

ORIGINAL PAPER

Measles-mumps-rubella vaccination experience in children with egg allergy

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ABSTRACT

Introduction: Measles, mumps, and rubella (MMR) vaccine is a part of the childhood routine immunization program. It is known that allergic reactions, from urticaria to anaphylaxis, may develop against MMR vaccines containing trace amounts of egg protein and other ingredients.

Aim: To determine whether children with any degree of egg allergy show allergic reactions to the MMR vaccine application and to draw attention to the fact that children without a history of anaphylaxis can be vaccinated safely by practitioners and/or family physicians in health centers.

Material and methods: The files of 90 patients who were vaccinated between 2017 and 2022 in the pediatric allergy clinic were retrospectively analyzed. These patients were those who were followed up due to egg allergy in our outpatient clinic or were referred from the family health centers because the family said that the baby had an egg allergy.

Results: A total of 94 doses of vaccination were given to 90 patients. Four doses were for those who were vaccinated for a second time. All skin prick tests with 94 doses of MMR vaccine were negative, and only 1 patient (1/94, 1.06%) developed nonspecific macular rash 0.5 h after vaccination. No other allergic reactions or anaphylaxis were observed.

Conclusions: No serious allergic reaction developed after MMR vaccination in IgE-mediated egg allergy patients. We think that there is no harm in administering MMR vaccine to these patients in family health centers where other vaccines are applied, without testing with the vaccine and without the need for divided doses.

KEY WORDS

egg hypersensitivity, measles, vaccination.

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INTRODUCTION

Cow's milk and egg allergies are the most common food allergies in children. Egg allergy is the second most common after cow's milk allergy. The incidence of egg allergy under the age of 5 is 1.8–2% worldwide [1]. Immunoglobulin E (IgE)-mediated food allergy is the most common form of egg allergy, as well as non-IgE-mediated or mixed-type reactions. In cases with IgE-mediated egg allergy, urticaria, angioedema or anaphylaxis may occur. Atopic dermatitis and eosinophilic esophagitis are seen in mixed-type cases. A skin prick test (SPT) and serum-specific IgE measurement can be performed for diagnosis. However, the gold standard in the diagnosis of food allergy is elimination by responsible food and double-blind placebo-controlled food provocation [2].

There are more than twenty glycoproteins in egg white. The five major proteins that cause allergies more frequently are ovomucoid (Gad d 1), ovalbumin (Gad d 2), ovotransferrin (Gad d 3), lysozyme (Gad d 4), and ovomucin. The most allergenic protein is ovomucoid, and the most abundant protein is ovalbumin. Vaccines produced in chicken embryo fibroblast cultures are measles-rubella-mumps (MMR), yellow fever, and influenza vaccines. There is a trace amount (≤ 1 nanogram) of ovalbumin in the MMR vaccine [3]. It has been reported in the literature that anaphylactic reactions developing after the MMR vaccine are at similar rates between cases with and without egg allergy [4]. It is stated that allergic reactions due to the vaccine mostly occur due to other vaccine components such as gelatin or neomycin, but in most cases, the responsible allergen cannot be determined [5].

Since 2006, the MMR vaccine has been administered in 2 doses within the scope of the Turkey National Extended Immunization Program [6]. According to this program, the first dose is administered in the 12th month and the 1st grade of primary school. With the recommendation of the immunization advisory board, it was decided to make an additional dose at 9–11 months in regions with an epidemic risk in 2019, and to change the vaccine dose in the first grade of primary school to the 48th month in 2020.

In our national immunization program, it is stated that children with egg allergies can safely receive the MMR vaccine, and egg allergies do not prevent vaccination, except for anaphylaxis [6]. Despite this, there is a serious concern when vaccinating children with egg allergies in families and healthcare professionals, and children are directed to upper medical centers.

AIM

Our study aims to determine whether children with egg allergy show anaphylactic/allergic reactions to the MMR

vaccine and to draw attention to the fact that children without a history of anaphylaxis can be vaccinated safely in health centers.

MATERIAL AND METHODS

We retrospectively evaluated 90 of the patients who applied to our pediatric allergy outpatient clinic for vaccination between 2017 and 2022 due to family complaints and suspicion of egg allergy as a result of blood and/or skin tests. Our study was carried out and written according to the Declaration of Helsinki. Permission for the study was obtained from the ethics committee of Sakarya University. In addition, all participants and their parents were informed about the study, and verbal and written consent was obtained.

SKIN PRICK TESTS (SPTS)

An SPT was performed by a specialist physician using a lancet with a whole egg allergen extract. 10% histamine phosphate was used as positive control and glycerin-saline was used as negative control (Stallergenes, France). An induration diameter of 3 mm or greater than the negative control, evaluated 20 min after the test, was considered positive.

