

Lessons from Cases of Mortality due to Food Allergy in Israel: Cow's Milk Protein should be Considered a Potentially Fatal Allergen

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ABSTRACT: **Background:** Most reports in the medical literature on food allergy mortality are related to peanut and tree nut. There is limited knowledge regarding these reactions and often only a partial medical history is described.

Objective: To record and characterize all known cases of mortality due to food allergy in Israel occurring during the period 2004–2011.

Methods: All cases of food allergy-related mortality that were known to medical personnel or were published in the Israeli national communications media were investigated. We interviewed the parents and, when feasible, physicians who treated the final event.

Results: Four cases of food-related mortality were identified: three cases were due to cow's milk and one to hazelnut. All were exposed to a hidden/non-obvious allergen. All four had a history of asthma but were not on controller medications, and none had experienced previous non-life threatening accidental reactions. Three of the four patients had not been evaluated by an allergist, nor were they prescribed injectable epinephrine. The one patient who had been prescribed injectable epinephrine did not use it during her fatal anaphylactic attack.

Conclusions: Fatal reactions to cow's milk and hazelnut but not to peanut are the only reported food mortality cases in Israel. Although these patients had previous reactions following accidental exposures, none had experienced a life-threatening reaction. Patients at risk are not adequately evaluated by allergists, nor are they prescribed and instructed on the proper use of injectable epinephrine. Cow's milk should be considered a potentially fatal allergen.

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and emergency department visits as well as hospital-related discharge diagnoses related to food allergy [1-3]. The allergenic foods with the highest prevalence are peanut, tree nut, fish and seafood, egg, cow's milk protein, sesame, and soy [4]. Peanut, tree nut and seafood, however, are the foods most often associated with fatal or severe anaphylaxis [5]. Interestingly, cow's milk protein and egg, although quite prevalent as allergens, are relatively uncommon causes of food-induced anaphylaxis in the U.S. For example, in a relatively detailed description of 51 cases of food-induced anaphylaxis, no reaction was attributed to cow's milk protein, two (4%) were due to eggs, while over 50% of cases were attributed to peanut and tree nut [6]. That report included two cases of mortality, one related to tree nut and the second of unknown cause [6]. More recently, of 36 food-related anaphylaxis cases among children and adolescents enrolled in a health maintenance organization in Washington State, 22 were related to peanut or tree nut and 3 to seafood, with none attributed to cow's milk protein [7].

In contrast, a review of 40 food-related anaphylactic reactions presenting to a major pediatric medical center in Israel revealed 17 cases (42.5%) related to milk, while 10 (25%) were nut related and 4 (10%) were due to egg allergy [8]. The authors did not distinguish between peanut and tree nut [8].

The number of fatal food-induced anaphylaxis in the U.S. has been estimated at 150–200 cases per year [2]. Of 69 detailed food-related deaths in the U.S., 60 were attributed to peanut and tree nut [9-11]. The picture from Britain, the only other country with detailed reports of food-related mortality, is similar, although not as striking. Of the 108 cases of food-related mortality 75 were due to peanut and tree nut [12-14]. Interestingly, tree nut was the leading cause of food-related fatalities in the U.K., whereas in the U.S. peanut accounted for two-thirds of such deaths.

In nearly all published food allergy mortality cases, the patients had a history of asthma and a known history of allergy to the food to which they had a fatal reaction but were unaware that the food consumed actually contained the ingredient [15]. In addition, in nearly all cases, epinephrine was not adminis-

In recent years, national health surveys in the United States have indicated that the prevalence of food allergy has increased, a trend reflected in data of reported ambulatory

tered in a timely manner, that is, immediately after ingestion and before the onset of respiratory symptoms, even though in the vast majority of cases these patients had experienced previous accidental exposures and reactions [10,11,14]. In his study of fatal reactions to foods in the UK, Pumphrey [12,13] noted that 42 of 47 cases suffered respiratory arrest involving the upper or lower airways or both, which occurred in a median time of less than 30 minutes after ingestion. Cutaneous symptoms preceding the fatal moment were not reported in the UK series [13]. Sampson et al. [11] reported six fatal and seven non-fatal food-related reactions and noted that all the children and adolescents with non-fatal reactions but only one child in the fatal reaction group had cutaneous signs during the anaphylactic event.

