

Fatal Food-Induced Anaphylaxis

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Fatal food-induced anaphylaxis is rarely reported. In 16 months, we identified seven such cases involving five males and two females, aged 11 to 43 years. All victims were atopic with multiple prior anaphylactic episodes after ingestion of the incriminated food (peanut, four; pecan, one; crab, one; fish, one). In six cases the allergenic food was ingested away from home. Factors contributing to the severity of individual reactions included denial of symptoms, concomitant intake of alcohol, reliance on oral antihistamines alone to treat symptoms, and adrenal suppression by chronic glucocorticoid therapy for coexisting asthma. In no case was epinephrine administered immediately after onset of symptoms. Premortem or postmortem serum samples were available from six victims; in each case elevated levels of IgE antibodies to the incriminated food were demonstrated. Food-sensitive individuals must self-administer epinephrine promptly at the first sign of systemic reaction. Emergency care providers should be aware of cricothyrotomy as a life-saving procedure.

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ALTHOUGH foods are widely recognized as a cause of anaphylaxis,¹ there are virtually no data on the incidence of fatal or nonfatal food-induced anaphylaxis.² In a classic report on the pathology of anaphylaxis,³ none of 43 fatalities was caused by food. Conversely, Golbert et al⁴ reported 15 cases of anaphylactic reaction to ingested antigens, 12 of which involved food, but none of

which was fatal. More recently, Stark and Sullivan⁵ prospectively studied 25 cases of anaphylaxis over a two-year period; only two episodes were fatal, and in only one of three cases thought to be due to foods was an IgE-mediated reaction demonstrable.

Our research group⁶ and others⁷ have measured venom-specific IgE antibodies in postmortem serum samples from victims of fatal *Hymenoptera*-sting anaphylaxis. As a result of these reports, we were contacted by individual forensic pathologists and medical examiners concerning food-specific IgE antibody measurements in victims of fatal food-induced anaphylaxis. Seven cases were identified in a 16-month period and form the basis of this report.

Materials and Methods

Serum Samples.—Serum samples were available from six of the seven

cases and were collected during resuscitation attempts or at autopsies, which were performed up to several hours after death. Serum samples were stored at 4°C or -20°C for up to one year prior to shipment to the Allergen Resource Reference Laboratory at Mayo Clinic.

Food-Specific IgE Antibodies.—Levels of food-specific IgE antibodies were measured by solid-phase radioimmunoassay.⁸ Locally purchased peanuts and pecans were crushed, defatted with petroleum ether using a Soxhlet's apparatus, extracted in phosphate-buffered saline (pH 7.4), and covalently coupled to polyacrylamide beads (Matrex Pel 102, Amicon Corp, Danvers, Mass) or to cyanogen bromide-activated microcrystalline cellulose particles (Avicel, Brinkmann Co, Westbury, NY) as previously described.⁸ We also utilized cod and peanut allergens linked to paper disks that are available commercially (Pharmacia Diagnostics, Piscataway, NJ). Positive and negative control serum samples were included in each assay. Results were expressed as the radioactive counts bound by the test serum samples divided by the radioactive counts bound by the negative control serum, multiplied by 100. Values of 300% negative control or greater were considered elevated.

Report of Cases

CASE 1.—An atopic, 18-year-old, female college freshman had a long-standing history of asthma and allergy to "nuts" and had undergone immunotherapy with inhalant allergens in the past. Within a few minutes of eating two bites

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of chili containing peanut butter at a restaurant near campus, she developed progressive dyspnea but refused to be taken to the hospital. She was taken instead to the home of a friend, whose physician-father administered 0.1 mL of epinephrine in suspension (Susphrine) and called the rescue squad. En route to the hospital she developed cardiopulmonary arrest; resuscitation efforts for one hour were unsuccessful. Autopsy showed marked angioedema of the lips, tongue, and supraglottic area, with mild hyperinflation of the lungs and microscopic features of chronic asthmatic bronchitis, and an incidental pituitary adenoma was noted.

