

Measles-mumps-rubella Vaccination and Egg Allergy

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Abstract There has been long standing concern about the safety of measles-mumps-rubella vaccine in children with history of egg allergy. We review our experience in vaccinating such children in our hospital over a four-year period. Clinical evidences on the risk of anaphylactic reaction after measles-mumps-rubella vaccination is reviewed. A revised recommendation for the vaccination of children with history of egg allergy is proposed.

Key words Anaphylaxis; Egg allergy; Measles-mumps-rubella vaccine

Introduction

The measles-mumps-rubella (MMR) vaccine has been proven to be very safe and effective in protecting children from measles, mumps and rubella infection. The vaccine strains of the commonly used MMR vaccine in Hong Kong, MMR II, are grown in chick embryo cells (measles and mumps) and human diploid cell culture (rubella), resulting in concerns over the safety of these vaccines in children with history of egg allergy. Therefore children with history of egg allergy are usually referred to two major hospitals in Hong Kong for MMR vaccination. We will review our experience on this group of children referred to us over a 4-year period as well as the literature on this issue.

Methods

The case records of children referred to our department for MMR vaccination due to the presence of risk factors

were retrospectively reviewed. There were a total of one hundred and forty-six children admitted for this purpose from January 1996 to December 1999. Patients were immunized with the standard dose of MMR vaccine and were observed for any adverse reactions. The reason for referral, the allergic history and any adverse reactions observed during hospitalisation were analyzed.

Results

A total of 146 records were reviewed. The mean age of the population was 7.5 years. The male to female ratio was 1.18:1 (79:67). Of these 146 children, only 96 had history of allergy to eggs. Other children were referred because they had allergic reaction to other substances including drug, other vaccines, food or herbs; had no history of egg ingestion or had other medical problems.

In the group of children with positive history of egg allergy, most of them had mild reaction of non-specific skin rashes (65/96, 67.7%) or urticaria (24/96, 25%). Only seven children reported angio-oedema after egg intake. None had history of systemic reaction after egg ingestion. In most children (84/96, 87.5%), the component of egg that caused the allergic reaction was not identified.

Ninety-seven percent of children were observed for more than one hour after the MMR vaccination. Only one patient developed non-specific rash over the face, 15 minutes after the vaccination. Another child developed fever, rash and some coryzal symptoms five days later. These symptoms

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were probably caused by non-specific viral upper respiratory tract infection and were unlikely to be attributed to the vaccine. No patient developed severe adverse reaction or cardiopulmonary disturbances. For the seven children with history of angio-oedema after egg ingestion, none developed any reaction after the vaccination.

In a group of 1200 consecutive children with history of egg-allergy attending the Special Immunization Clinic of Princess Margaret Hospital in Hong Kong, none developed severe acute reaction following MMR vaccination (personal communication, CW Leung).

Discussion

Evidences on the Safety of MMR Vaccine in Children with History of Egg Allergy

Evidences to support the safety of MMR vaccination of egg-sensitive children are ample. In a review of studies published between 1963 and 1995, only two of the 1227 patients with history of egg allergy had any symptoms suggestive of anaphylaxis after a single dose of MMR vaccine.¹ In this study, blinded food challenges were positive in 284 patients and positive skin-test responses were obtained in 1209 patients. None of these patients had any adverse reactions, indicating that at least 99% of children with positive food challenge and 99.75% of children with positive skin-test can receive MMR vaccine. On the other hand, 38 immediate anaphylactic reactions had been reported in patients without allergy to eggs in the same review.¹ Therefore, hypersensitivity to other vaccine constituents, such as gelatin or neomycin, which are present in much larger quantities than is egg protein, has been proposed.

In another recent review, a total of 53 cases of cardiopulmonary reactions to MMR vaccine had been reported since 1963.² Forty-three children had no known history of allergy to eggs; among whom seven had history of allergy to gelatin. Ten children had history of egg allergy but the clinical criteria for defining allergy to eggs was weak. Not all of them had skin tests or specific IgE testings and none of them had food challenges. Five of these ten children also had evidence of coexisting allergy to gelatin. Only three out of these ten children had detailed history of egg allergy. All three of them had life threatening reaction after exposure to eggs or had asthma. Therefore, co-existing asthma is considered a risk factor for anaphylaxis.²⁻⁴

In a recent population study in Finland, 73 allergic reactions had occurred in 2,990,000 doses of MMR II vaccine.⁵ Thirty of them developed anaphylaxis, thirty had

urticaria, ten had asthmatic attack, one had Stevens-Johnson syndrome and two had Henoch-Schonlein purpura. The reporting rate for anaphylaxis is 1.0/100,000 doses. Majority of the patients developed anaphylaxis within 10 minutes (16/18, 88.9%) and 1 hour (17/18, 94.4%). Only one patient developed anaphylaxis 9 hours after vaccination, shortly after eating chicken. Allergy to chicken was suspected in this case.