PATIENTS AND METHODS

We investigated all known food allergy mortality cases in Israel during the years 2004–2011. The information on the three milk-related deaths was collected from regional allergists after a preliminary presentation of the current data at a recent (October 2010) national allergy society conference and from the Israeli national media. The parents and the physicians who treated the final events were interviewed and asked specifically about the type and amount of food ingested, the onset and progression of symptoms, use of epinephrine, response of the emergency medical services, and course of hospital treatment. In addition, information regarding asthma and allergy history, current medications and prior education about food allergy were ascertained. The information on the most recent death due to hazelnut (July 2011) was gathered only from the media since the case is under legal consideration. Complete medical records were not available for any of these patients. The study was approved by the local institutional review board.

RESULTS

We retrieved the data on four cases of food-related mortality: three were due to the ingestion of milk and one to hazelnut. All three milk-related cases had been known to local allergists and had been discussed informally at periodic allergy society meetings. All four cases had been reported and published in the media, including online news, newspapers and television. The Israel National Forensic Pathology office had no information of additional cases (personal communication).

The milk-related fatalities involved youngsters aged 6, 10 and 16. The hazelnut death involved an adult, age 26. The cases are briefly summarized below and are compared in Table 1.

CASE 1

A 6 year old girl had a history of asthma and a known cow's milk protein allergy. Her first allergic reaction occurred at the age of 8 months when she was weaned from breastfeeding and

Table 1. Clinical characteristics of four food related fatalities in Israel

	Case 1	Case 2	Case 3	Case 4
Age (yrs)	6	10	16	26
Gender	F	M	F	F
Location of ingestion	School	Bakery	Party	Restaurant
Location of death	Clinic	ICU	ICU	ICU
Age when milk allergy was first diagnosed	8 months	Infancy	Infancy	Unknown
Regular allergy follow-up	No	No	Yes	No
Prescription of injectable epinephrine	No	No	Yes	No
Use of epinephrine during final event	No	No	No	No
Previous reactions	Yes	Yes	Yes	Yes
Previous food-related life-threatening event	No	No	No	No
Time to reaction	< 10 min	< 10 min	< 10 min	< 10 min
Type of food	Chocolate	Cake, hidden	Pastry, hidden	Waffle
Estimated amount consumed	180 mg	Several milligrams	Several milligrams	Unknown
Asthma	Yes	Yes	Yes	Yes
Controller treatment for asthma	No	No	No	No
Cutaneous signs	No	No	No	No

ICU = intensive care unit

given a cow's milk-based formula. At the age of 13 months she was accidentally exposed to a cow's milk protein-containing candy labeled as non-dairy and she developed shortness of breath and rash. The family filed a complaint with the company, claiming improper product labeling. In addition, she had asthma with relatively mild, although frequent attacks. She was not prescribed an asthma controller. She was never formally evaluated by an allergist and was not prescribed injectable epinephrine. On the day of the fatal event she unknowingly ate a piece of chocolate that contained milk protein. Several minutes later she complained of shortness of breath and received an inhalation with her β_2 agonist bronchodilator. When this treatment failed, she was brought to a local clinic where her airway symptoms worsened but resuscitation was unsuccessful. Information was obtained from the parents by a journalist and from a colleague pediatrician of the treating physician since both parties refused direct communication.

CASE 2

A 10 old boy had a history of asthma and known cow's milk protein allergy since infancy. He had experienced several

previous reactions to milk-containing products during childhood and was educated by his parents to always inquire about possible hidden allergen sources of milk protein. He suffered mild attacks of asthma during the spring and fall months and did not have an asthma controller medication. The patient was not prescribed injectable epinephrine and was not followed by an allergist. Every Friday he would eat a certain “non-dairy” cake at a local bakery. On the day of the fatal event he ate a piece of this same cake, not knowing that the tray had previously held a dairy-containing item. Within minutes, the patient experienced shortness of breath, used his inhaled β_2 bronchodilator, and collapsed. Emergency medical services were called and he was treated by the paramedics for about 30 minutes with epinephrine, intravenous fluids and oxygen. He was transported to a nearby hospital but died in the intensive care unit after arriving comatose, later determined as brain dead. The information was obtained from the patient’s parents, the paramedic record and the attending physician from the intensive care unit.

