

Anaphylaxis following ingestion of candy fruit chews

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CHIEF COMPLAINT

Allergic reaction after eating candy fruit chews.

MEDICAL HISTORY

History of Present Illness

The patient is a 5-year-old boy with known peanut and egg allergy. He ingested a large number of candy fruit chews (Gummy Bears) while at a carnival, and 45 minutes later he complained of an itchy mouth and throat. He next took one bite of a hot dog and a sip of a lemon-lime soda and immediately began to vomit. He then developed diffuse urticaria. An emergency department evaluation included treatment with diphenhydramine, epinephrine, and prednisone.

Past Medical History

The patient's past medical history is significant for food hypersensitivities to egg and peanuts characterized by perioral pruritus and vomiting. He also has mild persistent asthma and mild seasonal allergic rhinitis. He has a history of infantile atopic dermatitis. Medications included fluticasone, 44 µg 2 puffs twice a day, albuterol as needed, cetirizine as needed during the fall season, and epinephrine (EpiPen Jr) as needed. He had no known drug allergies. He was not taking antihistamines at the time of the reaction. Immunizations were up to date by report, and there were no adverse reactions to vaccinations, including diphtheria and tetanus toxoids and acellular pertussis (DTaP), measles-mumps-rubella (MMR), *Haemophilus influenza* type b, and hepatitis B.

Physical Examination

On physical examination at the time of follow-up for an allergy evaluation, the patient generally appeared to be well. Vital signs were normal. He had mildly boggy nasal turbinates. Chest examination revealed clear breath sounds bilaterally. The skin was clear, with no rash or lesions. Results of the remainder of the examination were unremarkable.

QUESTIONS

1. What is the differential diagnosis?

The symptoms are consistent with anaphylaxis. The fact that symptoms began with mouth itching after ingestion of the candy fruit chews makes this candy the most likely trigger. The reaction may be caused by an ingredient in the candy fruit chews or may be due to contamination with egg or peanut, foods already known to cause allergic symptoms in this child. It is less likely that the hot dog caused this reaction. Other possibilities include other causes of anaphylaxis found at a carnival, such as ingestion of other food or medication, insect sting, exercise-induced reaction, food poisoning, or acute gastroenteritis. However, this patient had no known insect sting, was not exercising or overheated, and had no other known ingestions at the time of the reactions. The candy was taken from its original packing.

2. What additional history would be helpful?

Since gummy candy is the primary suspected trigger, it would be helpful to know more about the child's prior ingestion of this candy and its components, which include corn syrup, sugar, gelatin, modified potato starch, natural and artificial flavors, mineral oil, carnauba wax, and FD&C red 40, FD&C yellow 5 and 6, and FD&C blue 1. Indeed, the history discloses that the patient has previously complained of an itchy mouth with colored yogurts and candies that contain gelatin. However, he has tolerated smaller quantities of candy fruit chews, as well as Jell-O and marshmallows, which also contain gelatin. In addition, he has tolerated gelatin contained in vaccines.

Although it is possible that the yogurts also had egg and/or peanut contamination, there are other components indicated on the ingredient labels that are common to both the chewy candies and yogurts. These common ingredients include food coloring. The patient has previously ingested foods with the same added colors without difficulty. Furthermore, sensitivities to food colorings are rare, with an incidence of approximately 0.2%, and food colorings have been implicated as causes of milder reactions such as urticaria or asthma exacerbations.¹ Although there are many reports of allergic reactions associated with food additives, most have not been confirmed to have a causative role with blinded and placebo-controlled food challenges. The food coloring most commonly reported to cause adverse reactions is tartrazine (FD&C yellow 5), which has been implicated as a cause of asthma exacerbations and chronic urticaria.² Criticisms of these reports include lack of confirmation of a causal rela-

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tionship with double-blind, placebo-controlled food challenges, use of very high doses not usually found in foods, and withdrawal of asthma or chronic urticaria medications during the challenges.³ Similar limitations have been seen with reports of adverse reactions to the other food colorings. In regard to this patient, food colorings were tolerated in many other food products and medications.

Other components of the gummy candies may have caused this reaction. Carnauba wax is often found in products that contain gelatin and should be considered as well. There has been a case report of carnauba wax in mascara causing allergic contact dermatitis.⁴ However, this wax has not been reported to cause acute allergic reactions. The natural flavor was not identified by the manufacturer to contain egg. In contrast, gelatin is one of the primary components of candy fruit chews and has been reported to cause various allergic symptoms, ranging from urticaria to anaphylaxis.^{5,6} Therefore, gelatin remains a prime candidate by history.

