A Case of Anaphylaxis to Measles Vaccination in an Infant with Cow's Milk Allergy

Sevgi Sipahi, MD,¹ Deniz Ozceker, MD,² Gulbin Gokcay, MD,³
Nermin Guler, MD,¹ and Zeynep Tamay, MD¹

Background: Cow's milk is one of the most common of the foods that cause food allergies in children. Here, we present a 10-month-old male who was diagnosed with having an allergy to cow's milk and who developed an anaphylactic reaction after being recently vaccinated with a measles vaccine.

Case: The patient had been diagnosed with atopic dermatitis and cow's milk allergy at 40 days old after a rash appeared on his face and arms while exclusively breastfeeding. At 9 months, on his routine welfare outpatient appointment, he developed a facial rash and swelling, wheezing, difficulty breathing, and cyanosis within 10 min of having his first measles vaccination (M-VAC[®]; Serum Institute of India, Hadapsar, Pune, India). After an allergy evaluation and a physical examination that showed that he was otherwise healthy, he was diagnosed with an allergy to cow's milk, which was then eliminated from his diet. Laboratory evaluations were as follows: serum immunoglobulin E (IgE) to cow's milk: 36.2 kU/L, α -lactalbumin: 9.39 kU/L, β -lactoglobulin: 8.74 kU/L, casein: 34.2 kU/L, latex-specific (sp)IgE: 0.10 kU/L, gelatin spIgE: <0.35 kU/L (normal levels <0.35 kU/L; Pharmacia, Uppsala, Sweden). Results revealed lactalbumin hydrolysate as one of the M-VAC ingredients according to the manufacturer's package insert.

Conclusion: In most cases with a cow's milk allergy, vaccines are administered without any problems because the amount of milk proteins contained in the vaccines is not sufficient to represent a risk factor for anaphylaxis; however, the vaccine content should be examined for possible allergens, particularly for children with food allergies, before vaccinating. We should keep in mind when determining the agent responsible for an allergic reaction that the risk from a residual component of milk protein in vaccines can differ according to the nutritional habits of the population.

Keywords: anaphylaxis, measles, vaccination, cow's milk, allergy

Introduction

COW'S MILK IS ONE of the most common of the foods that cause allergies in childhood. Its prevalence in infancy is ~2%–3% but gradually decreases throughout childhood with a rate of $\leq 1\%$ in children ≥ 6 years old.¹ There are ~20 protein components in cow's milk that can cause antibody formation in humans.² Cow's milk protein comprises 80% casein with casein subgroups of α s1, α S2, β , and κ casein, and 20% whey proteins. Whey protein comprises β -lactoglobulin, α -lactalbumin, bovine serum albumin (BSA), and various other proteins, such as lactoferrin, transferrin, lipase, and esterase, in small amounts.

The most common allergens in cow's milk protein are casein, β -lactoglobulin, and α -lactalbumin moieties.³ Allergic reactions to cow's milk are classified as immunoglobulin E

(IgE) mediated, non-IgE mediated (cellular), and mixed type in which both reactions are involved. IgE-mediated reactions are immediate reactions with an acute onset; the most severe form is anaphylaxis, in which ≥ 2 systems are involved, such as skin, respiratory, cardiovascular, or gastrointestinal systems.⁴

Allergic reactions from the measles–mumps–rubella (MMR) vaccine are infrequent. Most cases of anaphylaxis associated with MMR vaccine have been traced to the gelatin content, which is used as a stabilizer; however, after switching to a hypoallergenic form of gelatin or gelatin-free vaccines, anaphylaxis/allergic reactions to live MMR vaccines have been very rarely reported.⁵ Although the MMR vaccine is grown in a chicken fibroblast cell culture and contains trace amounts of egg antigen, the amount is not sufficient to elicit an allergic

¹Division of Pediatric Allergy and Immunology, Department of Pediatrics, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey.

²Department of Pediatric Allergy and Clinic Immunology, Okmeydanı Training and Research Hospital, Istanbul, Turkey.

³Well Child Unit, Department of Pediatrics, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey.

reaction; therefore, concerns regarding the risk of an allergic reaction after MMR immunization have been abandoned.⁶

According to the 2012 Republic of Turkey, Ministry of Health National Immunization Program, single-component measles vaccines were administered to children 9 months old because of a measles epidemic, and MMR vaccines were administered to children who were 12 months old and to those who were in the first grade of primary school; however, because there had been no measles case reports since June 2016, it was decided to not continue administering the single-component measles vaccine. Here, we present a patient who was diagnosed as having an allergy to cow's milk and who had an anaphylactic reaction after receiving a M-VAC at 9+ months old.

