

Cases of systemic immediate-type urticaria associated with acellular diphtheria–tetanus–pertussis vaccination

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The authors found eight children who had systemic urticaria within 30 min after administration of acellular diphtheria–tetanus–pertussis (DTP) vaccines which contain gelatin as a stabilizer. The authors measured the specific IgE to gelatin and DTP toxoids in their sera, and found that none of the children had anti-gelatin IgE. Of the eight children, two had detectable levels of anti-toxoid IgE. As a negative control, of the 10 children who showed no allergic reaction to the acellular DTP vaccines, four also had detectable levels of anti-toxoid IgE. From these results, there was no obvious relationship between the specific IgE to the vaccine's component proteins and systemic urticaria to acellular DTP vaccines. © 1998 Elsevier Science Ltd. All rights reserved

Keywords: allergic reaction; urticaria; gelatin; IgE; diphtheria–tetanus–pertussis (DTP) vaccine

After diphtheria–tetanus–pertussis (DTP) vaccine injection, the most common local reactions seen at injection site are pain, redness and swelling¹. Systemic reactions such as fever, drowsiness, fretfulness and anorexia also are frequent². Severe reactions, which include high fever, persistent crying, collapse and convulsions, occur infrequently². Recently, it was reported that a child showed systemic urticaria which began 10 min after the administration of acellular DTP (DTaP) vaccine³.

Kelso *et al.*⁴ recently reported that a patient who suffered anaphylaxis to gelatin-containing measles–mumps–rubella (MMR) vaccine had anti-gelatin IgE. The authors also found that most of children who showed systemic reactions to live and inactivated virus vaccines, including gelatin, had anti-gelatin IgE^{5–9}.

Children immunized with DTP, DT or T vaccines have also been reported to have specific IgE to the toxoids^{10–12}. It was suggested that there is a relationship between anti-toxoid IgE and the local side effects to these vaccines¹³.

The authors report here eight children who had systemic immediate-type urticaria and/or respiratory symptoms after injection of DTaP vaccines containing gelatin. To clarify the relationship between the systemic urticaria and the components proteins (gelatin

and the toxoids) of the vaccines, the authors measured the specific IgE to those proteins in these children's sera.

MATERIALS AND METHODS

Children

Serum samples and the clinical reports of children who had systemic immediate-type reactions to gelatin-containing DTaP vaccines were sent to the Japan National Institute of Infectious Diseases (formerly the National Institute of Health) in 1995 and 1996 for the measurement of anti-gelatin IgE (the authors have at present no information on the systemic allergic reactions to DTaP vaccines without gelatin). *Table 1* gives information on these children (4 boys and 4 girls) (mean age $\pm$ SD, 1 year 6 months $\pm$ 11 months). As a negative control, 10 children (6 boys and 4 girls) (mean age $\pm$ SD, 1 year 5 months $\pm$ 5 months) who had no reaction to gelatin-containing DTaP vaccines were employed. Of these ten children, nine had received DTaP vaccines three times, and one had four times.

Vaccines and purified toxoids

In Japan, alum-adsorbed DTaP vaccines have been produced by six manufacturers, replacing the vaccines containing *Bordetella pertussis* whole cells. Four of the six DTP vaccines contain gelatin (24–100 μ g dose⁻¹) as a stabilizer. Each purified component of DTP toxoids was supplied by a vaccine manufacturer.

Assays for specific IgE

IgE antibodies to bovine gelatin (Wako Pure Chemical Industries, Osaka, Japan) and tetanus toxoid

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were measured by the Pharmacia CAP system (Pharmacia, Uppsala, Sweden)⁵.

Specific IgE antibodies to diphtheria and pertussis toxoids were determined by a fluorometric ELISA⁶. Briefly, microplates were coated with gelatin and each toxoid protein (1 µg ml⁻¹). After incubation of the serum samples and a reference serum (a pooled serum with anti-gelatin IgE) with the immobilized antigens, anti-human IgE antibody conjugated with β-D-galactosidase (Pharmacia) was added. The enzyme reaction substrate was 0.2 mM 4-methylumbelliferyl-β-D-galactoside (Sigma Chemicals, St. Louis, MO, USA). Fluorescence was measured on a fluorometric microplate reader (Fluoroskan, Flow Laboratory, McLean, VA, USA). The levels of the specific IgE antibody were expressed as arbitrary unit ml⁻¹. The units of each serum in the ELISA were calculated from standard titration curves of the anti-gelatin reference serum with known CAP units (Ua ml⁻¹), corresponding to the CAP values.

RESULTS

Clinical findings in children with systemic urticaria to the DTaP vaccine

Clinical findings in the children with systemic symptoms to gelatin-containing DTaP vaccine are shown in Table 1. Of these eight children, two had systemic urticaria, with wheezing or a cough. The other six had only systemic urticaria. All the children developed the allergic reactions within 30 min after vaccination. These children had not shown systemic reactions to a previous vaccination.