3. What additional tests may help determine the diagnosis?

The diagnosis of gelatin allergy was confirmed with skin prick testing and serum IgE testing. Skin prick testing was performed with the following wheal/flare results: histamine, 4/14 mm; saline, 0/0 mm; egg, 9/19 mm; and a test with liquefied gummy candy (1:1 dissolution in water), 3/12 mm. The gummy candy skin test caused no skin response in 6 healthy patients. Serum was sent for IgE to specific antigens (CAP-FEIA system, Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden) with the following results: egg white, 34.6 kIU/L; peanut, 29.6 kIU/L; porcine gelatin, 6.2 kIU/L; and bovine gelatin, 11.4 kIU/L.

Double-blind, placebo-controlled food challenge is the gold standard for the diagnosis of food allergy.⁷ However, this was not conducted in this patient, because he had already had several reactions to foods that contained gelatin, including anaphylactic reactions, and he had evidence of specific IgE to gelatin on skin testing and in serum. Food challenge would be considered in the future if his specific IgE to gelatin decreased to determine if he outgrew this allergy.

4. What is gelatin and why would this child react to some forms and not others?

Gelatin, a derivative of animal collagen, is a high-molecular-weight peptide with 300 to 4,000 amino acids primarily of glycine, proline, and hydroxyproline. It is a hydrocolloid composed of water, mineral salts, and protein (85%) and is used as a stabilizer in various products to prevent settling, phase separation, foam collapse, or crystallization. Gelatin may be found as a component of foods, medications, cosmetics, and vaccines (Table 1). It is the main component in gummy candies and is found also in lunch meats and as a clarifying agent in wines and juices.⁹ In vaccines, gelatin is primarily used in live virus vaccines to stabilize the viability of the virus.¹⁰

Processing of gelatin can influence its allergenicity. Animal collagen that has been extensively hydrolyzed has a lower molecular weight and lower gel melting point,¹¹ which can render it less allergenic.¹² Dosage differences also con-

Table 1. Products That Contain or May Contain Gelatin*

Type	Product
Food	Jell-O
	Gummy candy
	Marshmallow
	Lunch meat
	Frozen desserts
Medicine	Wine and juices
	Gelcaps
Cosmetics	Some hard capsules
	Face cream
Vaccines†	Lotion
	Shampoo
	DTaP (Tripedia)
	DTaP/Hib (TriHiBit)
	Influenza (Fluzone)
	Japanese encephalitis (JE-Vax)
	Mumps (MumpsVax)
	MMR (MMR II)
	Rubella (Meruvax II)
	Typhoid (oral TY21a)
	Varicella (Varivax)
	Yellow fever (YF-Vax)

Abbreviations: DTaP, diphtheria and tetanus toxoids and acellular pertussis; Hib, *Haemophilus influenzae* type b; MMR, measles-mumps-rubella.

* Data are from package inserts, organic Materials Review Institute,⁹ Pool et al.²² and Madaan and Maddox.⁸

† Amount of gelatin in vaccines: DTaP (gelatin used for the pertussis part), 15 µg per dose in Wyeth brand and 28 µg per dose in Aventis brand; MMR II (Merck), 14.5 mg of hydrolyzed gelatin per dose; Varivax (Merck), 12.5 mg of hydrolyzed gelatin per dose; and Fluzone (Aventis), 250 µg of gelatin.

tribute to food allergic reactions. These factors may explain why our patient had no reactions to candy fruit chews previously or to Jell-O and marshmallows but had mild reactions to yogurts with gelatin.

There have been multiple reports of allergic reactions attributed to gelatin, including IgE- and non-IgE-mediated reactions. The earliest report described 3 patients who had urticaria and anaphylaxis to modified gelatin in intravenous fluid that was used as a volume expander.¹³ Other reports describe reactions to Gummy Bears, Epogen, chloral hydrate suppository, and a gelatin-containing surgical sponge.^{5,14-16} There is one case of allergic reactions to Gummy Bears in which gelatin could not be consistently implicated.¹⁷ The authors concluded that the natural and artificial flavors were the likely culprit; however, inconsistent results caused by processing variability of the different gummy candies cannot be excluded.

Both IgE- and non-IgE-mediated reactions have been reported from vaccines that contain gelatin, specifically the MMR and varicella vaccines. In 1993, Kelso et al⁶ described a 17-year-old patient who had symptoms of anaphylaxis 10 minutes after receiving the MMR vaccine. Further testing revealed that she had positive skin test results to Jell-O and

Knox gelatin and evidence of gelatin-specific serum IgE. Additionally, this patient reported having a history of throat itching and tongue swelling after ingesting gelatin-containing food products. Another report described 2 children who developed urticaria 8 and 24 hours after receiving the varicella vaccine.¹⁸ Both patients had positive intradermal skin test results to gelatin, but neither had reactions with ingesting gelatin.

