

Fatal food-induced anaphylaxis

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In the beginning of this century, Schlossman (1905) reported a patient who developed acute shock after the ingestion of cow's milk (1), but the first series of food-induced anaphylaxis in man was not published until 1969 (2). Goldbert et al. described 10 cases of anaphylaxis following the ingestion of various foods, including different legumes, fish, and cow's milk. Food-induced anaphylaxis is an allergic syndrome manifested by an abrupt onset of symptoms within minutes to hours of ingesting a food and is associated with the classic features of IgE-mediated hypersensitivity. The syndrome results from the generation and release of various potent biologically active mediators and their combined effects on various target organs. Anaphylaxis is recognized by cutaneous, respiratory, cardiovascular, and gastrointestinal signs and symptoms occurring singly or in combination. Most food-induced anaphylactic reactions in the USA and Europe are the result of allergic reactions to peanuts, tree nuts, fish, and shellfish.

Prevalence

The true prevalence of severe and fatal food-induced anaphylactic reactions is not known. Sorensen et al. reviewed all cases of anaphylactic shock occurring outside the hospital in the Thisted Hospital catchment area, in Denmark (3). Twenty cases of anaphylaxis were identified, or 3.2 cases per 100 000 inhabitants per year, and 5% were fatal. These investigators found that 40% of patients had been given an incorrect *International Classification of Diseases* code at the time of discharge. Given this significant rate of misdiagnosis and the lack of requirement to report food-induced anaphylaxis, the possibility of obtaining reliable information regarding the prevalence and mortality rate of

food-induced anaphylaxis is slight. In a retrospective survey, Yocum & Khan reviewed all cases of anaphylaxis treated in the Mayo Clinic Emergency Department (USA) over a 3.5-year period (4). Records were reviewed on all patients experiencing respiratory obstructive symptoms and/or cardiovascular symptoms plus evidence of allergic mediator release: urticaria, angioedema, etc. A total of 179 patients were identified; 66% were female, 50% 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 (33%), bee sting (14%), medications (13%), and exercise (7%). Allergic reactions to food were the leading single cause of anaphylactic reactions outside the hospital, more frequent than reactions to bee sting and drugs combined. Similar findings were reported more recently in other surveys of anaphylactic reactions (5-7). Severe anaphylaxis in children treated in emergency departments is due to foods in about 50% of cases (8). Assuming similar rates of severe anaphylaxis in the USA as found in Denmark (3), about 8300 cases of anaphylaxis could be anticipated in the USA each year, with about 415 deaths. According to the etiologic distribution reported by Yocum & Khan (4), there would be about 2500 food-induced anaphylactic reactions in the USA each year, with about 125 deaths.

The first of several reports on fatal food-induced anaphylaxis was published in 1988 by Yunginger et al., who reported seven cases of fatal anaphylaxis evaluated during a 16-month period (9). In all but possibly one case, the victims unknowingly ingested a food that had provoked a previous allergic reaction. In 1992, we reported six fatal and seven near-fatal food-induced anaphylactic reactions in children (aged 2-17 years) that occurred in three

Table 1. Foods most frequently implicated in food-induced anaphylaxis

Peanut	
Tree nuts	(walnuts, hazelnuts [filberts], cashews, pistachios, Brazil nuts)
Fish	(less often tuna)
Shellfish	(shrimp, crab, lobster, oyster, scallop)
Milk	(cow, goat)
Chicken egg	
Seeds	(cottonseed, sesame seed, pine nuts, psyllium)
Fruit	(kiwi)
Cereal grains	(wheat)

metropolitan areas over a 14-month period (10). Common risk factors for these severe reactions included the following: asthma (even if well controlled); inability to identify food allergen in a meal; and previous allergic reactions to the incriminated food, although in most cases symptoms had been much milder. In addition, all patients had immediate symptoms, with about half experiencing a quiescent period before a major respiratory collapse. In both series, no patient who died received epinephrine immediately; however, three patients with near-fatal reactions did receive epinephrine 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. None of the patients studied had a significant increase in serum tryptase, raising some question about the exact mechanism of food-induced anaphylaxis (10).

