workers so that they understand the potential severity and scope of the problem. If a patient ingests a food prepared outside the home, they must always be very cautious and not hesitate to ask very specific and detailed questions concerning ingredients of foods they are planning to eat. Unfortunately, it is not uncommon for patients dining in restaurants to ingest a food that they were assured did not exist in the meal they were eating.

Prognosis

For many young children diagnosed with anaphylaxis to foods such as milk, egg, wheat, and soybeans, there is a good possibility that the clinical sensitivity may be out-

grown after several years [10, 11]. Children who develop their food sensitivity after 3 years of age are less likely to lose their food reactions over a several year period. Allergies to foods such as peanuts, tree nuts, fish, and seafood are generally not outgrown no matter at what age they develop. These individuals appear likely to retain their allergic sensitivity for a lifetime. Consequently, several groups are evaluating new strategies to 'desensitize' patients to these foods.

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