Case Report

A 10-month-old male patient was referred to our outpatient allergy clinic after having an allergic reaction to the measles vaccine. The patient was born full term weighing 3,650 g, and diagnosed with atopic dermatitis and a cow's milk allergy at 40 days old after developing a rash on his face and arms while exclusively breastfeeding. The symptoms disappeared after his mother eliminated cow's milk and milk products from her diet while still breastfeeding and after local treatment for atopic dermatitis. At 6 months old when the patient began to eat supplementary food, cow's milk was eliminated from his diet.

At 9 months old, on his routine welfare outpatient appointment, the patient developed a facial rash and swelling, wheezing, difficulty breathing, and cyanosis within 10 min of receiving his first measles vaccination (M-VAC[®]; Serum Institute of India, Hadapsar, Pune, India). He was immediately treated with intramuscular epinephrine, parenteral pheniramine maleate, and methyl prednisolone, which completely eliminated the anaphylaxis symptoms. The results of the patient's physical examination were normal; however, cow's milk continued to be eliminated from his diet because of the positive allergy test.

The results of the laboratory evaluations were as follows: serum IgE to cow's milk: 36.2 kU/L, α -lactalbumin: 9.39 kU/L, β -lactoglobulin: 8.74 kU/L, casein: 34.2 kU/L, BSA: <0.35 kU/L, egg white-specific (sp) IgE: 2.23 kU/L, latex spIgE: 0.10 kU/L, gelatin spIgE: <0.35 kU/L (normal levels <0.35 kU/L; Pharmacia, Uppsala Sweden). We conducted a skin-prick test using 5 g gelatin powder in 5-mL normal saline, the results of which were also negative. We observed that lactalbumin hydrolysate was listed among the M-VAC vaccine ingredients according to the manufacturer's package insert (Fig. 1). We did not perform a skin-prick test using the

FIG. 1. Pharmaceutical particulars. List of excipients: gelatin, sorbitol, histidine, alanine, tricine, arginine, lactalbumin hydrolysate.

vaccine because there was no doubt that the patient was allergic given the episode of anaphylaxis after receiving the vaccine, which had been confirmed and documented by his family practitioner.

The patient was also reported to the Turkish Vaccine Adverse Events Reporting System. At 12 months old, according to the national vaccination schedule, the child received the MMR (Priorix[®]; GlaxoSmithKline, Canada) vaccine as a second dose without any reaction. We did not perform a skin-prick test/ID with the MMR vaccine before the vaccination because it differed from M-VAC, the monovalent measles vaccine, in that it did not contain any milk protein residues as the potential allergen.

Discussion

Anaphylaxis is a rare but potentially life-threatening vaccination-related adverse effect that usually occurs within the first 20 min after the vaccine is administered.^{7,8} Anaphylaxis is estimated to occur at a rate of ~ 1 per million vaccine doses. In a large retrospective study conducted in California, the potential risk of vaccine-associated anaphylaxis in children and adolescents was reported to be 0.65 case/million doses after administration of 7,644,049 vaccine doses during 1991–1997.⁸ Another study from the United Kingdom reported no vaccine-related anaphylaxis cases out of ~ 5.5 million vaccinations routinely performed on pre-school children and infants over a 1-year period.⁷

Vaccines contain active components, the antigens, which induce the immune response, and additional components, such as preservatives, adjuvants, and stabilizers, and residual components of the culture medium, such as milk, eggs, and gelatin. Milk, eggs, and gelatin were reported as the culprits in cases of anaphylaxis associated with the MMR vaccines.

The immediate allergic reactions associated with the MMR vaccine from the gelatin component were reported mainly in Japan,⁹ where red meat consumption is lower than that in Western countries. The presence of IgE to gelatin in patients with an allergic reaction to MMR was reported less in the United States¹⁰ and Finland¹¹ than in Japan. Since the end of 1998, marketed vaccines using the live measles virus are either gelatin free or contain a hypoallergenic form of gelatin. Red meat is routinely consumed by Turkish people, and neither a red meat nor gelatin allergy is frequent in that country. Our patient routinely consumed beef, and both the serum spIgE and skin-prick test for gelatin were negative.

