

# Food allergy to gelatin in children with systemic immediate-type reactions, including anaphylaxis, to vaccines

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**Background:** Anaphylaxis to measles-mumps-rubella vaccines has been reported. We have suspected that most such reactions are caused by gelatin contained in the vaccines.

**Objective:** To confirm the relation between systemic allergic reactions to vaccines and the presence of anti-gelatin IgE, we measured anti-gelatin IgE in children who demonstrated allergy to gelatin-containing vaccines. Furthermore, to clarify the relation between allergic reactions to gelatin in vaccines and foods, we surveyed the occurrence of allergic reactions to gelatin-containing foods in the same children.

**Methods:** Serum samples were taken from 26 children who had systemic immediate-type reactions, including anaphylactic shock, to vaccines and the same number of children without allergic reactions. Specific IgE to gelatin in these samples was measured. We then surveyed whether these children had allergic reactions to gelatin-containing foods before and after vaccination.

**Results:** Twenty-four of the 26 children with allergic reactions to vaccines had anti-gelatin IgE ranging from 1.2 to 250 Ua/ml. Seven had allergic reactions on ingestion of gelatin-containing foods. Of these, two had reactions before vaccination, and five had reactions after vaccination. All the control children without allergic reactions to vaccines had no anti-gelatin IgE.

**Conclusion:** We reconfirmed a strong relationship between systemic immediate-type allergic reactions, including anaphylaxis, to vaccines and the presence of specific IgE to gelatin. Moreover, some of the children also had allergic reactions to food gelatin before or after vaccination. (*J Allergy Clin Immunol* 1996;98:1058-61.)

**Key words:** Anaphylaxis, food allergy, gelatin, IgE, vaccines

Anaphylaxis to measles-mumps-rubella (MMR) vaccines has been reported and has been suggested to be caused by allergy to egg proteins present in the vaccines.<sup>1</sup> However, immediate allergic reactions have also been described in children who tolerated eggs.<sup>2-6</sup> Such reactions may be caused by egg proteins or some other vaccine constituents.<sup>6</sup> Kelso et al.<sup>7</sup> reported that a patient who had anaphylaxis in response to MMR vaccine had IgE antibody to gelatin. Previously, we found that 10 of

#### Abbreviation used

MMR: Measles-mumps-rubella

11 children who had systemic immediate-type reactions, including anaphylactic shock, to vaccines had anti-gelatin IgE.<sup>8</sup> We considered that most of the allergic reactions after vaccination were caused by gelatin present in the vaccines.

It was reported that a woman who experienced urticaria after chewing gelatin-containing fruit gum had IgE antibody to gelatin, as detected by RAST.<sup>9</sup> Kelso et al.<sup>7</sup> reported that the patient with anaphylaxis to MMR vaccine also had allergic reactions after eating gelatin-containing foods. We also found that two children who had allergic reactions to vaccines had systemic urticaria after eating gelatin-containing candies.<sup>8</sup>

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**TABLE I.** Children with systemic allergic reactions, including anaphylaxis, to vaccines and anti-gelatin IgE levels in the serum

Children			Vaccines		
No.	Age	Sex	Vaccine	Amount of gelatin (mg/shot)	Anti-gelatin IgE (Ua/ml)
1*	1 yr 11 mo	M	Measles	1.5	250.0
2†	1 yr 8 mo	F	Measles	1.5	98.0
3†	1 yr	M	Measles	1.0	62.0
4*	3 yr	F	Mumps	10.0‡	46.0
5*	1 yr	M	Measles	1.5	40.0
6†	1 yr 8 mo	M	Mumps	1.0	40.0
7	2 yr 4 mo	F	Measles	1.0	36.0
8	3 yr 6 mo	M	Mumps	1.0	34.0
9	4 yr 11 mo	F	Mumps	1.0	33.0
10*	1 yr 7 mo	F	Measles	1.5	28.0
11†	1 yr 6 mo	M	Measles	1.5	27.0
12†	1 yr 5 mo	M	Measles	2.5	27.0
13*	3 yr	M	Mumps	10.0‡	22.0
14*	3 yr	M	Measles	1.5	15.0
15	1 yr 6 mo	M	Measles	1.0	15.0
16*	3 yr	F	Measles	10.0‡	14.0
17	2 yr 1 mo	F	Measles	1.5	11.0
18	2 yr 5 mo	F	Measles	1.5	8.0
19	1 yr 5 mo	M	Measles	1.5	6.4
20*	1 yr 6 mo	M	Measles	1.5	4.5
21†	3 yr 7 mo	F	Measles	2.5	3.5
22	2 yr	F	Measles	1.5	3.5
23	2 yr 11 mo	M	Rubella	2.5	2.4
24†	1 yr	F	Measles	1.5	1.2
25	1 yr 7 mo	M	Measles	1.5	<0.35
26*	1 yr	F	Measles	1.5	<0.35

