

Systemic immediate-type reactions to gelatin included in Japanese encephalitis vaccines

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Three children had systemic immediate-type reactions to Japanese encephalitis (JE) vaccine which contains gelatin as a stabilizer. We found that all the children had anti-gelatin IgE in their sera. Further, two of the three also had experienced systemic allergic reactions to gelatin-containing foods before the vaccination. We assume that the systemic allergic reactions to JE vaccines might be caused by gelatin in the JE vaccine. Copyright © 1997 Elsevier Science Ltd.

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A new pattern of reactions to Japanese encephalitis (JE) vaccine has been reported since 1989, consisting of systemic allergic reactions including generalized urticaria and/or angioedema¹⁻⁴. The immunological mechanism of these reaction has not been defined. To date in Japan, however, there has been no published reports on the systemic immediate-type reactions including anaphylaxis to the JE vaccine.

Anaphylactic reactions to measles, mumps, rubella, and combined measles–mumps–rubella (MMR) vaccines have been frequently reported and are suggested to be caused by an allergy to the egg proteins contained in the vaccines⁵. The immediate allergic reactions following administration of MMR vaccines, however, have been described in children who have tolerated eggs⁶. Recently, Kelso *et al.* reported that a patient who suffered from anaphylaxis to MMR vaccine had IgE antibody to gelatin detected by an immunoblotting method⁷. In a previous study, we found that 10 of 11 children who showed the systemic reactions including anaphylaxis to measles or mumps vaccines had the antigelatin IgE antibody and assumed that most of the reactions might be caused by the gelatin which is contained in the vaccines as a stabilizer⁸.

In this study, we report on three children who had systemic immediate-type reactions to the JE vaccine containing gelatin. To clarify the relationship between the gelatin in the vaccine and the allergic reactions, we measured anti-gelatin IgE in their sera.

Patients' sera together with clinical reports were sent to the Japan National Institute of Health in 1995 and

1996. As a control, 50 children (25 male, 25 female; 4 years old), who were selected without regard to vaccine and allergy history, were supplied from the WHO and Serum Reference Bank, National Institute of Health, Tokyo, Japan. The inactivated and purified JE vaccine which is derived from infected mouse brain contains gelatin (0.1 mg per shot) as a stabilizer. IgE antibody to bovine gelatin (Wako Junyaku, Tokyo, Japan) was measured by the CAP system (Pharmacia, Uppsala, Sweden)⁸.

Clinical data for the three children are shown in *Table 1*. In Patient 1, mild anaphylaxis (systemic urticaria with pruritis and wheezing) began 30 min after receiving the JE vaccine. She received the treatment and the symptoms with the exception of pruritis disappeared after 2 h, and recovered completely by the next morning. Interestingly, she had showed systemic urticaria after taking food containing gelatin before the vaccination. In Patient 2, his parents reported systemic urticaria 1 h after the JE vaccination. He received the treatment and the symptoms disappeared after 2 h. He had also showed systemic urticaria and wheezing after eating food containing gelatin before the vaccination. In Patient 3, mild anaphylaxis (systemic urticaria with pruritis and wheezing) began 20 min after receiving the vaccine. He received the treatment. After 3 days he returned to the clinic and his doctor found that he had recovered completely. He had experienced no systemic reaction after eating food containing gelatin.

The three children had anti-gelatin IgE (*Table 1*). All the 50 control children had no anti-gelatin IgE. It might be relatively rare for children to possess anti-gelatin IgE. No etiologic relationship exists between egg allergy and the allergic reactions to the JE vaccine, because this vaccine is produced from JE virus-infected mouse brain. Furthermore, it is interesting to note that two of the three children had experienced systemic reactions to

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Table 1 Clinical and laboratory findings for children with systemic allergic reactions to JE vaccines

Child No.	Age	Sex	Allergic reaction to vaccine	Specific IgE to gelatin (Ua ml ⁻¹)	Food allergy to gelatin
1	4 years, 4 months	F	Systemic urticaria, wheezing	11.6	+
2	4 years, 4 months	M	Systemic urticaria	12.0	+
3	4 years, 9 months	M	Systemic urticaria, wheezing	6.7	-

gelatin-containing foods before the vaccination. We had previously reported that similar reactions occurred in some children with systemic reactions upon measles and rubella vaccination⁷⁻⁹.

All the JE vaccines produced in Japan contain 0.05–0.1 mg gelatin (liquid type for general use in Japan) or 0.5 mg (frozen dry type for export) per shot. We reported elsewhere that 1.0 mg of gelatin in a measles vaccine may cause anaphylaxis^{8,9}. Furthermore, in immunotherapy for ragweed pollinosis, ragweed pollen extract including 0.1–10 µg of Amb a 1 protein (which is a major allergen) caused systemic allergic reactions in some patients¹⁰. Some cases of systemic allergic reactions to the JE vaccine (frozen dry type) that have been reported in several countries¹⁻⁴ might have been caused by gelatin (0.5 mg per shot). JE vaccines must be used with the same caution as for the MMR vaccine³.

At this point, we like to stress a fact that systemic immediate-type reactions to the JE vaccine which contains gelatin (0.1 mg per shot) have been very rare (only three cases as reported here) in spite of its nationwide use in Japan, and that the symptoms were milder than those with measles and mumps vaccines which contain a more gelatin per shot. Probably, the larger the amount of gelatin injected into the body, the more severe the systemic reactions.

Animal gelatin has long been used as a stabilizer both in live and in inactivated virus vaccines, and has been believed to have no antigenicity to humans. To prevent systemic allergic reactions to gelatin on vaccination, alternative stabilizers that have no antigenicity to humans must be explored.

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