Food allergies are common in early childhood. Egg and cow's milk are the most common causes of food allergies in infancy worldwide, with an incidence rate of $\sim 1\%$ – 2% .¹² Some vaccines contain trace amounts of milk proteins to prevent virus degradation.^{12,13} Those containing casein are diphtheria–pertussis–tetanus (DTaP; Infanrix[®], Daptacel[®]) and tetanus–diphtheria–pertussis (Tdap; Adacel[®]).^{14–17} Although rare, allergic reactions in patients after administration of certain vaccines containing cow's milk have been reported.^{17–23}

Kattan et al.⁷ have reported 8 cases of an anaphylactic reaction developing after receiving DTaP (Daptacel, Infanrix) or Tdap (Adacel) vaccines in patients with a severe allergy to cow's milk; however, these patients were selected based on reports of these reactions in children and not because of a history of milk or any other food allergy. Interestingly, all of

them had very high serum milk spIgE levels, which were documented within 2 years of the reaction to the vaccine (58.9 to >100 kU/L).

Six of the patients had a history of immediate and severe allergic reactions to cow's milk, 4 of whom had also reacted to even a trace amount of exposure, showing a severe allergy to IgE-mediated cow's milk. Two patients had a delayed onset of the cow's milk allergy, presenting with atopic dermatitis and proctocolitis but with high serum IgE levels, showing both IgE- and non-IgE-mediated allergies to cow's milk (>100 and 82.9 kU/L, respectively). The authors also confirmed the presence of casein (8.1–18.3 ng/mL) in the DTaP and Tdap vaccine samples.¹⁷

Parisi et al. have evaluated children who had experienced immediate-type hypersensitivity reactions after vaccination with the oral polio vaccine (OPV, Trivalent vaccine Polioral[®]; Sclavo, Siena, Italy) and measles–rubella vaccine (MRV[®]; Serum Institute of India Ltd.) in the 2009 vaccination campaign conducted in Argentina.¹⁸ There were 4 children who had immediate vaccine-related reactions, and all had history of severe IgE-mediated allergies to cow's milk; all of their skin-prick tests for milk proteins (α -lactalbumin, β -lactoglobulin, casein, and whole milk) were positive. In addition, it was observed that the Sabin vaccine was used for the skin-prick test, and that the children receiving the test with positive results had a detectable amount of the serum Sabin vaccine spIgE. The authors also confirmed the presence of α -lactalbumin in the OPV using the enzyme-linked immunosorbent assay method.

Yavuz et al.¹⁹ have reported 3 cases of anaphylaxis after MMR vaccination in children sensitized to chicken eggs and cow's milk. Two of the patients had been diagnosed with atopic dermatitis at 4 and 6 months old, respectively, and responded well to avoiding eggs and cow's milk; however, both experienced an anaphylactic reaction after their first immunization with MMR (Tresivac[®]; Serum Institute of India) at 1 year old. The third patient, a 6-year-old girl, who had a history of anaphylaxis after her first MMR vaccination (Tresivac; Serum Institute of India) at 1 year old, developed an anaphylactic reaction after an injection with only 10% of the MMR vaccine. This child also had a history of transient milk, eggs, and beef allergies in infancy.

The authors measured spIgE levels to cow's milk, eggs, and gelatin during the anaphylactic reaction in all patients, and the results showed the presence of cow's milk (>100, 3.34, and 13.7 kU/L, respectively) and eggs (73.6, 1.94, and 0.77 kU/L, respectively) sensitization and absence of gelatin (<0.35 kU/L) sensitization. MMR vaccine (Tresivac) contains the mumps virus produced in chicken fibroblast cultures, and measles and rubella viruses produced in human diploid cell cultures; therefore, it contains only trace amounts of egg proteins, mostly ovalbumin, which are not considered to be sufficient to cause an adverse allergic reaction.

In addition, egg protein was not detected in the vaccines administered to the children, and spIgE to eggs was negative in 2 of the 3 cases; therefore, the mechanism for the reaction was undefined. With the mechanism undefined, the authors have suggested that the children who were sensitized or allergic to food might have developed the reactions after MMR vaccination.

A study conducted in Sri Lanka has shown that the majority of patients who developed immediate hypersensitivity reactions to vaccines, including MMR, had beef and/or cow's milk allergies, and concluded that BSA might be the allergen

responsible for the vaccine-associated allergic reactions.²⁴ The prevalence of a beef allergy is likely to be higher in Sri Lanka than in Western countries because beef consumption is less in this country; the majority of individuals in Sri Lanka are either Buddhists or Hindu, and they do not consume beef. The study has shown a sensitization to BSA in a majority of patients, which is a major allergen in beef, and the absence of sensitization to gelatin. They have also reported an immediate allergic reaction in patients who had never consumed beef but who had an allergy to cow's milk.

In addition, the majority of children with an allergy to cow's milk were highly sensitized to BSA but not to β -lactoglobulin or casein, which is in contrast with the results of Western studies. There are several single-component measles vaccines (Rouvax[®], M-VAC) manufactured throughout the world. Rouvax (Sanofi-Pasteur, France) contains the live measles virus, human albumin, neomycin, and lactose. M-VAC, a single-component measles vaccine imported from India, contains lactalbumin and gelatin.