Ways to Predict/Identify Those Who Are at Risk of Severe Allergic Reactions

Skin prick and intradermal testing have been used to predict allergic reactions in patients with history of egg allergy. Serum IgE reactive with ovalbumin related antigens in the vaccine had also been demonstrated in some children with allergic reactions. The usefulness of skin prick or intradermal testing of egg-allergic individuals before vaccination has been debated.

An early study in a small group of children with egg allergy using skin prick testing with ovalbumin and measles vaccine showed that children with history of severe reactions to eggs were more likely to have a positive skin reaction and positive IgE antibodies to ovalbumin.⁶ However, a large-scale study by Aicken et al in 1994 showed the contrary.⁷ In this study, skin prick testing with MMR vaccine was performed in 410 children allergic to eggs. Five children had a positive skin test. All patients were subsequently vaccinated with a standard dose of MMR vaccine but none of the five skin-test-positive children developed a reaction. Four children had a minor reaction to the vaccine, all of them had negative skin tests.⁷

On the other hand, there is some evidence to support the use of intradermal tests. A skin prick test followed by an intradermal test was performed in 150 children allergic to eggs.⁸ Of the five children with positive skin tests, four had negative intradermal tests and were vaccinated safely. The only child who had both positive skin test and intradermal test developed a severe local reaction as well as systemic reaction 10 minutes after the intradermal test. The 145 children with negative skin prick and intradermal tests were safely immunized without allergic reactions. This suggests that while it is not useful to skin prick test all children with egg allergy, a positive skin test may to some extent predict allergy to some component of the vaccine and may increase the risk of an allergic reaction.⁸

Several other studies, including the review by James et al,¹ showed that skin testing for reactions to vaccine lacks specificity and sensitivity in predicting serious allergic reactions.^{3,9} These tests also carry the risk of triggering

anaphylactic reactions.⁸ Therefore, skin testing probably has no place in the management of children who are allergic to eggs and who require vaccination against measles.² The 2000 Red Book also stated that skin testing of children with history of egg allergy is not predictive of reactions to MMR vaccination.¹⁰

On the other hand, as highlighted by Khakoo,² a history of life threatening reactions on exposure to eggs or a history of co-existing asthma may be significant risk factors for anaphylaxis.

Evidences That Substances Other Than Egg May Cause Allergic Reactions in MMR Vaccine

In double blinded, placebo controlled studies of food allergy, the minimal oral doses that elicit objective allergic reactions are usually between 50 mg and 100 mg, although they can occasionally be as low as 2 mg.¹¹ Analyses of MMR II vaccine showed that it contains at most 0.5-1 ng of ovalbumin per 0.5 mL dose.^{3,6,12} The amount of ovalbumin in MMR vaccine therefore seems to be far too small to cause an allergic reaction.

As mentioned above, there is also substantial evidence to show that actually more allergic reactions after MMR vaccination have occurred in individuals without history of egg allergy.² Therefore, other vaccine components that may cause the allergy have been sought. Each dose of MMR II contains 13.5 mg of gelatin and 25 microgram of neomycin, both are known to cause severe allergic reactions and are present in larger doses than ovalbumin.¹³

Gelatin

Gelatin is used as stabilizer in various vaccines including MMR, varicella, diphtheria, tetanus, and acellular pertussis vaccines. In 1993, Kelso first suggested that anaphylactic reactions to MMR may be due to allergic reaction to gelatin.¹⁴ Both immediate and delayed-type of hypersensitivity reactions can occur after exposure to gelatin. In a small cohort of 26 patients with immediate reactions to MMR vaccine, 24 of them had IgE antibody to gelatin while none of the control patients had this antibody.¹⁵ Seven children who were allergic to gelatin but were not allergic to eggs have been reported to have severe allergic reactions after measles vaccination.^{14,16,17} There was also evidence of a co-existing allergy to gelatin in five children who were allergic to eggs and who had severe cardiopulmonary reactions to MMR vaccine.¹⁶

Neomycin

Contact hypersensitivity and systemic allergic reactions

to neomycin are well known.¹⁸ One case of a possible allergy to neomycin has been reported in a seven-year-old boy.¹⁹ Evidences to support the avoidance of MMR vaccine in children with contact sensitivity to neomycin are conflicting.²⁰ However, it was generally agreed that children who have had anaphylactic reactions to topical or systemic administration of neomycin should not be vaccinated.

