

Anaphylaxis after vaccination in a pediatric patient: further implicating alpha-gal allergy



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Clinical Implications

- We report a pediatric patient with preexisting alpha-gal allergy who developed anaphylaxis immediately after receiving his routine 5-year vaccinations. Further investigation implicates alpha-gal allergy as another mechanism in pediatric anaphylaxis to gelatin-containing vaccines.

TO THE EDITOR:

It is increasingly well known that specific IgE antibodies to galactose- α -1,3-galactose (alpha-gal) are associated with delayed anaphylaxis to mammalian meat and gelatin-based products.¹ Recently, we reported that gelatin or bovine calf-serum-containing vaccines are capable of inducing immediate hypersensitivity and anaphylaxis in alpha-gal allergic adult patients, though not all patients have reactions.²⁻⁴ Importantly, multiple vaccines used during the routine series of pediatric immunizations contain gelatin and potentially alpha-gal.⁵ We report a case of vaccine-induced anaphylaxis associated with alpha-gal allergy in a child.

The patient is a 5-year-old boy with a history of alpha-gal allergy who presented 1 week after an allergic reaction on receipt of measles, mumps, and rubella (MMR) (Merck), varicella (Merck), and diphtheria, tetanus, and acellular pertussis and inactivated polio vaccine (DTaP/IPV) (GSK) vaccines. Five minutes after receiving the vaccines, he developed shortness of breath, wheezing, disseminated urticaria, and angioedema of the face and oropharynx, prompting an emergency room visit where he received epinephrine, diphenhydramine, prednisone, and famotidine with relief of symptoms within 10 minutes. Eight months before this episode he had been diagnosed with alpha-gal allergy (alpha-gal sIgE of 8.19 kU/L, total IgE of 149 kU/L) after several episodes of urticaria and facial angioedema 4 to 6 hours after ingestion of mammalian meat, following a tick bite, and was avoiding mammalian meat at the time of his vaccine reaction. He had no history of egg, latex, dairy, or gelatin allergy, and had uneventfully received all prior childhood vaccinations.

We repeated his sIgE titers, demonstrating an increase in the galactose- α -1,3-galactose sIgE concentration to 26.9 kU/L, a beef sIgE of 14 kU/L, a lamb/mutton sIgE of 5.64 kU/L, a pork sIgE of 11.2 kU/L, porcine gelatin sIgE of 0.78 kU/L, and a bovine gelatin sIgE of 0.22 kU/L (reference for all <0.35 kU/L).



FIGURE 1. The patient was skin tested to undiluted vaccines and gelatin. Skin prick tests were placed and read at 15 minutes, with appropriate controls. MMR was positive with a 5-mm wheal and 14-mm erythema, and varicella was positive with a 4-mm wheal and 12-mm erythema. Porcine gelatin was positive with a 6-mm wheal and 18-mm erythema. The histamine control had a 7-mm wheal and 20-mm erythema. DTaP/IPV and DTaP only vaccines were deemed negative on skin prick testing and at 1:100 intradermal testing (not shown). DTaP, Diphtheria, tetanus, and acellular pertussis; H, histamine control; I, DTaP only vaccine; IPV, inactivated polio vaccine; J, porcine gelatin; K, DTaP/IPV combination vaccine; MMR, measles, mumps, rubella vaccine; S, saline control; V, varicella vaccine.

We next reviewed the ingredients for the vaccines he had received. Both MMR and varicella vaccines contain large amounts of gelatin per dose when compared with other vaccines (14,500 μ g per 0.5 mL dose and 12,500 μ g per 0.5 mL dose, respectively). MMR, varicella, and DTaP/IPV combination vaccine also contain bovine calf serum, quantity unreported. Skin prick testing was performed to the vaccines he had received, plus DTaP (without IPV) vaccine from the same manufacturer and porcine gelatin (Figure 1).⁵ He demonstrated positive skin test responses to MMR vaccine, varicella vaccine, and porcine gelatin on undiluted prick.

We reviewed publicly available data from the Vaccine Adverse Event Reporting System database from 2009 onward for severe adverse events occurring on the same day of administration of the MMR or varicella vaccines, along with the keywords “beef,” “pork,” or “alpha-gal.”⁶ We found 10 reactions consistent with

TABLE I. Serologic assays for alpha-gal in selected vaccines

(A) IgE binding (IU/mL) to biotinylated vaccines assayed with alpha-gal positive sera from the patient, with and without alpha-gal to deplete alpha-gal sIgE*											
	DTaP	HiB	Yellow fever	MMR	MMRV	Varicella	Zoster	Bovine gelatin immunocap c74	Cat serum albumin (rFel d 2)		
Patient	<0.1	0.11	0.12	2.33	1.15	0.89	1.74	0.16	1.68		
w/alpha-gal beads	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	0.13	1.7		
w/PBS	<0.1	0.10	0.13	2.29	1.19	0.84	1.84	0.14	1.65		
(B) serum alpha-gal IgE (IU/mL) levels at baseline and after overnight incubation with vaccines, gelatins, and PBS†											
	Baseline	DTaP	HiB	Yellow fever	MMR	MMRV	Varicella	Zoster	Porcine gelatin	Bovine gelatin	PBS
Patient	29.3	29.1	28.7	29	9.21	13.6	21.7	19.4	28.3	27.5	28.9

All values are in units of IU/mL.