CASE 3

A 16 year old girl had a history of asthma and known cow’s milk protein allergy from infancy. She had experienced several prior accidental exposures to cow’s milk protein, which usually manifested as respiratory symptoms and which responded to an inhaled bronchodilator. Inhaled corticosteroids were prescribed but were used only on an ‘as needed’ basis. While attending a party, she ate a non-dairy pastry, unaware that it had been previously packed in a bag containing a dairy item. Within minutes she felt shortness of breath and called her parents. One of her parents arrived within 10 minutes and an ambulance was called. The patient had been prescribed injectable epinephrine several months prior to the episode but it was not used during her anaphylactic attack. She died in the intensive care unit of a local hospital. The information was provided by the patient’s parents who additionally commented that they did not fully understand the significance of incorporating the injectable epinephrine into their daily routine.

CASE 4

The fourth case was a 26 year old woman with a history of asthma and a known history of tree nut and sesame seed allergy. She had had previous reactions but none severe enough to require admission to the ICU. She had not been prescribed injectable epinephrine. On the day of the fatal event, the patient ordered a waffle in a restaurant that, unknown to her, contained hazelnut paste. Within minutes she began to experience chest symptoms and used her β_2 bronchodilator. No rash was noted. The symptoms worsened and she was eventually admitted to the emergency room where treatment was initiated. Despite aggressive treatment,

she died in the intensive care unit. The case is under legal consideration and further details were not available.

We are not aware of additional cases of death due to food allergy. However, there were at least 10 cases reported in the local media of emergency department treatment or ICU admission for severe food allergic reactions. All but one (peanut) were related to cow’s milk protein.

DISCUSSION

The food allergy mortality cases reported in Israel share common characteristics with those reported in the U.S. and Britain. All four patients were aware of their food allergy, had experienced previous reactions, had a history of asthma, were older than 6 years, and unknowingly ate a food that either contained or was cross-contaminated with the allergen. As in other food allergy mortality reports, the fatal event occurred outside the home or other non-medical environment; therefore, even though detailed medical information was not available we feel that essential relevant information had been collected [9,10,11,14]. These cases reinforce the observations made by other authors characterizing the features of fatal food-induced anaphylaxis: the reaction occurred within minutes, and in three of the four patients injectable epinephrine was not prescribed. In one patient the epinephrine, although previously prescribed, was not used during the final event. In addition, in three of the patients, clinical evaluation and regular follow-up with an allergy specialist was not part of their routine medical care. All four patients had asthma, a risk factor identified for food allergy-induced mortality, but they were not prescribed inhaled corticosteroid controller medications [16]. Interestingly, the four patients in this small series showed no cutaneous signs of anaphylaxis such as urticaria or flushing that had been noted in previous mortality reports [11].

An important point of information obtained in the interview process and described in the current case series is the estimated amount of protein consumed that triggered the fatal event. This amount ranged from an estimated few milligrams (patient 2 and 3) to approximately 180 mg (patient 1). In a review of six severe non-fatal accidental reactions to cow’s milk protein, three patients reportedly consumed less than 1 ml of milk, or the equivalent of less than 30 mg of milk protein. The onset of the reaction in these cases was less than 15 minutes [17]. Using primarily double-blind challenges with milk protein, multiple investigators have demonstrated that the lowest threshold dose provoking a reaction ranged from 1.5 to 180 mg [18]. This information illustrates the minute amounts of allergen that may be involved in triggering anaphylaxis and provides background to the understanding of how cross-contamination may be fatal, as in cases 2 and 3 of the present series where a non-dairy baked good came

into contact with a dairy item. The information regarding patient 4 is unknown.