Reports of food-associated exercise-induced anaphylaxis appear to be increasing, possibly due to the increased popularity of exercising over the past decade. Two forms of food-associated exercise-induced anaphylaxis have been described: reactions following the ingestion of specific foods (e.g., celery, shellfish, wheat) (11–13) and rarely reactions following the ingestion of any food (14). Typically, anaphylaxis occurs when a patient exercises within 2–4 h of ingesting a specific food. Otherwise the patient can ingest the food without any apparent reaction and can exercise without any apparent reaction as long as the specific food (or any food in the case of nonspecific reactors) has not been ingested within the past several hours. This disorder appears to be twice as common in females, and over 60% of cases occur in individuals less than 30 years of age. In a recent survey of 199 individuals experiencing exercise-induced anaphylaxis, ingestion of food within 2 h of exercise was felt to be a factor in the development of attacks in 54% of the cases (14). Symptoms generally start with a sensation of pruritus on the forehead that becomes more generalized. Urticaria and erythema usually appear next, followed by respiratory obstruction,

and sometimes cardiovascular collapse. Patients with specific food-dependent, exercise-induced anaphylaxis generally have positive prick skin tests to the food that provokes symptoms and occasionally have a history of reacting to the food when they were younger.

Foods implicated in fatal anaphylactic reactions

A large variety of foods have been implicated in the pathogenesis of anaphylactic reactions. The list of foods that potentially induce anaphylactic reactions is unlimited; in theory, any food protein can cause an anaphylactic reaction. As indicated in Table 1, certain foods tend to be cited most frequently as the cause of severe or fatal anaphylaxis, although any food may be the cause. These include peanuts and tree nuts (4, 6, 9, 10), fish (e.g., cod, whitefish), shellfish (shrimp, lobster, crab, scallops, oyster) (5), some fruits (kiwi), and seeds (cottonseed, sesame seed, psyllium). Unfortunately, these food sensitivities are the ones that children typically do not “outgrow,” in contrast to those to other foods such as milk, eggs, and soybeans. 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, tree nuts, and seafood, microgram quantities are sufficient to induce an anaphylactic reaction.

Clinical manifestations of food-induced anaphylaxis

Symptoms of food-induced anaphylactic reactions may appear within seconds to a few hours following the ingestion of a food allergen. The vast majority of symptoms begin within the first hour after exposure. Generally, the later the onset of anaphylactic signs and symptoms, the less severe the reaction. About one-third of patients will experience a biphasic reaction (10), during which they develop classical symptoms of anaphylaxis initially, appear to recover (and may become asymptomatic), and then experience the recurrence of major, often catastrophic or fatal symptoms. Bronchospasm tends to be severe and largely refractory to β -agonists, and hypoxia quickly ensues. There are several cases of food-allergic patients being discharged from emergency departments prematurely following a reaction and dying during the second phase of the biphasic response because adequate emergency help was not immediately available. The intervening quiescent period may last up to 1–3 h, so no patient should be discharged in less than 4 h. In our report, three of

Table 2. Clinical signs and symptoms of anaphylaxis

<i>Respiratory</i> (major shock organ)
Laryngeal – pruritus and sensation of tightness in throat, dysphagia, dysphonia and hoarseness, dry “staccato” cough, and sensation of itching in external auditory canals
Lung – shortness of breath, dyspnea, chest tightness, “deep” cough, and wheezing
Nose – pruritus, congestion, rhinorrhea, and sneezing
<i>Skin</i>
Flushing, pruritus, urticaria, angioedema, morbilliform rash, and pilor erecti
<i>Oral</i>
Pruritus of lips, tongue, and palate, and edema of lips and tongue
<i>Gastrointestinal</i>
Nausea, abdominal pain (colic), vomiting (large amounts of “stringy” mucus), and diarrhea
<i>Cardiovascular</i>
Feeling of faintness, syncope, chest pain, arrhythmia, hypotension
<i>Other</i>
Periorbital pruritus, erythema and edema, conjunctival erythema, and tearing; uterine contractions in women; and aura of “doom”

seven patients with near-fatal anaphylaxis experienced protracted anaphylaxis, with symptoms lasting from 1 day to 3 weeks (10). Most reports suggest that the earlier epinephrine is administered in the course of anaphylaxis, the better the chance of a favorable prognosis. However, this does not necessarily affect the prevalence of biphasic or protracted symptoms, and the author is aware of three patients who received epinephrine immediately but still progressed to fatal anaphylaxis. Fortunately, this is a rare occurrence. In very rare patients who receive appropriate treatment in a medical facility, the anaphylactic reaction proves impossible to reverse.