There are some reports on the immediate hypersensitivity reactions with the use of a single-component measles vaccine.^{20,21,24,25} Erlewyn-Lajeunesse et al.²⁰ have reported 4 cases of anaphylaxis between 2003 and 2007 after administration of single-component measles or rubella vaccine. The estimated incidence of anaphylaxis after receiving the single-component measles vaccine was 18.9 cases/100,000 doses. A case of anaphylaxis with a single-component measles vaccine (Rouvax; Sanofi Pasteur) was reported in a 15-month-old child without a known history of atopy.

Caffarelli et al.²¹ have evaluated immediate-type reactions after administration of the single-component measles vaccine (Moraten, Berna) during a M-VAC campaign in Italy between 1990 and 1992. The vaccine is produced in a human fibroblast culture, and only 3 cases of 3,300 children 13 months to 10 years old were reported to have had serious allergic reactions,¹⁶ and all 3 of these cases had a history of food allergies. The authors have concluded that the reactions might have been from cross reactivity between the constituents of the vaccine and either eggs or cow's milk proteins. When we examined the vaccine contents, we determined that it did not contain cow's milk protein, but did contain lactose and d-sorbitol as excipients; however, children who developed anaphylaxis might have been vaccinated with a particular vaccine lot that was contaminated with milk peptide fragments.

Uysal et al.²⁵ have reported anaphylaxis after a measles vaccine (M-VAC; Serum Institute of India) in a patient with a severe allergy to cow's milk. The patient was diagnosed as having a cow's milk allergy at 3 months old, when she developed an immediate hypersensitivity reaction after ingesting the milk. The authors have determined that the patient had sensitized to milk proteins as follows: spIgE to cow's milk: 52.6 kU/L, α -lactalbumin: 21.3 kU/L, β -lactoglobulin: 31.8 kU/L, casein: 65.3 kU/L; she was not sensitized to gelatin (gelatin spIgE: <0.35 kU/L). The authors have concluded that the anaphylactic reaction was related to the milk component in the vaccine. Our case is very similar to this case showing an immediate hypersensitivity systemic reaction to the lactalbumin component in the vaccine.

In conclusion, immediate allergic reactions associated with the MMR vaccine are rare, and residual milk proteins or gelatin contents are not in quantities high enough to elicit hypersensitivity reactions in susceptible individuals with milk, red meat, and/or gelatin allergies. The nutritional habits

of the population determine the responsible component of the food protein that elicits an allergic reaction to the vaccine. Although BSA and gelatin can be the culprit proteins that induce allergic reactions in Japan and Sri Lanka, where red meat consumption is relatively rare compared with that in Western countries, lactalbumin can be responsible for allergic reactions in countries where an allergy to cow's milk is more frequent than one to meat.

New-generation MMR vaccines contain negligible amounts of milk protein that is not sufficient to trigger an allergic reaction, and they are either gelatin free or contain a hypoallergenic form of gelatin. Our case demonstrated that the measles vaccine, M-VAC, which contains lactalbumin, can induce an immediate allergic reaction in children who have an allergy to cow's milk, which was also reported by Uysal et al.²⁵ This might be the result of contamination of a particular vaccine lot with larger milk peptide fragments.

In most cases, vaccines are administered without any problems, even to those with an allergy to cow's milk. This can be explained by the fact that the amount of milk proteins contained in the vaccines is not sufficient to represent a risk factor for anaphylaxis. Nevertheless, the vaccine content should definitely be examined for possible allergens, particularly for children with food allergies, before vaccinating. We should keep in mind when determining the agent responsible for the reaction that the risk of an allergic reaction to a residual component in the milk protein in vaccines can differ according to the nutritional habits of the population.

Author Disclosure Statement

No competing financial interests exist.