Specific IgE levels to vaccine-component proteins in children with and without allergic reactions to the vaccines

Table 2 shows specific IgE levels to gelatin and tetanus toxoid determined by the CAP system in sera of the eight children. None of them had detectable

Table 1 Clinical findings for children with systemic allergic reactions to DTaP vaccines

Child			Amount of gelatin (µg dose ⁻¹)	Total number of DTaP vaccinations (times)	Allergic reaction to vaccine	Time of onset after vaccination (min)
No	Age	Sex				
1	1 year	M	33.5	3	Systemic urticaria	10
2	2 years	M	100	2	Systemic urticaria, wheezing	10
3	1 year	M	33.5	3	Systemic urticaria, cough	10
4	1 year, 3 months	F	33.5	2	Systemic urticaria	10
5	3 years	F	100	1	Systemic urticaria	20
6	7 months	F	100	1	Systemic urticaria	10
7	2 years, 8 months	F	33.5	4	Systemic urticaria	5
8	6 months	M	33.5	1	Systemic urticaria	30

Table 2 Allergen-specific IgE in children with systemic allergic reactions to DTaP vaccines

Child no.	Specific IgE (Ua ml ⁻¹) by CAP		Specific IgE (Ua ml ⁻¹) by ELISA	
	Gelatin	Tetanus toxoid	Diphtheria toxoid	Pertussis toxoid
1	<0.35	0.47	0.75	0.94
2	<0.35	0.61	<0.35	<0.35
3	<0.35	<0.35	<0.35	<0.35
4	<0.35	<0.35	<0.35	<0.35
5	<0.35	<0.35	<0.35	<0.35
6	<0.35	<0.35	<0.35	<0.35
7	<0.35	<0.35	<0.35	<0.35
8	<0.35	<0.35	<0.35	<0.35

Table 3 Allergen-specific IgE in children with no allergic reaction to DTaP vaccines

Child no.	Specific IgE (Ua ml ⁻¹) by CAP		Specific IgE (Ua ml ⁻¹) by ELISA	
	Gelatin	Tetanus toxoid	Diphtheria toxoid	Pertussis toxoid
9	<0.35	3.31	3.02	1.35
10	<0.35	2.17	0.66	2.23
11	<0.35	0.61	0.69	0.68
12	<0.35	<0.35	<0.35	0.74
13	<0.35	<0.35	<0.35	<0.35
14	<0.35	<0.35	<0.35	<0.35
15	<0.35	<0.35	<0.35	<0.35
16	<0.35	<0.35	<0.35	<0.35

anti-gelatin IgE. Two children had detectable levels of anti-tetanus toxoid IgE, 0.47 (no. 1) and 0.61 (no. 2) Ua ml⁻¹. Six children (nos. 3–8) had no anti-tetanus toxoid IgE. The authors also measured IgE antibody activities to diphtheria and pertussis toxoids in their sera using the ELISA (Table 2) because there is no CAP system for anti-diphtheria and -pertussis toxoid IgE. One child (no. 1) had detectable levels of anti-diphtheria and -pertussis toxoid IgE, whereas the other seven (nos. 2–8) had no specific IgE to these toxoids.

Table 3 shows the specific IgE levels to gelatin and DTP toxoids determined by the CAP system and ELISA in the sera of 10 children without allergic reactions to DTaP vaccines. No child had anti-gelatin IgE. Of these 10 children, three (nos. 9–11) had detectable levels of anti-DTP toxoid IgE. One child (no. 12) had detectable levels of anti-pertussis IgE only. The other six children (nos. 13–18) had no anti-DTP toxoid IgE.

DISCUSSION

In Japan, six manufacturers produce DTaP vaccines and the vaccines from four of them contain gelatin (24–100 µg dose⁻¹). It has been reported that most of children with systemic immediate-type reactions to gelatin-containing live and inactivated virus vaccines, had anti-gelatin IgE^{4–9}. In this study, the children who had systemic urticaria to gelatin-containing DTaP vaccine, however, had no anti-gelatin IgE. The authors speculate that the systemic urticaria to DTaP vaccines does not reflect gelatin allergy.

The protein concentrations of DTP toxoids in the six vaccines range from 9.8 to 15.1 (D), 2.0 to 2.7 (T) and 5.5 to 14.0 (P) µg ml⁻¹, respectively¹⁴. In this study, the authors found that some children who had systemic urticaria to DTaP vaccine had detectable levels of anti-DTP toxoids IgE, but some children who had no reaction to the DTaP vaccines also had detectable levels of anti-DTP toxoid IgE. The authors did not find that there was an obvious relationship between the specific IgE to DTP toxoids and the systemic urticaria.

