

Beware of α -lactalbumin as a hidden allergen in measles, mumps, and rubella vaccine in the patients with cow's milk allergy

To the Editor,

Cow's milk and hen's egg are the most common food allergies in infants and young children.¹ Cow's milk contains more than 20 different proteins and glycoproteins. Casein (Bos d 8) and its subgroups consist of 80% of cow's milk allergens, and the rest of them are whey proteins such as β -lactoglobulin (Bos d 5), α -lactalbumin (Bos d 4), bovine serum albumin (Bos d 6), and various other proteins.

Anaphylactic reactions have been reported in a small number of cases after measles, rubella, and mumps (MMR) vaccination for several decades. Previously, there were some concerns regarding risk of allergic reaction following MMR vaccination in egg-allergic children due to the use of chicken embryonic fibroblasts as culture medium. Since MMR vaccine contains less than the minimum amount of egg antigen required to elicit an allergic reaction, currently guidelines recommend that children with egg allergy can be safely vaccinated with MMR vaccine in primary care settings.² In late 1990s and early 2000s, gelatin was considered to be the responsible ingredient of the vaccine for anaphylactic reactions.^{1,3} After switching to a hypoallergenic form of gelatin or gelatin-free vaccines, reports of anaphylaxis with live MMR vaccines had dramatically decreased. However, in recent reports, anaphylactic reactions with measles vaccine have been reported in patients with cow's milk allergy due to the α -lactalbumin component of the vaccine.^{4,5} To the best of our knowledge, this is the first report of anaphylaxis in children with severe cow's milk allergy after the MMR vaccine associated with the alpha-lactoglobulin component of milk.

1 | CASE

A 4-year-old male patient was referred to our pediatric allergy outpatient clinic with the diagnosis of cow's milk allergy with recurrent anaphylaxis due to accidental exposure to cow's milk. His physical examination, weight, and height percentiles were detected within normal ranges at his first evaluation. The patient had been advised a strict elimination diet for dairy products, in addition to a written emergency action plan for an accidental exposure and had been prescribed an epinephrine auto-injector.

The MMR vaccination was planned according to the routine national immunization schedule. Within 10 min after the MMR vaccination (TRESIVAC®, Serum Institute of India), the patient showed signs of restlessness, constant and hoarse crying, and difficulty in breathing, drooling, nasal congestion and discharge, angioedema of lips. His blood pressure was measured as 72/46 millimeters of mercury (mmHg). He was treated with intramuscular epinephrine and was referred to our outpatient clinic for further evaluation in terms of vaccine-induced anaphylaxis.

Partially hydrolyzed gelatin, sorbitol, L-histidine, L-alanine, tri-cin, L-arginine hydrochloride, and lactalbumin hydrolysate were listed among the TRESIVAC® vaccine ingredients according to the manufacturer's package (https://www.seruminstitute.com/product_ind_tresivac.php). Culprit vaccine and the ingredients of the other commercially available MMR vaccines are summarized in Table 2. The vaccine vial stoppers and syringe plungers contain natural latex rubber. We considered lactalbumin content of the vaccine as the culprit agent for anaphylaxis as the reaction was compatible with the patient's medical history and laboratory findings. Therefore, we did not need to perform a skin test with the whole vaccine. The patient's allergic work up results are presented in Table 1. Furthermore, about 5 months later, we observed a second case of anaphylaxis with the same brand of the MMR vaccine in a 1-year-old female infant. Her medical history revealed anaphylaxis with cow's milk, hen's egg, and chicken meat. The patient's allergic work up results are summarized in Table 1. She was on an elimination diet with culprit foods when the routine childhood vaccination was administered. Five minutes after the vaccination, the patient had difficulty in breathing, hoarse crying, and a cutis-like appearance on her body. Her blood pressure was 55/30mmHg. Intramuscular adrenaline was administered immediately to the patient and all the symptoms were improved with one dose of IM adrenaline.

2 | DISCUSSION

Vaccines are the most effective method in terms of cost and safety in protecting children and adult health and preventing infectious