The symptoms of anaphylaxis are generally related to the gastrointestinal, respiratory, cutaneous, and cardiovascular systems (Table 2). The sequence, timing, and severity of symptoms vary from one individual to the next. In addition, a patient who develops anaphylaxis to more than one type of food may experience different symptoms with each food. While many patients develop similar allergic symptoms on subsequent food-allergen exposures, patients with asthma and peanut and/or tree nut allergy appear to be less predictable. Peanut-allergic children, who reacted with minimal cutaneous and gastrointestinal symptoms before developing asthma, not infrequently experience severe anaphylactic reactions after ingesting peanut in their teenage years.

The first symptoms experienced in a food-allergic reaction often involve the oral cavity and throat. Symptoms may include tingling, pruritus, and edema of the lips, oral mucosa, palate, and pharynx. Young children may be seen scratching at their tongue, palate, anterior neck, or external

auditory canals. Evidence of laryngeal edema includes a “dry staccato” cough and/or dysphonia and dysphagia. Gastrointestinal symptoms frequently follow, including nausea, vomiting, crampy abdominal pain, and diarrhea. Vomiting generally contains large amounts of “stringy” mucus. Skin symptoms during anaphylaxis may include flushing, urticaria, angioedema, and/or erythematous macular rash, but are frequently absent in severe reactions (10). Respiratory symptoms may consist of a deep repetitive cough, stridor, dyspnea, and/or wheezing. The development of cardiovascular symptoms, along with airway obstruction, is of greatest concern in anaphylactic reactions. In the second phase of the biphasic response, it is often extremely difficult to ventilate patients due to extreme bronchospasm, and tension pneumothorax is a frequent complication of high ventilatory pressure. Cardiovascular symptoms may include syncope, a feeling of faintness, palpitations, and/or chest pain. Hypotension or shock may be the result of vascular collapse, cardiac arrhythmia, or asphyxia. Anaphylaxis may be complicated by myocardial ischemia.

Other signs and symptoms reported frequently in food-induced anaphylaxis include periorbital and nasal pruritus, sneezing, diaphoresis, disorientation, fecal or urinary urgency or incontinence, and uterine cramping. Patients often report a “sense of doom.” In some instances, the initial manifestation of anaphylaxis may be the loss of consciousness. Death may ensue in minutes but has been reported to occur days to weeks after anaphylaxis (15). Late deaths are generally manifestations of organ damage experienced early in the course of anaphylaxis.

In a review of 43 fatal cases of anaphylaxis, mostly due to the injection of medications, Delage & Irey noted that symptoms developed within 20 min in 86% of cases, and death occurred within 30 min in 33% of cases and within 1 h in about 50% of cases (16). Respiratory distress and circulatory collapse were the presenting symptoms in 37% and 33% of cases, respectively, and skin symptoms were the presenting symptom in only 7% of cases. In six cases of fatal food-induced anaphylaxis (10), initial symptoms developed within 3–30 min and severe respiratory symptoms within 20–150 min. Symptoms involved the lower respiratory tract in all children, the gastrointestinal tract in five of six, and the skin in only one of six children. *The absence of skin symptoms does not rule out anaphylaxis.* Similarly, three patients experiencing severe anaphylaxis while undergoing intentional bee stings developed no skin symptoms (17). While symptoms affecting the throat are common, severe laryngeal

