

Clinical Communications

Hypersensitivity reactions to measles-mumps-rubella vaccine in patients with IgE-mediated cow's milk allergy

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Clinical Implications

- Patients with IgE-mediated cow's milk allergy could develop allergic reactions after the administration of measles-mumps-rubella vaccines containing hydrolyzed cow's milk allergens, especially those with high specific IgE. Precautions may be appropriate in this population.

TO THE EDITOR:

Immunization is an effective and safe way to reduce vaccine-preventable diseases. Although minor adverse events after immunization are common,¹ hypersensitivity reactions are infrequent and the risk of anaphylaxis after immunization is 1.31:1,000,000 doses.^{2,3} Among vaccines, the measles-mumps-rubella (MMR) vaccine is commonly involved in allergic reactions, with a reported rate of vaccine-specific anaphylaxis of 5.14:1,000,000 doses.³ During 2018, an unusually high frequency of MMR-associated allergic reactions was noticed in several centers in Chile. This was corroborated by the Chilean pharmacovigilance program, which includes a nationwide registry with mandatory reporting of all reactions to vaccines. According to national data, the rate of MMR-associated anaphylaxis increased from an average of 2.6:1,000,000 doses during the period 2012 to 2017 to 10:1,000,000 in 2018. During this same period, 6 cases of anaphylaxis to the diphtheria, tetanus, and pertussis (Tdap) vaccine were reported, but no other vaccines had a significant proportional reporting ratio.

We reviewed the medical history of 9 children with acute-onset reactions after MMR vaccination. All patients had been diagnosed with IgE-mediated cow's milk allergy (CMA) within their first year of life, before receiving their first dose of MMR, and had a history of acute allergic symptoms after exposure to cow's milk; however, none of them had a history of anaphylaxis. All patients had allergy testing within 1 year of the reaction to MMR, milk sensitization was documented by specific IgE (sIgE) in all patients, skin testing was done in 5 patients, and 6 patients had component-resolved testing. Five patients had an sIgE level greater than 100 kU_A/L to milk or casein. In the period between CMA diagnosis and vaccination, all patients strictly avoided cow's milk, but 5 patients reacted to accidental milk exposure. Five patients were sensitized to additional foods (Table 1).

All reactions occurred after the patients received the MMR vaccine manufactured by the Serum Institute of India (Pune, Maharashtra, India). In Chile, MMR is administered at age 12

months and in first grade (ie, 6-7 years). In 6 cases MMR was given concomitantly with other vaccines: 4 with Tdap; 1 with bivalent oral polio vaccine, hepatitis A vaccine, and pentavalent vaccine (*Haemophilus influenzae*, cellular pertussis, tetanus, diphtheria, and hepatitis B); and 1 with Prevnar 13 and conjugated meningococcal vaccine. All reactions occurred within 60 minutes after immunization, except for 1 case in which the patient had a reaction after 90 minutes. Six patients fulfilled criteria for anaphylaxis according to the Brighton Collaboration case definition.⁴ In 2 cases, the reactions were limited to respiratory symptoms and 1 patient experienced only cutaneous manifestations. None of the 9 patients were hospitalized, and all of them recovered completely. Five patients were of school age at the time of the reaction and had been previously immunized with MMR. Only 1 of them had respiratory symptoms after immunization. All these 5 patients had been diagnosed with CMA before age 12 months.

Reactions after immunization can be attributed to the vaccine, especially if no other exposures were present.² Most acute-onset reactions within 4 hours of immunization correspond to IgE-mediated reactions against a vaccine component.⁵ Several components may elicit hypersensitivity reactions, including gelatin, a component previously found at high concentration in MMR, and latex.¹ Food allergens, including milk proteins, have been previously found as contaminants in the Tdap and oral polio vaccines. In those reports, all patients suffering anaphylaxis after immunization with the Tdap and oral polio vaccines were found to be sensitized to cow's milk. The presence of casamino acids, a mixture of amino acids and small peptides derived from casein, was demonstrated in 8 batches of the Tdap vaccine, and α -lactalbumin in the oral polio vaccine.^{6,7} Most recently, Fantinato et al⁸ reported 7 cases of anaphylaxis after immunization of patients with CMA with the MMR vaccine manufactured by the Serum Institute of India, although no information was provided on clinical characteristics or sensitization status of patients with CMA. According to the study of Fantinato et al, patients with CMA have an odds ratio of 51.62 ($P = .00002$; 95% CI, 5.59-476.11) of developing anaphylaxis after immunization with the MMR manufactured by the Serum Institute of India, a vaccine that lists hydrolyzed lactalbumin as a component. MMR vaccines produced by other manufacturers do not contain milk proteins.