References

1. Sicherer SH. Epidemiology of food allergy. *J Allergy Clin Immunol* 2011; 127:594–602.
2. Wal JM. Cow's milk allergens. *Allergy* 1998; 53:1013–1022.
3. Fiocchi A, Schünemann HJ, Brozek J, et al. Diagnosis and rationale for action against cow's milk allergy (DRACMA): a summary report. *J Allergy Clin Immunol* 2010; 126:1119–1128.
4. Fiocchi A, Brozek J, Schünemann H, et al. World Allergy Organization (WAO) Special Committee on Food Allergy. Diagnosis and Rationale for Action against Cow's Milk Allergy; the WAO DRACMA guideline. *Pediatr Allergy Immunol* 2010; 21 Suppl 21:1–125.
5. Dreskin SC, Halsey NA, Kelso JM, et al. International Consensus (ICON): allergic reactions to vaccines. *World Allergy Organ J* 2016; 9:32.
6. Caubet J-C, Rudzeviciene O, Gomes E, et al. Managing a child with possible allergy to vaccine. *Pediatr Allergy Immunol* 2014; 25:394–403.
7. Erlewyn-Lajeunesse M, Hunt LP, Heath PT, et al. Anaphylaxis as an adverse event following immunisation in the UK and Ireland. *Arch Dis Child* 2012; 97:487–490.
8. Bohlke K, Davis RL, Marcy SM, et al. Risk of anaphylaxis after vaccination of children and adolescents. *Pediatrics* 2003; 112:815–820.
9. Nakayama T, Aizawa C, Kuno-Sakai H. A clinical analysis of gelatin allergy and determination of its causal relationship to the previous administration of gelatin-containing acellular pertussis vaccine combined with diphtheria and tetanus toxoids. *J Allergy Clin Immunol* 1999; 103:321–325.
10. Pool V, Braun MM, Kelso JM, et al. Prevalence of anti-gelatin Ig E antibodies in people with anaphylaxis after measles-mumps-rubella vaccine in the United States. *Pediatrics* 2002; 110:e71.
11. Patja A, Mäkinen-Kiljunen S, Davidkin I, et al. Allergic reactions to measles-mumps-rubella vaccination. *Pediatrics* 2001; 107:e27.
12. Franceschini F, Bottau P, Caimmi S, et al. Vaccination in children with allergy to non active vaccine components. *Clin Transl Med* 2015; 4:3.
13. Anonymous. Allergens in Vaccines. Institute for Vaccine Safety, Johns Hopkins Bloomberg School of Public Health 2015. www.vaccinesafety.edu/components-Allergens.htm Accessed August 15, 2019.
14. FDA. Sanofi Pasteur 306—Adacel® full prescribing information. 2017. www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm142764.pdf Accessed August 15, 2019.
15. [www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing Information/Infanrix/pdf/INFANRIX.PDF](http://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing%20Information/Infanrix/pdf/INFANRIX.PDF)
16. FDA. Sanofi Pasteur 253—DAPTACEL® full prescribing information. www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM103037.pdf Accessed August 15, 2019.
17. Kattan JD, Konstantinou GN, Cox AL, et al. Anaphylaxis to diphtheria, tetanus, and pertussis vaccines among children with cow's milk allergy. *J Allergy Clin Immunol* 2011; 128:215–218.
18. Parisi CA, Smaldini PL, Gervasoni ME, et al. Hypersensitivity reactions to the Sabin vaccine in children with cow's milk allergy. *Clin Exp Allergy* 2013; 43:249–254.
19. Yavuz ST, Sahiner UM, Sekerel BE, et al. Anaphylactic reactions to measles-mumps-rubella vaccine in three children with allergies to hen's egg and cow's milk. *Acta Paediatr* 2011; 100:e94–e96.
20. Erlewyn-Lajeunesse M, Hunt LP, Heath PT, et al. Anaphylaxis following single component measles and rubella immunisation. *Arch Dis Child* 2008; 93:974–975.
21. Caffarelli C, Cavagni G, Deriu FM, et al. Adverse reactions to measles immunisation. *BMJ* 1994; 309:808.
22. Demicheli V, Rivetti A, Debalini MG, et al. Vaccines for measles, mumps and rubella in children. *Cochrane Database Syst Rev* 2012:CD004407.
23. Pearce A, Law C, Elliman D, et al. Factors associated with uptake of measles, mumps, and rubella vaccine (MMR) and use of single antigen vaccines in a contemporary UK cohort: prospective cohort study. *BMJ* 2008; 336:754–757.
24. de Silva R, Dasanayake WMDK, Wickramasinha GD, et al. Sensitization to bovine serum albumin as a possible cause of allergic reactions to vaccines. *Vaccine* 2017; 35:1494–1500.
25. Uysal P, Alan Ş, Demir F, et al. Anaphylaxis developing after measles vaccine in an infant with cow's milk allergy. *Asthma Allergy Immunol* 2017; 15:171–174.

Address correspondence to:

Sevgi Sipahi, MD

Division of Pediatric Allergy and Immunology

Department of Pediatrics

Istanbul Faculty of Medicine

Istanbul University

Çapa, Fatih

Istanbul 34093

Turkey

E-mail: sevgisipahi1983@gmail.com

Received for publication January 14, 2019; accepted after revision June 8, 2019.