The most distinctive feature in these cases is that cow's milk protein appears to be a major cause of food-induced anaphylactic mortality in Israel. This is in contrast to the mortality reports from the U.S. and the UK where peanut and tree nut are the most common allergens causing death. This finding raises the possibility that we may have missed cases of food-related death. Although this is a possible explanation, we feel this is unlikely. Firstly, Israel is a relatively small country of approximately 7.5 million people, and although it does not have a national food allergy mortality registry, it does have a very dynamic and active communications media. We are confident that through our contact with national allergists, forensic pathologist review, and communications media search, the current report accurately reflects information on any cases of food allergy mortality that may have occurred in Israel from 2004 to 2011. Secondly, if we did miss cases, we would have also missed cases related to cow's milk protein as well as to peanut, tree nut and other allergens. Thirdly, the patients' clinical characteristics are similar to the reports of mortality by other authors where peanut and tree nut are the predominant triggers [15].

Interestingly, closer examination of the data from previously published mortality reports suggest that approximately 10% of cases are related to cow's milk protein [10,12-14]. From this it would appear that cow's milk protein allergy, although less common, is as potentially dangerous as peanut and tree nut allergy, with reactions no less catastrophic.

Several lines of evidence suggest that the differences in the prevalence of allergy to different foods cannot completely explain the differences in mortality related to that food. Firstly, in Israel, the prevalence of peanut and cow's milk protein allergy at 6 years of age is approximately in the same range, 0.17% for peanut and 0.2% for milk, if we consider that over 60% of patients diagnosed with cow's milk protein allergy recover by 4 years of age [19,21]. Secondly, the prevalence of seafood allergy in the U.S. is not lower than peanut allergy; yet seafood-related mortality, although not rare, is much less than that of peanut [9,10,22]. Thirdly, allergy to egg is very common, but fortunately deaths due to exposure to egg are very rare [23].

We think that peanut, tree nut, seafood and cow's milk protein are extremely dangerous foods for those who are allergic to them. In addition to the intrinsic characteristic of the food allergen we hypothesize that two other factors may be responsible for mortality-prone allergy. One factor is the role of repeated accidental exposures that may increase sensitization and subsequently amplify the allergic response in the susceptible individual. This is supported by evidence that failure to adhere to avoidance diets may reduce the probability of recovery from food allergy [24,25]. A second and somewhat related factor is the difficulty in completely avoiding exposure

to a "hidden" or obscure allergen. In contrast to the U.S., peanuts or peanut butter are not commonly used as fillers in Israeli food products. Although the locally produced peanut-coated corn puff snack known as Bamba[®] is very prevalent, it is also very clearly identified as a peanut-containing food. In addition, children and parents of children with peanut allergy are quite aware of this popular product and its danger. Therefore, it seems that peanut-allergic patients may be able to avoid or limit accidental allergen exposures.

The current series also highlights the difficulties in treating patients with severe food allergy and the attempts to prevent mortality. Our present standard of care of these patients emphasizes allergen avoidance and treatment with readily available injectable epinephrine when indicated [16]. Appropriate avoidance measures include education on proper label reading and, more importantly, helping patients and their families identify problematic food situations outside the home such as restaurants, bakeries and social events where cross-contamination and hidden allergen issues may present themselves. All four patients reported in this series ate items outside the home.

Finally, the mortality prone patient may not have experienced a previous life-threatening reaction. This observation is in agreement with previously published cases of food-related mortality [9-11,14] as well as an additional unpublished series of 26 cases (S.A. Bock, personal communication).

In summary, four fatal food-related reactions were noted in Israel, a country where the peanut and cow's milk protein allergy prevalence rates by 6 years of age are similar. Frequent accidental and hidden allergen exposure to cow's milk protein, which is present in many foods in contrast to the lack of peanut protein in local food products may be responsible for augmenting the observed severe reactions in patients allergic to cow's milk protein. Patients with a history of asthma, lack of injectable epinephrine, no previous life-threatening reaction, and without follow-up by an allergy specialist characterize these mortality-prone individuals. Cow's milk protein should be considered a major mortality-prone allergen risk, along with peanut, tree nut and seafood.

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