DTaP, Diphtheria, tetanus, and acellular pertussis; HiB, haemophilus influenza B; MMR, measles, mumps, and rubella; MMRV, measles, mumps, rubella, and varicella; PBS, phosphate buffered saline.

*Alpha-gal-coated beads were used in 4-h preincubation with serum at room temperature, followed by immunoassay for each respective biotinylated vaccine or immunocap.

†Baseline values are the patient's serum alpha-gal IgE values before overnight incubation.

allergy to either MMR or varicella vaccines in patients with preexisting beef, pork, alpha-gal, or gelatin allergy. Six of these cases were consistent with anaphylaxis, as defined by the World Health Organization (Table E1, available in this article's Online Repository at www.jaci-inpractice.org).

We proceeded to assay 7 candidate vaccines for alpha-gal antigen-related interactions with our patient's serum (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). Our previous investigation had suggested that alpha-gal antigen in vaccines might be due to content of either bovine/porcine-derived gelatin or bovine calf serum.^{2,5,7}

We performed direct biotinylation of each vaccine in full prescribed dose, after which protein concentration was determined and 5 µg of biotinylated antigen was added to each streptavidin ImmunoCAP, in 2 identical trials. Forty microliters of undiluted serum from our index patient was used in each sIgE assay to assess for IgE binding to the vaccines or gelatin (commercially available ImmunoCAP assay c74), similar to previously published methods.^{1,8} Serum from the subject was also preincubated with 50 µg of galactose-alpha-1,3-gal (Product code NGP1203, Dextra Labs, Reading, UK), coupled to sepharose bead slurry to deplete alpha-gal sIgE. Assays for binding to biotinylated vaccines were then repeated in 2 trials to determine whether binding decreased after preincubation with alpha-gal, which would suggest that any observed binding was due to alpha-gal epitopes present in a vaccine.⁸

The largest direct binding responses that could be removed by the presence of alpha-gal were to MMR (2.33 IU/mL), zoster (1.74 IU/mL), measles, mumps, rubella, and varicella (MMRV) combination (1.15 IU/mL), and varicella vaccines (0.89 IU/mL) (Table IA). The direct binding "vaccine caps" method suggests the presence of an epitope in these gelatin containing vaccines that is recognized by alpha-gal sIgE in sera from our patient (Table IA).

We next measured the baseline alpha-gal sIgE titers in sera from our patient. To ascertain the presence of vaccine epitopes that would bind/remove alpha-gal specific IgE in excess of that expected for gelatin alone, we incubated sera samples from the index patient overnight, separately, with 100 µg from each of the 7 vaccines, bovine gelatin, porcine gelatin, and then remeasured alpha-gal IgE titers (Table IB). The effect of phosphate buffered

saline on the measurement of alpha-gal and gelatin sIgE was estimated to be approximately 1.4%.

Incubation of the sera samples overnight showed partial depletion of the alpha-gal sIgE response in sera preincubated with MMR, MMRV, zoster vaccine, and varicella vaccines, greater than that for gelatin alone. We did not observe any evidence of epitope binding to alpha-gal sIgE binding with DTaP, haemophilus influenza type B, or yellow fever vaccine.

Based on agreement between skin and *ex vivo* testing, MMR and/or varicella vaccines appear to have been the cause of our alpha-gal allergic patient's vaccine-associated anaphylaxis. We have previously demonstrated that MMR and zoster vaccine can bind and deplete sIgE to alpha-gal.² We now show that MMRV and varicella vaccine also demonstrate binding and depletion of alpha-gal sIgE. Evaluating our previous findings in light of new information in this report suggests that increased gelatin content, and not bovine calf serum, may determine the alpha-gal content in vaccines. Bovine gelatin has already been demonstrated to contain alpha-gal as an additional allergenic epitope.¹ Yellow fever vaccine does not appear to bind alpha-gal sIgE from patients as consistently,² but has one-half the gelatin content of the other vaccines, and an unreported gelatin type. Our current patient's lower total concentration of alpha-gal sIgE may have made our previous report more sensitive to differences.²

Both this alpha-gal allergic child and our previous alpha-gal allergic adult who reacted to alpha-gal/gelatin-containing vaccines had low serum concentrations of gelatin sIgE.² Notably, alpha-gal allergic patients have been reported to react to gelatin even with negative gelatin sIgE.⁹ A previous study by Mullins et al¹ showed 30 of 40 (75%) red meat allergic patients with positive skin testing to gelatin, but only 12 of 40 (30%) reacted to gelatin on clinical challenge. Hence, alpha-gal allergy may confound the clinical diagnosis and testing of gelatin allergy. Although porcine and bovine gelatin sensitivity has been described in children with anaphylaxis to gelatin containing vaccines *in vitro*,⁵ this is the first case of vaccine-induced anaphylaxis in a pediatric patient that implicates alpha-gal allergy as another possible contributory mechanism. The copresence of gelatin sIgE may indicate the context in which an alpha-gal allergic patient will react to vaccines, as not all alpha-gal allergic patients will react to gelatin-containing vaccines.²⁻⁴ It needs to be determined if alpha-gal content may vary by gelatin

concentration, gelatin source (bovine, porcine), or by manufacturer. Going forward, *a priori* skin testing and measurement of gelatin sIgE should be evaluated to determine if these tests can predict the safety of gelatin-containing vaccines in individual alpha-gal allergic patients. Caution should be used in parenteral administration of gelatin-containing products in alpha-gal allergic patients.¹ It also needs to be determined whether reduction in vaccine gelatin content might increase vaccine safety for alpha-gal allergic patients.