Table 3. Acute management of food-induced anaphylaxis

<i>Rapid assessment of</i>
Extent and severity of symptoms
Adequacy of oxygenation, cardiac output, and tissue perfusion
Suspected cause of reaction
<i>Initial therapy</i>
Epinephrine – 0.01 mg/kg/dose up to 0.3–0.5 mg s.c. or i.m. up to three times every 20 min; more frequent if necessary
Oxygen – 40–100% by mask
Intravenous fluids – 30 ml/kg of crystalloid up to 2 l (or more depending upon blood pressure and response to medications)
<i>Secondary medications</i>
Nebulized albuterol – may be continuous
Antihistamines – H ₁ -antagonist (diphenhydramine – 1 mg/kg up to 75 mg)
H ₂ -antagonist (cimetidine – 4 mg/kg up to 300 mg)
Corticosteroids – solumedrol – 1–2 mg/kg/dose
Dopamine – for hypotension refractory to epinephrine (2–20 µg/kg per min)
Norepinephrine – for hypotension refractory to epinephrine
Glucagon – for hypotension refractory to epinephrine and norepinephrine; especially patients on β-blockers

obstruction has not occurred in 27 cases of fatal food-induced anaphylaxis known to the author.

Several factors appear to predispose individuals to more severe food-induced anaphylaxis, including a personal history of atopy, older age, food to which the patient is allergic, and the presence of asthma (10, 18, 19). In the reports of Yunginger et al. (9) and Sampson et al. (10), patients were highly atopic and all had histories of asthma. Although atopy reportedly does not predispose individuals to an increased risk of anaphylaxis (20), it does tend to predispose to more severe reactions.

Diagnosis

In light of its abrupt and dramatic nature, the diagnosis of systemic anaphylaxis is generally readily apparent (Table 2). Often when a food is implicated, the responsible food is apparent from the temporal relationship between its ingestion and the onset of symptoms. When evaluating the cause of anaphylaxis, a very careful history is critical, especially when the cause of the episode is not straightforward. Specific questions should include whether any other precipitating factors appear to be involved, such as exercise. In cases where the cause 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 often is a minor ingredient in the meal or a contaminant (21).

The laboratory evaluation of a food-induced anaphylactic reaction is limited and generally directed at identifying specific IgE antibodies to the food in question. Limited prick skin testing or RAST determinations are necessary to confirm the suspected etiologic agent of the anaphylactic

reaction. Intradermal skin tests are sometimes performed following negative prick/puncture skin tests, but a positive intradermal test following a negative prick/puncture test is of questionable significance, is probably of no clinical benefit (22), and probably should not be performed. Anaphylactic reactions have been documented following intradermal skin tests to foods (23). 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 (24–26). Plasma histamine rises over the first several minutes of a reaction and generally remains elevated for a brief period of time. Measurement requires special collection techniques and consequently is impractical except in research situations. Whether measurement of urinary methyl-histamine 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 stable at room temperature and can be obtained from postmortem specimens. While tryptase is generally markedly elevated in cases of bee sting- or drug-induced anaphylaxis (25, 26), it is rarely elevated in food-induced anaphylaxis (10). The reason for this is not clear, but this fact suggests that other cells, such as basophils or monocytes/macrophages, may be more important in food-induced anaphylaxis.

Food challenges are usually contraindicated in patients with an unequivocal history of anaphylaxis following the isolated ingestion of a food to which they show 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. 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.

Treatment

Acute management (Table 3)

Death may occur if treatment of a food-induced anaphylactic reaction is not immediate. A review of fatal anaphylactic reactions due to bee stings indicated that the longer the initial therapy is delayed, the greater the incidence of complications and death (15). Initial treatment must be preceded by a rapid assessment to determine the extent and severity of the reaction, the adequacy of oxygenation, cardiac output, and tissue perfusion, any potential confounding medications, and the

suspected cause of the reaction (27). Initial therapy should be directed at the maintenance of an effective airway and circulatory system. Epinephrine (adrenaline) is the drug of choice in the treatment of anaphylaxis. The first step in the management of anaphylaxis is the intramuscular injection of 0.01 ml/kg of aqueous epinephrine 1:1000 (maximal dose 0.3–0.5 ml, or 0.3–0.5 mg) (28). Intravenous administration of epinephrine may cause fatal arrhythmias or myocardial infarction, particularly in adults, and should be reserved for refractory hypotension requiring cardiopulmonary resuscitation. In patients with pulmonary symptoms, supplemental oxygen should be administered.