CASE 2.—A 16-year-old boy with severe, steroid-dependent asthma was taking inhaled beclomethasone dipropionate, oral theophylline, and alternate-day prednisone. There was a long-standing history of allergy to peanuts and pecans. While working as a busboy at a local restaurant, he unknowingly ate a piece of cheesecake that contained ground pecans in the crust. He immediately became cyanotic and collapsed. A waitress began cardiopulmonary resuscitation; the boy vomited during resuscitation. His parents were dining in the same restaurant, but neither they nor the boy was carrying the epinephrine kit prescribed by his physician. The rescue squad that responded also had no epinephrine. The boy was transported first to a nearby physician's office, where epinephrine was administered sublingually. On arrival at the hospital, he was extremely acidotic and soon became asystolic. He was successfully resuscitated except for coma; seizure activity developed the following day. He was declared brain dead eight days later. Autopsy showed severe acute and chronic asthmatic bronchitis, *Staphylococcus aureus* pneumonia, adrenal atrophy, generalized tissue eosinophilia, and anoxic encephalopathy.

CASE 3.—A 19-year-old female college sophomore had a history of childhood eczema, asthma, and allergic rhinitis, with multiple previous systemic reactions after ingestion of eggs, poppy seeds, peanuts, peas, or fish. She unknowingly ate a peanut-containing cookie at a college dormitory party, became ill shortly thereafter, and collapsed after self-administering oral medication. She was transported by automobile to the campus health service, but there was no pulse or respiration on arrival. Two doses of epinephrine were administered during subsequent resuscitation attempts, which were unsuccessful. Autopsy showed focal pulmonary hyperaeration, aspiration of food into the tracheobron-

Clinical and Laboratory Data From Seven Cases of Fatal Food-Induced Anaphylaxis

Case No.	Age, y/Sex	Atopic History*	Reaction		IgE Antibody (% Negative Control)
			Locale	Food	
1	18/F	BA	Restaurant	Peanut	12 300
2	16/M	BA	Restaurant	Pecan	2514
3	19/F	E, BA, AR	Dormitory	Peanut	NA
4	40 + /M	Unknown	Home	Crab	1618
5	43/M	BA	Restaurant	Peanut	529
6	11/M	BA	School	Peanut	8323
7	31/M	Unknown	Restaurant	Cod	4377

*BA indicates bronchial asthma; E, eczema; AR, allergic rhinitis; and NA, not available.

chial tree, and no significant laryngeal edema. No postmortem serum was available for study.

CASE 4.—An alcoholic man in his 40s had been hospitalized on at least two prior occasions for anaphylaxis after eating crab. After returning home late one night, he consumed an unknown quantity of crab salad from the kitchen refrigerator. He immediately became ill and called for assistance. He was transported to the hospital, but was dead on arrival. Autopsy showed massive edema of the lips, mouth, and larynx, along with cirrhosis and coronary arteriosclerosis.

CASE 5.—A 43-year-old atopic man had a history of asthma and severe allergy to peanuts. While dining at a Vietnamese restaurant he was specifically assured that the dishes contained no peanuts. After eating one bite of his entree, he again queried the waitress and was then told that there were slivered peanuts atop the dish. He refused the remainder of that dish, took an unknown oral medication, and then consumed the rest of his meal. Approximately 90 minutes later, he felt ill and apparently self-administered epinephrine in the rest room. He collapsed five minutes later, was given a second epinephrine injection by a local physician, and was then transported to a nearby emergency department, where resuscitation attempts were unsuccessful. Autopsy showed pulmonary hyperinflation, microscopic evidence of asthmatic bronchitis, and minimal laryngeal edema.

CASE 6.—An 11-year-old boy had a history of asthma and allergy to peanuts. He unknowingly consumed one bite of a peanut-containing cake in the school lunchroom and within several minutes developed vomiting and wheezing. He was picked up from school by his mother and taken to his physician's office. Because of increasing respiratory distress, he was subsequently transferred to the local hospital. He developed cardiopulmonary arrest en route but was resuscitated and placed on life

support for four days prior to being declared brain-dead. The autopsy findings were unremarkable except for cerebral edema.