\*Severe anaphylaxis with airway obstruction or anaphylactic shock.

†Systemic urticaria only.

‡As polygeline.

These findings suggest that some children who had anaphylaxis to vaccines have a food allergy to gelatin.

To clarify the relationship between the allergic reactions to vaccines and gelatin-containing foods, we surveyed the presence of food allergy to gelatin in 26 children who had systemic immediate-type reactions to vaccines.

## METHODS

### Children

Physicians and vaccine manufacturers submitted serum samples from children who had systemic immediate-type reactions, including anaphylaxis, to live vaccines to the Japan National Institute of Health from May 1994 to August 1995. We conducted a mail survey of the doctors as to the presence of allergic reactions to gelatin-containing foods and were able to obtain information about such reactions in 26 children. Table I lists 26 children (14 boys and 12 girls) (mean age  $\pm$  SD, 2

years 4 months  $\pm$  1 year) who had systemic immediate-type reactions on vaccination. This list includes the 10 children with allergies to vaccines reported in our previous study.<sup>8</sup> As a negative control (sex- and age-matched), serum samples from 26 children who had no allergic reaction to measles vaccine containing 1.0 mg of gelatin were prepared shortly after vaccination.

### Vaccines

The vaccines used were measles vaccines from four vaccine manufacturers, a mumps vaccine, and a rubella vaccine. These vaccines included bovine or porcine gelatin or polygeline (polymer of bovine gelatin bridged by hexamethylene diisocyanate; Behringwerke, Frankfurt, Germany); the amount ranged from 1.0 to 10 mg per shot.<sup>10</sup>

### Measurement of gelatin-specific IgE antibody

The CAP system (Pharmacia, Uppsala, Sweden) was used to determine the concentration (in unit allergen

**TABLE II.** Children with food allergy to gelatin

Child No.	Food allergy to gelatin	
	Timing	Symptom
2	Post	Systemic urticaria, angioedema around eyes, vomiting
4	Post	Systemic urticaria
12	Post	Systemic urticaria
15	Post	Systemic urticaria, vomiting, wheezing, cough
16	Post	Systemic urticaria, airway obstruction with laryngeal edema
21	Pre	Systemic urticaria
24	Pre	Systemic urticaria, lip swelling

*Post*, Gelatin food allergy occurred after vaccination; *Pre*, gelatin food allergy occurred before vaccination.

per milliliter [Ua/ml]) of IgE to bovine gelatin (Wako Pure Chemical Industries, Osaka, Japan).<sup>8</sup>

Specific IgE to bovine and porcine gelatin were determined by a fluorometric ELISA, as described previously, for comparison of levels.<sup>11,12</sup> Briefly, microplates were coated with bovine or porcine gelatin (10 µg/ml). After incubation of the serum sample with the immobilized antigens, anti-human IgE antibody conjugated with β-D-galactosidase (Pharmacia) was added. The enzyme reaction substrate was 0.1 mmol/L 4-methylumbelliferyl-β-D-galactoside (Sigma Chemical Co., St. Louis, Mo.). The fluorescence unit was measured on a fluorometric microplate reader (Fluoroskan; Flow Laboratory, McLean, Va.).