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TABLE E1. Reported cases of anaphylaxis/cutaneous reactions associated with measles, mumps, rubella vaccine (MMRII), or varicella vaccine (Varivax) with coexisting beef, pork, or alpha-gal allergy

Case	Reaction	Associated allergy	Location
13-year-old boy (2009)	Large local reaction from the injection site on the thigh to the toes after varicella vaccine. Diagnosed as an allergic reaction by treating physician	Known beef, pork, and milk allergy. sIgE not reported	Location not reported
5-year-old boy (2010)	Large local reaction, disseminated urticaria, shortness of breath, nausea/vomiting after MMR, varicella, HiB, DTaP vaccines. Emergency department treatment with medications and diagnosis not reported	Known beef, pork, and milk allergy. sIgE not reported	New Jersey
2-year-old boy (2011)	Developed disseminated urticaria, shortness of breath, difficulty swallowing within an hour of receiving MMR, varicella, HiB, DTaP vaccines. Received Benadryl, orapred, and intramuscular 0.15 mg of epinephrine with resolution. Physician diagnosis of anaphylaxis	Known alpha-gal, beef, and pork allergy. sIgE not reported	Virginia
4-year-old boy (2012)	Developed vomiting, itching, flushing, difficulty breathing within 5 min of vaccination with MMR, varicella, HiB, DTaP vaccines. Treated with antihistamines and 2 doses of intramuscular epinephrine. Diagnosed as anaphylaxis by treating physician	Known gelatin, beef, and pork allergy	Michigan
4-year-old boy (2014)	Disseminated erythematous rash with itching, aching, facial swelling, emesis after DTaP/IPV, MMR, and varicella vaccination	Known pork allergy, with suspected gelatin allergy	Wyoming
4-year-old boy (2016)	Details not reported. Physician diagnosis of anaphylaxis after MMR, varicella, polio, DTaP, flu vaccination	Reported skin test positive pork allergy, no reports of other meat or alpha-gal allergy, no reported sIgE titers	Ohio
16-year-old boy (2016)	Developed disseminated urticaria, shortness of breath, respiratory distress within 20 min of MMR, Hep B, polio, and TDaP vaccination. Treated with antihistamines and steroids in emergency department	Known beef, pork, milk allergy, no sIgE or alpha-gal results reported	California
5-year-old boy (2017) Our case, not yet reported in VAERS	Developed disseminated urticaria/angioedema, wheezing, shortness of breath with MMR, varicella, polio, DTaP vaccination. Was taken to emergency department, received intramuscular epinephrine with resolution of symptoms within 30-40 min. Diagnosed as anaphylaxis by treating physician	Patient with known preexisting alpha-gal allergy	Tennessee
55-year-old woman (2017)	Developed disseminated urticaria and peripheral edema within 30 min of booster MMR vaccine. Treated at home with Benadryl	Known preexisting alpha-gal allergy, titers not reported	Virginia

DTaP, Diphtheria, tetanus, and acellular pertussis; HiB, haemophilus influenza B; IPV, inactivated polio vaccine; MMR, measles, mumps, and rubella; VAERS, Vaccine Adverse Event Reporting System.

TABLE E2. Reported gelatin or mammal derived product content of selected vaccines used in skin or *ex vivo* testing in this report

Vaccine	Reported gelatin content of vaccine	Reported type of gelatin or animal-derived product	How vaccine was used in this report: skin testing (S) or <i>ex vivo</i> (E)
Diphtheria, tetanus, and acellular pertussis (DTaP) (GSK)	None	Bovine casein, bovine extract	S, E
Diphtheria, tetanus, acellular pertussis and inactivated polio vaccine combination (DTaP/IPV) (GSK)	None	Mueller's medium, bovine calf serum	S
Haemophilus influenza B (GSK)	None	None	E
Yellow fever (Sanofi Pasteur)	7,500 µg per 0.5 mL dose	Gelatin, type not reported	E
Measles, mumps, and rubella (MMR) (Merck)	14,500 µg per 0.5 mL dose	Bovine gelatin, bovine calf serum	S, E
Measles, mumps, rubella, and varicella (MMRV) (Merck)	11,000 µg per 0.5 mL dose	Hydrolyzed gelatin, bovine calf serum	E
Varicella (Merck)	12,500 µg per 0.5 mL dose	Hydrolyzed gelatin, bovine calf serum	S, E
Zoster (Merck)	15,580 µg per 0.65 mL dose	Porcine gelatin, bovine calf serum	E