Local Situation

Our retrospective review is small, involving only about 100 children with history of egg allergy. The ascertainment of allergy to other vaccine components including gelatin and neomycin and history of asthma may be incomplete. However, if we also include the experiences from another hospital, no patient had developed any cardiopulmonary reactions after MMR vaccination in nearly 1300 children with history of egg allergy. This is in agreement with other reports that MMR vaccination can be safely given to the vast majority of children, regardless of history of egg allergy.

Recommendations

The Committee on Infection and Immunization of the Royal College of Paediatrics and Child Health, and the British Society of Allergy and Clinical Immunology proposed a new recommendation for using MMR vaccine in children allergic to eggs in 2000, after a review of the clinical evidence.² In the recommendation, only children with a history of cardiorespiratory reaction to eggs or who have an allergy to eggs and coexisting active, chronic asthma are considered at risk for future life threatening reactions. This group of children should be immunized in pediatric departments with appropriate precautions. As most severe reactions occur within a few minutes after the injection and it is extremely unlikely that a child who appears completely well 30 minutes after the vaccination will subsequently develop a severe reaction,²¹ these high-risk children should be observed for 2 hours. The cardiopulmonary status should be continuously monitored in the first 20 minutes, followed by close monitoring for 2 hours. In addition, an anaphylaxis management protocol should be available but routine setting of an intravenous cannula is not required. The authors have not elaborated why an intravenous cannula is not required. However, the most important drug for use in severe anaphylaxis is epinephrine and the most commonly recommended route of administration is by subcutaneous or intramuscular route.²² A recent study showed that epinephrine absorption is complete and more rapid in children treated by intramuscular route.²³ Basing on this,

both the UK consensus panel on emergency guidelines as well as the International Consensus Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care recommended intramuscular epinephrine for the treatment of anaphylaxis.^{24,25} There has also been recent concern over the potential hazardous effects of large doses of epinephrine, especially if epinephrine is administered intravenously. These included hypertension, myocardial ischaemia, arrhythmias and pulmonary oedema. Intravenous administration of epinephrine is therefore reserved for those with persistent and profound hypotension, those with cardiac arrest or those who failed to respond to intravenous volume replacement and several injected doses of epinephrine.²⁶

Since there is always a potential risk of severe allergic reactions after vaccination in any children, regardless of the type of vaccine used and whether there is history of egg allergy, all institutions performing routine vaccination for children should be equipped with adrenaline and resuscitation measures. It is also recommended that patients should be observed for 30 minutes following vaccination.

Basing on the above discussion and literature review, we would also like to propose that the current practice for all children with history of egg allergy be vaccinated in a tertiary hospital be revised. An algorithm for administering MMR vaccine in children who are allergic to eggs, modified from the recommendations from the Royal College of Paediatrics and Child Health, is proposed. In addition, a question about allergy to the vaccine, gelatin or neomycin should be included in the pre-vaccination screening.

Last but not least, the formation of a registry with full reporting of history of allergy and reaction clearly defined would be most helpful in understanding the causes of allergy to MMR. Those who had allergic reaction to MMR vaccine should have further assessments to define the timing and nature of the reaction, and possible allergens involved in the reaction should be evaluated and properly defined.

Conclusion

The administration of MMR vaccine in a single dose is safe in children who had mild allergic reactions to egg. Skin test is not useful in predicting those at risk of developing severe allergic reactions. Only those children with a history of cardiorespiratory reaction to eggs or who have co-existing active, chronic asthma should be vaccinated in the hospital under close supervision.

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Proposed Recommendations

(Modified from Khakoo 2000, endorsed by Committee on Infection and Immunisation of the Royal College of Paediatrics and Child Health, and the British Society of Allergy and Clinical Immunology)²