SPECIFIC IGE TESTS

The fluorescent enzyme immunoassay method was used for measurements of whole egg specific IgE, egg white specific IgE, and egg yolk specific IgE (UniCAP, Phadia; Uppsala, Sweden). For egg (whole, white, yellow) specific IgE, ≥ 0.35 KU/l results were considered positive.

VACCINE ADMINISTRATION PROTOCOL

Skin prick test and specific IgE tests were evaluated in patients with egg allergy and/or allergic disease. The patients were admitted to the pediatric service, and vascular access was established for any intervention. Skin prick tests were performed with positive (histamine), negative (saline) control, and without reconstitution of the vaccine itself. Twenty minutes later, 2 divided doses of the vaccine were administered after the tests were evaluated and found negative. First, 1/2 of the vaccine was administered in a controlled manner, and after 30 min, the other half of the vaccine was administered to the patients who did not develop a reaction. If there was no increased risk e.g., higher SPT induration (> 5 mm), specific IgE ($>$ class IV) level or anamnesis, neither intradermal testing was performed nor divided doses was administered. The patients who were observed in the service for at least

4 h and did not develop any reaction were discharged. If there was a suspicious rash, the patient was followed up for 1–2 days by being called in the next days. Our application for those with egg allergy was adapted from the protocol for influenza vaccination (2010 BSACI) in such patients [7].

RESULTS

Of the 90 patients included in the study, 33 (36%) were females and 57 (64%) males. The age of the patients ranged from 10 months to 53 months. Egg-related specific IgE value was > 0.35 kU/l in 79 (87.7%) cases. Two patients had no clinical complaints but had egg-specific IgE positivity. As to clinical findings of 84 patients, 34 (40%) had atopic dermatitis, 21 (25%) urticaria, 18 (21%) nonspecific macular rash, 3 (3.5%) anaphylaxis, 3 (3.5%) proctocolitis, 2 (2.3%) food protein-induced enterocolitis, 1 (1.1%) were followed with mastocytosis (Table 1). A total of 94 doses of vaccine were administered to 90 patients. The 2nd dose of vaccine was given to 4 patients. (Clinical findings of 4 patients could not be reached from their files.)

Post-vaccine reaction did not develop in 3 cases with a history of anaphylaxis with eggs as well (Table 2). The egg white specific IgE value of these 3 cases was varying from 0.94 to 44.7 kU/l. The SPT with the vaccine was negative in these patients and there was no post-vaccine reaction. The clinical characteristics of patients with specific IgE positivity class IV (≥ 17.5 kU/l, excluding anaphylaxis) who did not react to the MMR vaccine are shown in Table 3. A nonspecific macular rash developed 30 min after vaccination in a male patient with atopic dermatitis and egg white specific IgE value of 6.32 kU/l. The lesions regressed without treatment in the follow-up. In our study, the post-vaccine reaction rate was found to be 1/94 (1.06%).

DISCUSSION

The MMR vaccine is of concern among pediatricians and family physicians when it comes to children with egg allergy, due to the rare cases of anaphylaxis with vaccines in egg-allergic patients and inconsistencies in the literature about vaccine skin testing. Conditions that are contraindicated for MMR vaccine; anaphylaxis after the

TABLE 1. Diagnostic distribution of the 84 patients

Diagnosis	Patient numbers	%
Atopic dermatitis	34	40.4
Urticaria	21	25
Nonspecific macular rash	18	21.4
Anaphylaxis	3	3.5
Food protein-induced proctocolitis	3	3.5
Food protein-induced enterocolitis	2	2.3
Reactive airway	1	1.1
Reaction to the previous vaccine	1	1.1
Mastocytosis	1	1.1

first dose of the vaccine, severe allergic reaction to neomycin, gelatin, or other vaccine components, pregnancy, immunodeficiencies, lymphoma, leukemia or other malignancies, systemic immunosuppressive therapy, and conditions where the immune response is impaired due to HIV infection are counted as well. Egg allergy is not an absolute contraindication of the MMR vaccine [8]. In our study, we administered the MMR vaccine to patients with egg allergies and observed whether they develop any reaction or not.

It is a controversial issue to perform an SPT or intradermal test with MMR vaccine before vaccination for patients with egg allergy. There are conflicting results regarding the use of vaccine SPTs and intradermal tests in predicting allergic reactions in patients with egg allergy. Baxter et al. applied an SPT with a vaccine to a total of 200 cases of egg allergy, including 20 patients with a history of anaphylaxis, and they found the SPT positive in 5 cases. They then performed an intradermal test with the vaccine in 150 cases, and in 4 of the 5 cases they detected a positive SPT, they demonstrated the intradermal test as negative and administered the vaccine without complications. The other 50 patients, whose SPT was found to be negative for the vaccine, were administered the full dose of the vaccine without intradermal testing, and they reported that no reaction was observed. Since anaphylaxis developed in the 15th min of the intradermal test in a 15-month-old patient with atopic dermatitis who had

TABLE 2. Clinical characteristics of cases who presented with anaphylaxis and did not react to MMR vaccine

Patient	Gender	Age	Egg white Sp IgE	Egg yolk Sp IgE	Egg SPT	Vaccine SPT	Administration	Reaction
1	Male	13 m	12.6	3.4	Negative	Negative	Divided	None
2	Male	14 m	44.7	8.6	3 mm	Negative	Divided	None
3	Female	13 m	0.94	0.45	N/A	Negative	Divided	None

m – month, Sp IgE – specific immunoglobulin E, SPT – skin prick test, N/A – not available.