All the DTaP vaccines contain thimerosal (a mercury-containing compound), now most often used as an injectable drug preservative¹⁵. Hypersensitivity to thimerosal is reported to be common¹⁶. Okada *et al.*³ reported that a child who had systemic urticaria to DTaP vaccines had an immediate-type positive skin test to thimerosal. Moreover, DTaP vaccines contain alum (aluminum hydroxide gel) as an adjuvant. There is aluminum allergy; patients with local reactions to aluminum-bound DTP vaccines had a positive patch test to AlCl₃¹⁵. However, there is no method for measuring anti-thimerosal and -alum IgE. In future, the method to measure anti-thimerosal and -alum IgE should be developed.

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REFERENCES

- 1 Mortimer, E.A. Pertussis vaccine. In: *Vaccine* (Eds Plotkin, S.A. and Mortimer, E.A.). W.B. Saunders, Philadelphia, PA, 1994, pp. 91–135.
- 2 Tuttle, J., Chen, R.T., Hadler, S.C., Watson, J.C. and Terraciano, G.J. Update: vaccine side effects, adverse reactions, contraindications, and precautions. *MMWR* 1996, **45**, (RR-12), 1–35.
- 3 Okada, K., Miyazaki, T., Kusuhashi, K., Hidaka, Y., Inai, I., Kadoya, A. and Ueda, K. Adverse reactions after inoculation of DPT vaccines. Relationship between skin rash and constituents of vaccines. *Infect. Immun. Children* 1995, **7**, 99–102 (in Japanese).
- 4 Kelso, J.M., Jones, R.T. and Yunginger, J.W. Anaphylaxis to measles, mumps, and rubella vaccine mediated by IgE to gelatin. *J. Allergy Clin. Immunol.* 1993, **91**, 867–872.
- 5 Sakaguchi, M., Ogura, H. and Inouye, S. IgE antibody to gelatin in children with immediate-type reactions to measles and mumps vaccines. *J. Allergy Clin. Immunol.* 1995, **96**, 563–565.
- 6 Sakaguchi, M., Nakayama, T. and Inouye, S. Food allergy to gelatin in children with systemic immediate-type reactions, including anaphylaxis, to vaccines. *J. Allergy Clin. Immunol.* 1996, **98**, 1058–1061.
- 7 Sakaguchi, M., Yoshida, T., Asahi, T., Aoki, T., Miyatani, Y. and Inouye, S. Development of IgE antibody to gelatin in children with systemic immediate-type reactions to vaccines. *J. Allergy Clin. Immunol.* 1997, **99**, 720–721.
- 8 Sakaguchi, M., Yoshida, M., Kuroda, W., Harayama, O., Matsunaga, Y. and Inouye, S. Systemic immediate-type reactions to gelatin included in Japanese encephalitis vaccines. *Vaccine* 1997, **15**, 121–122.
- 9 Sakaguchi, M., Yamanaka, T., Ikeda, K., Sano, Y., Fujita, H., Miura, T. and Inouye, S. IgE-mediated systemic reactions to gelatin included in the varicella vaccine. *J. Allergy Clin. Immunol.* 1997, **99**, 263–264.
- 10 Nagel, J., Svec, D., Waters, T. and Fireman, P. IgE-synthesis in man. I. Development of specific IgE antibodies after immunization with tetanus–diphtheria (Td) toxoids. *J. Immunol.* 1977, **118**, 334–341.
- 11 Matuhasi, T. and Ikegami, H. Elevation of levels of IgE antibody to tetanus toxin in individuals vaccinated with diphtheria–pertussis–tetanus vaccine. *J. Infect. Dis.* 1982, **146**, 290.
- 12 Cogné, M., Ballet, J.J., Schmitt, C. and Bizzini, B. Total and IgE antibody levels following booster immunization with aluminum-adsorbed and nonadsorbed tetanus toxoid in human. *Ann. Allergy* 1985, **54**, 148–151.
- 13 Mark, A., Björkstén, B. and Granström, M. Immunoglobulin E responses to diphtheria and tetanus toxoids after booster with aluminum-adsorbed and fluid DT-vaccines. *Vaccine* 1995, **13**, 669–673.
- 14 Sato, Y. and Sato, H. Diphtheria–tetanus–pertussis (DTP) combined vaccine. In: *Vaccine Handbook* (Ed Researcher's Associates National Institute of Health). Maruzen, Tokyo, 1996, pp. 68–71.
- 15 Veien, N.K., Hattel, T., Justesen, O. and Norholm, A. Aluminum allergy. *Contact Dermatitis* 1986, **15**, 295–297.
- 16 Maibach, H.I., Dannaker, C.J. and Lahti, A. Contact skin allergy. In: *Allergy: Principles and Practice* (Eds Middleton, E.J., Reed, C.E., Ellis, E.F., Adkinson, N.F., Yunginger, J.W. and Busse, W.W.). C.V. Mosby, St. Louis, MO, 1993, pp. 1605–1647.