In order to ensure that patients receive epinephrine as early as possible, it is important that they, their family members, and other care providers be instructed in the self-administration of epinephrine. Preloaded syringes with epinephrine are available and should be given to any patients at risk of food-induced anaphylaxis, i.e., patients with a history of a previous anaphylactic reaction and patients with asthma and food allergy, especially if they are allergic to peanuts, tree nuts, fish, or shellfish. In the USA, premeasured doses of epinephrine can be obtained in two forms: Epi-Pen® and Ana-Kit®. Epi-Pen is a disposable drug-delivery system with a spring-activated concealed needle intended for a single intramuscular injection. It can be obtained in two sizes: Epi-Pen – 0.3 mg for adults – and Epi-Pen Jr – 0.15 mg for children lighter than 22–25 kg. Sustained-release preparations of epinephrine are not appropriate treatment for acute anaphylaxis. Inhaled epinephrine (either nebulized or via metered-dose inhaler; Primatine Mist® in the USA) has been recommended by the European Academy of Allergology and Clinical Immunology (29). A minimum of 20 puffs inhaled correctly can produce blood levels similar to an injection of 0.3–0.5 mg of epinephrine in adults, and 10–15 puffs in a child can deliver the equivalent of 0.15 mg injected subcutaneously (30, 31). Lesser doses may be beneficial to reverse laryngeal edema or persistent bronchospasm.

Once epinephrine has been administered, other therapeutic modalities may be of benefit. Studies have suggested that the combination of an H₁-antihistamine (i.e., diphenhydramine – 1 mg/kg up to 75 mg) either intramuscularly or intravenously and an H₂-antihistamine (i.e., 4 mg/kg up to 300 mg of cimetidine) administered intravenously may be more effective than either administered alone (32). Histamine antagonists should be infused slowly. Most authorities recommend giving prednisone (1 mg/kg orally) for mild to moderate episodes of anaphylaxis and solumedrol (1–2 mg/kg intra-

venously) for severe anaphylaxis in an attempt to modulate the late-phase response. Patients who have been receiving glucocorticosteroid therapy for other reasons should be assumed to have hypothalamic-pituitary-adrenal-axis suppression and should be administered stress doses of hydrocortisone intravenously during resuscitation. If wheezing is prominent, an aerosolized β -adrenergic agent (i.e., albuterol) is recommended intermittently or continuously, depending upon the patient's symptoms and the availability of cardiac monitoring. Hypotension, due to a shift in fluid from the intravascular to extravascular space, may be severe and refractory to epinephrine and antihistamines. Depending upon the blood pressure, large volumes of crystalloid (e.g., lactated Ringer's solution or normal saline) infused rapidly are frequently required to reverse the hypotensive state.

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 cause 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 of more severe anaphylactic reactions:

- 1) history of a previous anaphylactic reaction
- 2) history of asthma, especially if poorly controlled
- 3) allergy to peanuts, tree nuts, fish, and shellfish
- 4) being on β -blockers or ACE inhibitors
- 5) possibly being female.

An educational process is imperative to ensure that the patient and family understand how to avoid all forms of the food allergen and the potential severity of a reaction if the food is inadvertently ingested. In addition, patients at risk of food-induced anaphylaxis should carry medical information concerning their condition with them at all times; e.g., a Medic Alert bracelet. This information may be life-saving, as it will expedite the diagnosis and appropriate treatment of a patient experiencing an anaphylactic reaction.

For many young children diagnosed with anaphylaxis to foods such as milk, egg, wheat, and soybeans, there is a strong possibility that the clinical sensitivity will be outgrown after several years. Allergies to foods such as peanuts, tree nuts, fish, and seafood are generally not outgrown.

Consequently, several groups are evaluating new strategies to "desensitize" patients to these foods with mutated recombinant food proteins, plasmid DNA, and/or CpG immunostimulatory sequences.

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