In summary, we identified 9 IgE-mediated patients with CMA with acute-onset reactions after vaccination with a milk-containing MMR vaccine. The temporality and the absence of other exposures support a very probable vaccine-associated reaction. Although several of the patients received other vaccines concomitantly, MMR was the only vaccine consistently administered to all patients, making it the most likely culprit. The high levels of sIgE to milk detected in most patients and the fact that none of the patients were able to tolerate milk at the time of immunization raise the concern for reactions triggered by milk proteins in the vaccine. Causality could not be demonstrated because skin testing with the vaccines was not performed and the batches that caused the reactions were not available for further allergen detection. Another allergen that should be considered when evaluating patients with reactions to MMR is gelatin.⁵

TABLE I. Clinical findings in 9 cases of MMR-triggered hypersensitivity reactions

Case	Age (y)/sex	History of allergy	Skin test (mm)*	sIgE (kU _A /L)*	Vaccines	Onset after vaccination (min)	Symptoms	Brighton level	Treatment received
1	6/F	CMA AD	CM: 22 Egg: 10 Fish mix: 10 Shellfish mix: 9	CM: 17.4 CAS: >100 ALA: 50.1 BLG: 22.5	MMR	2	Local reaction, cough, dyspnea, rash, vomiting	3	Hydrocortisone, salbutamol, O ₂
2	6/F	CMPA	NDR	CM: >100 Wheat: 0.91 Soy: 0.37	MMR, Tdap	5	Cough, wheezing, dyspnea, desaturation	NA	NDR
3	7/F	CMA OAS	NDR	CM: 55.5 CAS: >100	MMR, Tdap	<60	Pruritus, urticaria, angioedema, dyspnea, loss of consciousness	1	Epinephrine, hydrocortisone, salbutamol
4	1.8/M	CMA AD	CM: 8.5 CAS: 11 ALA: 11 BLG: 7.5	CM: 14.9	MMR, Tdap, bOPV, pentavalent, HAV	3	Flushing, pruritus, generalized urticaria, angioedema, dyspnea	2	Epinephrine, hydrocortisone, antihistamines
5	1/M	CMA	CM: 12 Corn: 4 Walnut: 4	CM: >100 CAS: >100 ALA: 92 BLG: >100	MMR, Prevnar13, MenACWY	2	Wheeze, cough, sneezing	NA	NDR
6	6/F	CMA	CM: 5 CAS: 3 Beef: 3 Pork: 3	CM: class III CAS: class II ALA: class II BLG: class III	MMR, Tdap	90	Erythema, fatigue, flushing, urticaria, dyspnea, abdominal pain	3	Epinephrine
7	1/M	CMA	NDR	CM: 64 CAS: 54.2 ALA: 16.2 BLG: 14	MMR	10	Cough, angioedema	2	NDR
8	6/M	CMA Asthma	CM: 30 Beef: 15 Egg: 5	CM: >100 CAS: 31.5 BSA: 17.3	MMR, Tdap	<60	Generalized urticaria, angioedema, rhinorrhea	2	NDR
9	1/M	CMA	NDR	CM: 21.4	MMR	20	Urticaria, angioedema	NA	Prednisone, antihistamines

AD, Atopic dermatitis; ALA, α -lactalbumin; BLG, β -lactoglobulin; bOPV, bivalent oral polio vaccine; CAS, casein; CM, cow's milk; F, female; HAV, hepatitis A vaccine; M, male; MenACWY, meningococcal ACWY (the MenACWY vaccine helps to protect against disease caused by 4 of the main serogroups of meningococcal bacteria: A, C, W, and Y); NA, not applicable; NDR, no data reported; OAS, oral allergy syndrome.

*Class II: sIgE, 0.7-3.49 kU_A/L; Class III: sIgE, 3.5-17.49 kU_A/L.

Although this was evaluated in only 1 patient from our cohort who had negative sIgE to porcine gelatin (Immulate), it is less likely that all patients were also allergic to gelatin. It is important to be aware that patients can develop hypersensitivity reactions after immunization and although standard recommendations should apply to every vaccination,⁹ caution should be greater when administering vaccines that contain milk allergens to patients with CMA. Because CMA is common and this milk protein-containing MMR vaccine is almost universally administered in Chile and other countries, it is clear that most children with CMA do not react to the vaccine. Nonetheless, before the administration of a milk protein-containing MMR vaccine, caregivers or patients should be asked about severe reactions to the ingestion of cow's milk. In those who indicate such an allergy, precautions may be appropriate including the administration of an MMR vaccine not containing milk protein if available, observation for 1 hour after vaccine administration prepared to treat an allergic reaction, or referral to an allergy specialist.

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