TABLE 1 Laboratory findings of the patients

First case			
Total IgE: 603 kU/L			
Serum-specific IgE results		Skin prick test results	
Cow's milk	57 kU/L	Cow's milk	6 × 6 mm
α-lactalbumin	42.44 kU/L	Casein	5 × 5 mm
β-lactoglobulin	0.35 kU/L	Egg white	3 × 3 mm
Casein	55.4 kU/L	Egg yolk	3 × 3 mm
Lactoferrin	<0.35 kU/L	Gelatin	Negative
BSA	59.98 kU/L	Latex	Negative
Egg white	1.7 kU/L	Histamine	5 × 5 mm
Ovomucoid	<0.1 kU/L	Negative control	Negative
Egg yolk	0.93 kU/L		
Second case			
Total IgE: 90.5 kU/L			
Serum-specific IgE results		Skin prick test results	
Cow's milk	41.13 kU/L	Cow's milk	20 × 20 mm
α-lactalbumin	3.4 kU/L	Casein	15 × 15 mm
β-lactoglobulin	0.7 kU/L	Egg white	13 × 13 mm
Casein	17.8 kU/L	Egg yolk	7 × 7 mm
Lactoferrin	<0.35 kU/L	Chicken meat	7 × 7 mm
BSA	9.4 kU/L	Gelatin	Negative
Egg white	34.9 kU/L	Latex	Negative
Ovomucoid	<0.1 kU/L	Histamine	9 × 9 mm
Egg yolk	3.22 kU/L	Negative control	Negative

Abbreviations: BSA, bovine serum albumin; IgE, immunoglobulin E.

TABLE 2 Ingredients of manufactured MMR vaccine¹⁰

MMR Vaccines trade names	Manufacturer	Excipients
MMR-II®	Merck Sharp and Dohme	Sorbitol, sucrose, hydrolyzed gelatin (14.5 mg/0.5 ml) , recombinant human albumin, fetal bovine serum, other buffer and media ingredients, neomycin (25 mcg/0.5 ml)
Priorix®	Glaxo Smith Kline	Powder: amino acids, lactose (anhydrous), mannitol, sorbitol Solvent: water for injections
MMR vax pro®	Merck Sharp and Dohme	Powder; Sorbitol, sodium phosphate, potassium phosphate, sucrose, hydrolyzed gelatin (unspecified amount) , medium 199 with Hanks' salts, MEM, monosodium L-glutamate, neomycin (unspecified amount) , phenol red, sodium bicarbonate, hydrochloric acid, sodium hydroxide solvent: water for injections
ProQuad®	Glaxo Smith Kline	Sodium chloride, sodium phosphate, potassium phosphate, sodium bicarbonate, Sorbitol, hydrolyzed gelatin (11 mg/0.5 mL) , monosodium glutamate mono hydrate, potassium chloride
Tresivac®	Serum Institute of India	Hydrolyzed gelatin (unspecified amount) , sorbitol, L-histidine, L-alanine, Tricine, hydrolyzed lactalbumin (unspecified amount) , L-arginine hydrochloride, medium

Note: Bold phrases indicate allergenic ingredients of the vaccine.

diseases. Hypersensitivity reactions represent only a small proportion of all vaccine-related adverse reactions. Among them, although IgE-mediated allergic reactions are rare, systemic reactions such as anaphylaxis can be severe and life-threatening.^{6,7}

Vaccines contain both active microbial antigens and the additional ingredients, such as preservatives, adjuvants, stabilizers like gelatin and residual components of the culture medium such as milk, egg, and yeast.⁸ Hypersensitivity reactions usually

occur to the excipients of vaccines rather than active microbial antigens.⁹

Anaphylactic reactions have been reported in some cases with severe cow's milk allergy after vaccination with diphtheria, tetanus, and acellular pertussis (DTaP) vaccines.¹ In recent case reports, anaphylaxis has been observed in patients with IgE-mediated cow's milk allergy after measles vaccination in Turkey. The authors associated these reactions with residual milk allergen in the vaccines.^{4,5} We realized that the vaccine used in our cases and the vaccine used in those previous case reports of anaphylaxis after the measles vaccine belonged to the same manufacturer.^{4,5} From now on, we plan to vaccinate children with severe cow's milk allergy with another brand of MMR vaccine that does not contain any milk component. Ingredients of manufactured different brands of the MMR vaccines are summarized in Table 2.¹⁰

Vaccine hesitancy is a major problem in the community and significantly affects global health. Therefore, all vaccine manufacturers should take the maximum care and use standard vaccine components to produce safer vaccines in terms of allergic reactions.

In conclusion, healthcare professionals should be aware of the fact that in patients with IgE-mediated food allergies drugs and vaccines can be an accidental way of encountering hidden allergens. Especially in cases with severe food allergy, the medical history of the patients, the contents of the vaccine, and the package inserts should be carefully evaluated before vaccination.

AUTHOR CONTRIBUTIONS

Esra Yucel: Conceptualization (lead), writing—original draft (lead), review, and editing (equal). Çağla Karavaizoglu: writing—original draft (lead). Zeynep Hizli Demirkale: writing—review and editing (equal). Kazım Okan Dolu: writing—review and editing (supporting). Ayşe Suleyman: writing—original draft (supporting). Zeynep Ulker Tamay: supervision (lead)—review and editing (equal).

CONFLICT OF INTEREST

None.

PEER REVIEW

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