CASE 7.—A 31-year-old man had experienced multiple previous anaphylactic reactions to fish and other foods. While dining in a restaurant, he rapidly developed angioedema of the face and lips. His dining partners later related that the french fries they had eaten tasted like fish. He became unresponsive while attempting to locate and self-administer oral diphenhydramine hydrochloride, which he had used on previous occasions to premedicate himself to permit ingestion of allergenic foods. Emergency medical technicians were called, and a total of ten ampules of epinephrine were administered during unsuccessful resuscitation efforts at the restaurant and later at the local hospital. Autopsy revealed marked mucosal swelling of the entire larynx. Gastric contents were strained and examined grossly but did not contain identifiable food to which he had a known allergy.

Results and Comment

Selected clinical data, along with specific IgE antibody values, are summarized in the Table. Elevated levels of IgE antibodies to the incriminated foods were present in all cases where serum samples were available.

The individuals described shared many clinical features. The majority were highly atopic individuals with histories of asthma, eczema, and/or rhinitis. To our knowledge, none of the victims was taking β -adrenergic blocking drugs, which are known to potentiate anaphylaxis.⁹ All but one fatal reaction occurred away from home, in situations where the individuals were less likely to be certain of the ingredients in the food consumed. Their food sensitivities had been manifest on several previous occasions by generalized immediate reactions. The clinical reactions experienced by these individuals resembled those described by Fries,¹⁰ who reported clinical findings in 30 peanut-sensitive chil-

dren from his own practice and in 31 other peanut-sensitive patients from nine other practices. Many of these 61 patients had also experienced multiple previous reactions, but only one had a fatal reaction after inadvertently eating a small amount of peanut butter. To our knowledge, the only other food-induced anaphylaxis fatality reported in the medical literature was that of a 1½-year-old child with atopic dermatitis who had experienced facial angioedema and cutaneous itching on three separate occasions after eating peas.¹¹ The child developed facial angioedema, cyanosis, and cardiopulmonary arrest after being fed an in-hospital diagnostic "test meal" containing peas.

The rapidity with which cardiovascular symptoms developed in cases 2 and 3, in the absence of cutaneous angioedema, urticaria, or demonstrable laryngeal edema or pulmonary hyperinflation at autopsy, may have suggested a primary cardiovascular death rather than an anaphylactic event. While such a differentiation may be more difficult in middle-aged or older persons, anaphylaxis was more likely in these two cases, given the clinical histories and the relative youth of these victims. Although the postmortem findings of angioedema of the larynx or acute emphysema due to obstruction in the lower airways have been emphasized by some authorities,¹² these two findings were present in only 15 and 11 cases, respectively, of the 43 cases of fatal anaphylaxis carefully studied by Delage and Irey.³ In the latter study, there were 40 cases in which autopsy material was adequate; the most common pathological findings were pulmonary congestion (n=36), pulmonary edema (n=20), and intra-alveolar hemorrhage (n=18), all of which are nonspecific for anaphylaxis.

There seems to be little doubt about the cause of fatality in cases 1 through 6. The evidence for fish as the cause of the reaction in case 7 was more circumstantial. Based on interviews with two persons who had dined with the victim, it was postulated that the french fries were contaminated by cooking in oil that had previously been used to deep-fry fish. The local medical examiner attempted to obtain samples of both the french fries and the cooking oil for analysis, but these materials had been discarded by the restaurant the day following the incident.

Food-allergic persons should be provided with epinephrine-containing syringes and instructed how to promptly self-administer epinephrine at the first sign of allergic reaction. Ironical as it seems, one cannot assume that emergency rescue units will be supplied with

epinephrine (viz, case 2). In part as a consequence of case 2, ambulance attendants in Rhode Island are now required to carry and permitted to administer aqueous epinephrine for injection. Injectable epinephrine in oil or in suspension, epinephrine in metered-dose inhalers, and oral antihistamines are not appropriate as single therapeutic agents in moderate or severe anaphylaxis. Victims receiving concomitant glucocorticoid therapy should be assumed to have hypothalamic-pituitary-adrenal axis suppression and should receive liberal quantities of hydrocortisone intravenously during resuscitation. Physicians and emergency response personnel also need to be familiar with the indications for cricothyrotomy and its performance; this procedure can be lifesaving for persons with massive laryngeal edema.