The report by Kelso et al¹⁶ provided an alternative explanation for MMR reactions in patients not allergic to egg. In addition, many MMR vaccines had already been given without complications in many egg allergic patients, and the administration of measles vaccine in egg allergic children was considered safe.¹⁹ Subsequently, Sakaguchi et al²⁰ from Japan found that gelatin specific IgE was present in the serum samples of 24 (93%) of 26 patients with a history of immediate reactions to MMR vaccine. Seven of these patients also developed urticaria after ingesting gelatin. Of note, 5 of these children did not have reactions to foods that contained gelatin until after the vaccine reaction.

Although gelatin can be found in a wide variety of products, reports of gelatin reactions have not been as widespread. Nakayama et al²¹ reported that many allergic reactions to MMR vaccines in Japanese children were associated with serum specific IgE to gelatin, and most of these patients had previously received gelatin-containing DTaP vaccine. Interestingly, the immunization schedule in Japan from 1989 to 1993 was such that the primary series and booster of DTaP were given after the MMR vaccine. During this time, there were no reported reactions to the MMR vaccine. In 1994, the Japanese government changed the immunization schedule so that the primary series of the DTaP vaccine is given before the first MMR vaccine. An increased number of MMR vaccine-related reactions was reported after this change in the immunization schedule. The DTaP vaccines contain aluminum hydroxide, a potent adjuvant, in addition to gelatin, possibly facilitating sensitization in susceptible people.²¹ Sakaguchi et al¹⁰ similarly found that children with immediate reactions to MMR vaccine had a history of having received DTaP vaccine with gelatin as opposed to children without MMR reactions who had previously received DTaP vaccine without gelatin.

However, these findings were not universal. Pool et al²² found significantly fewer reports of MMR vaccine-associated reactions in the United States compared with the Japanese. Similar findings were reported in Finland.²³ In both countries, there was also a smaller proportion of MMR vaccine reactors who were found to have serum specific IgE to gelatin.

There may be several reasons for this disparity in gelatin-related vaccine reactions. Differences in vaccine gelatin concentrations and processing have been noted. The MMR II vaccine used in the United States contains porcine gelatin that is highly hydrolyzed with very low molecular weight, whereas the MMR vaccine in Japan in the 1990s had partially hydrolyzed bovine gelatin with small amounts of high-mo-

lecular-weight gelatin.²¹ Alternatively, the Japanese population may have increased susceptibility to gelatin allergy. Indeed, Kumagai et al²⁴ proposed that genetic differences may increase susceptibility to gelatin allergy in certain individuals. Of the 23 patients with immediate reactions to the MMR vaccine with evidence of IgE to gelatin, 13 (57%) of 23 had HLA-DR9. Dietary differences in Japan, the United States, and Finland may also play a role in sensitization. Most importantly, differences in the reporting of adverse events to vaccines in different countries can lead to overreporting or underreporting of vaccine reactions. Such variability in reporting procedures can contribute significantly to these different prevalences, since the numbers of reactions are so small in general. In addition, variable sensitivity of the different assays to detect serum IgE specific to gelatin may contribute to these findings.

5. How do you manage gelatin allergy?

There is still much to be learned regarding the etiology and natural history of gelatin allergy. Sakaguchi et al²⁵ demonstrated cross-reactivity among mammalian gelatins (eg, bovine, porcine), but there is no cross-reactivity between mammalian and fish gelatin. In the case we describe herein, the child had evidence of IgE-mediated allergy to gelatin based on skin prick testing and serum IgE, as well as immediate reaction after ingesting gelatin-containing candies. This patient was prescribed epinephrine and educated on strict allergen avoidance in foods and other products, including medications and vaccines. As described herein, variability in processing and final concentration of gelatin in food or medicinal products may influence the likelihood of an allergic reaction. Indeed, our patient experienced reactions to a variety of gelatin-containing foods, but not all. Gelatin is a common ingredient in foods and avoidance is difficult. Although it may be appropriate in some clinical circumstances to differentiate which foods with gelatin need to be avoided, for our young patient who experienced a severe reaction, we and the family agreed that all forms of gelatin should be avoided. We believed this to be the safest approach because the type, processing, and concentration of gelatin that might be found in foods may vary, even perhaps between lots of food products at different times.

Testing to the MMR vaccine was performed for this patient by another allergist and was reported to be positive on intradermal skin testing. Serum titers revealed the following: measles, 3.32 U; rubella, 3.54 U; and mumps, 3.65 U (all in the strong protective range). Although the skin test result to the MMR test was positive, the chances that the patient would react to the MMR vaccine are unknown. In addition, there are no published desensitization protocols for gelatin. Therefore, since the patient had already received his first MMR vaccine at 1 year of age and had protective titers to MMR, we elected to defer the booster MMR vaccine at this time. The natural course of gelatin allergy is unknown, so periodic reevaluation is planned, possibly with oral food challenges if IgE to gelatin wanes over time.

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