## RESULTS

### Anti-gelatin IgE levels in children with systemic immediate-type reactions including anaphylaxis to vaccines

Table I shows the anti-gelatin IgE concentrations in 26 children who had systemic allergic reactions on vaccine injection. Of the 26, 20 received measles vaccine, five received mumps vaccine, and one received rubella vaccine. Twenty-four of the 26 children had anti-gelatin IgE ranging from 1.2 to 250 Ua/ml (mean value ± SD, 34 ± 51) (Table I). We confirmed a strong relationship between the allergic reactions to vaccines and the presence of anti-gelatin IgE in the children's sera. Of the 26 children, nine showed severe anaphylaxis consisting of cutaneous signs (systemic urticaria or angioedema) plus airway obstruction (with laryngeal edema or wheezing) or anaphylactic shock (with hypotension and vascular

collapse); 10 had mild anaphylaxis (e.g., systemic urticaria and/or wheezing and cough and/or other symptoms) without severe symptoms; and seven had only systemic immediate-type urticaria. As the negative control, all the children who had no allergic reaction to vaccine had no anti-gelatin IgE (data not shown).

### Allergic reactions to foods

Table II shows the occurrence of food allergy to gelatin before and after vaccination in seven of the 26 children. Their clinical histories showed that these seven children had immediate-type reactions (e.g., systemic urticaria, angioedema, oral swelling, wheezing and cough, airway obstruction, or vomiting) on ingestion of gelatin-containing foods. The other 19 had demonstrated no allergic reaction to food gelatin before and after vaccination. Five of the seven children (nos. 2, 4, 12, 15, and 16) demonstrated food allergy within 1 month after the vaccination. They had not experienced food allergy to gelatin before vaccination. Two of the seven children had demonstrated a food allergy before vaccination: child no. 21 with systemic urticaria and child no. 24 with both systemic urticaria and oral swelling after eating gumdrops that contained gelatin. At the time of vaccination, the physicians did not know that the children had experienced food allergy to gelatin-containing food.

### IgE antibody levels to bovine and porcine gelatin

The vaccines and foods contain both bovine and porcine gelatin. We measured IgE antibody activities to bovine and porcine gelatin in the sera of the 26 children by the fluorometric ELISA, because there is no CAP system with porcine gelatin. There was a correlation between antibody levels to bovine and porcine gelatin (correlation coefficient of 0.639) (data not shown). Of the 26 children, two had no IgE to bovine and porcine gelatin, 20 had almost the same levels of IgE antibody activity to both types of gelatin, and four had higher levels to bovine gelatin than to porcine gelatin.

## DISCUSSION

Twenty-four of the 26 children who had allergic reactions had IgE to gelatin. As a negative control, all the children who had no allergic reaction to vaccine had no anti-gelatin IgE. In our previous study, 10 of 11 children who had allergic reactions to vaccines had IgE to gelatin.<sup>8</sup> We reconfirmed the results of our previous study. The extremely large amount of gelatin (1.0 to 10 mg per shot)

present in the vaccines may have caused the systemic allergic reactions on vaccination in vaccine recipients who had IgE antibody to gelatin.

In this study, seven children also demonstrated food allergy to gelatin. At present, we have no data on the incidence of food allergy to gelatin. The symptoms observed after gelatin ingestion were generally milder than those that occurred on vaccination; only one child (no. 16) had severe anaphylaxis with airway obstruction. There was no correlation between the level of anti-gelatin IgE and the occurrence of allergic reactions to gelatin-containing foods. Two of the seven children had reactions to gelatin before vaccination. Questioning of vaccine recipients and their parents about symptoms of allergy associated with the ingestion of gelatin-containing foods may help to prevent anaphylaxis in some children. Five of the seven children had immediate reactions to food gelatin within 1 month after vaccination. It appears that vaccination triggered the later onset of food allergic reactions to gelatin.

We measured the IgE to both bovine and porcine gelatin because both vaccines and foods contain these types of gelatin.<sup>10</sup> Most of the children had almost the same levels of IgE to bovine gelatin and porcine gelatin, and there was a correlation between the level of anti-bovine and anti-porcine IgE antibody activities. Moreover, these types of gelatin showed cross-reactivity on IgE-ELISA inhibition (data not shown). Therefore both bovine and porcine gelatin may cause allergic reactions in children.

We suspect that most of the systemic immediate-type reactions to vaccines and gelatin-containing foods were caused by gelatin. We think that the children with allergic reactions to vaccine had been immunized by the gelatin both in the vaccines and foods, and a sensitivity to gelatin developed. The relation of gelatin in vaccines and foods to development of gelatin allergy should be investigated further.

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