It is evident that fatal anaphylactic reactions can be induced by ingestion of what were probably milligram to gram quantities of food allergen. The key to preventing those fatalities is antigen avoidance, a process that requires heightened awareness of food allergy and increased commitment by many different parties. Although primary care physicians and allergists are familiar with IgE-mediated food reactions, they, as well as the sensitized persons themselves, must become more attuned to the potential risk attendant to this sensitization. Manufacturers of processed foods should provide unambiguous ingredient listings on package labels. Sensitized persons (or responsible adults, in the case of infants and young children) must become dedicated readers of these ingredient lists. Restaurants should be willing to provide timely and accurate information concerning the ingredients in all menu items prepared in-house; such information is being demanded with increasing frequency by patrons having nutritional concerns. The college attended by case 1 has begun to post dining room menus with ingredient listings one week in advance in an effort to prevent future food-related reactions (Sumner Hoffman, MD, oral communication, March 24, 1986). If antigenic foods were completely removed from the homes of sensitized persons, and if all foods consumed by these individuals were prepared at home, it would be theoretically possible to completely prevent reactions. However, considering the population and the greater proportion of meals being consumed outside the home, medical recommendations for such culinary monasticism are unrealistic and unlikely to be accepted in contemporary society.

Despite all these precautions, sensitized persons may be lulled into false security because of the reversibility of previous systemic reactions; may not appreciate possible inadvertent contamination of nonallergenic foods by allergenic foods (case 7); may deny the early signs and symptoms of generalized reactions (case 1); may not appreciate the gravity of symptoms when intoxicated (case 4); and may attempt to treat reactions inappropriately with oral medications (cases 3, 5, and 7) instead of injectable epinephrine. All things considered, it is unlikely that food-induced anaphylaxis fatalities can be completely prevented, but the number can be minimized by greater attention to the treatment and allergen avoidance guidelines offered in this article.

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References

1. Wasserman SI, Marquardt DL: Anaphylaxis, in Middleton E, Reed CE, Ellis EF, et al (eds): *Allergy Principles and Practice*. St Louis, CV Mosby Co, 1988, pp 1365-1376.
2. Anderson JA, Sogn DD (eds): *Adverse Reactions to Foods*, publication 84-2442. Bethesda, Md, National Institutes of Health, 1984, pp 2-6.
3. Delage C, Irey NS: Anaphylactic deaths: A clinicopathologic study of 43 cases. *J Forensic Sci* 1972;17:525-540.
4. Golbert TM, Patterson R, Pruzansky JJ: Systemic allergic reactions to ingested antigens. *J Allergy* 1969;44:96-107.
5. Stark BJ, Sullivan TJ: Biphasic and protracted anaphylaxis. *J Allergy Clin Immunol* 1986;78:76-83.
6. Schwartz HJ, Yunginger JW, Teigland JD, et al: Sudden death due to stinging insect hypersensitivity: Postmortem demonstration of IgE antivenom antibodies in a fatal case. *Am J Clin Pathol* 1984;81:794-795.
7. Hoffman DR, Wood CL, Hudson P: Demonstration of IgE and IgG antibodies against venoms in the blood of victims of fatal sting anaphylaxis. *J Allergy Clin Immunol* 1983;71:193-196.
8. Adolphson CR, Gleich GJ, Yunginger JW: Standardization of allergens, in Rose NR, Friedman H, Fahey JL (eds): *Manual of Clinical Laboratory Immunology*. Washington, DC, American Society for Microbiology, 1986, pp 652-659.
9. Jacobs RL, Rake GW Jr, Fournier DC, et al: Potentiated anaphylaxis in patients with drug-induced beta-adrenergic blockade. *J Allergy Clin Immunol* 1981;68:125-127.
10. Fries JH: Peanuts: Allergic and other untoward reactions. *Ann Allergy* 1982;48:220-226.
11. Von Starck: Primary specific allergy and idiosyncratic shock. *Monatsschr Kinderheilkd* 1926;32:119-127.
12. James LP Jr, Austen KF: Fatal systemic anaphylaxis in man. *N Engl J Med* 1964;270:597-603.