TABLE 3. Clinical features of the patients who did not react to MMR vaccine with specific IgE positivity above class-IV (≥ 17.5 kU/l, excluding anaphylaxis)

Case #	Gender	Age	Diagnosis	Egg white Sp IgE	Egg yolk Sp IgE	Whole Egg Sp IgE	Egg SPT	Vaccine SPT	Reaction
1	Male	15 m	N/A	28.1	6.89	19.4	Negative	Negative	None
2	Male	14 m	Urticaria	45.7	34.7	41.6	Negative	Negative	None
3	Male	12 m	N/A	36.4	5.29	27.8	4 mm	Negative	None
4	Male	15 m	Urticaria	40.5	9.9	43.3	4 mm	Negative	None
5	Female	13 m	Nonspecific macular rash	25.2	7.71	24.7	6 mm	Negative	None
6	Male	13 m	Reactive airway	83.2	40.2	67.9	5 mm	Negative	None
7	Male	16 m	AD	39	9.8	38.5	5 mm	Negative	None
8	Female	13 m	AD	27.6	6.04	26.2	3 mm	Negative	None
9	Male	12 m	AD	29.4	3.26	25.8	3 mm	Negative	None
10	Male	13 m	AD	37.5	9.79	34.1	5 mm	Negative	None
11	Male	14 m	Nonspecific macular rash	21.8	8.64	12.8	Negative	Negative	None
12	Male	14 m	AD	19.6	2.15	16.1	Negative	Negative	None
13	Male	14 m	Urticaria	83.2	25.5	83.5	10 mm	Negative	None
14	Female	14 m	Urticaria	> 100	87.1	> 100	6 mm	Negative	None
15	Male	12 m	Urticaria	24.1	5.45	20.3	Negative	Negative	None
16	Male	14 m	Urticaria	25.7	17.8	20.9	3 mm	Negative	None
17	Female	14 m	Nonspecific macular rash	28.2	3.45	16.1	N/A	Negative	None
18	Male	12 m	Urticaria	41.4	6.73	20.4	N/A	Negative	None
19	Male	79 m	Urticaria	> 100	50.9	> 100	6 mm	Negative	None
20	Male	13 m	Urticaria	42	23	30.5	8 mm	Negative	None
21	Male	15 m	Urticaria	> 100	> 100	> 100	6 mm	Negative	None
22	Female	13 m	AD	18.6	5.8	15.3	Dermatographism	Negative	None
23	Male	10 m	Urticaria	32.3	5.62	28.4	5 mm	Negative	None

m – month, AD – atopic dermatitis, Sp IgE – specific immunoglobulin E, SPT – skin prick test, N/A – not available.

a positive intradermal test, they discontinued the application and did not administer the vaccine. However, it could not be determined whether the case was allergic to the egg content of the vaccine or other components. As a result, they argued that pre-vaccine testing should be done in patients with egg allergy [9].

However, in studies conducted in the following years (more recently), it has been reported that skin tests performed with the vaccine before MMR vaccination in children with egg allergy cannot predict the reaction [4, 10]. Since 120 out of 500 patients with egg allergy had irritant reactions with the SPT performed before the vaccine and no reaction was observed with the full dose administration of the vaccine, the remaining 380 patients were vaccinated

as a full dose without testing, and they reported mild rash in only 5 patients. It has been stated that vaccine-related reactions may occur due to vaccine components and the MMR vaccine is not contraindicated in patients with egg allergy [11]. James *et al.* applied the SPT with the vaccine to 17 of 54 patients who were diagnosed with egg allergy and were not vaccinated with MMR before, and although positive results were found in 3 of them, they applied the vaccine as a full dose to all patients and reported that there was no reaction. They argued that even if there is a severe allergic reaction to eggs, such as anaphylaxis, the MMR vaccine can be safely administered to these patients [12]. In our study, 3 patients had a history of anaphylaxis with eggs. We performed the SPT in all patients with the vac-

cine. Although we found the SPT negative, we did not perform any intradermal testing. However, we administered the vaccine in two divided doses to those with negative SPTs due to a probable higher risk e.g., positive anamnesis. A macular rash developed approximately 30 min after vaccination in only 1 patient, and it regressed without treatment in the follow-up. We determined the reaction rate as 1.06% (1/94) per doses.

In many studies conducted in our country, it was reported that no serious allergic reaction was observed. Bahceci *et al.* observed no allergic reaction in any of the 82 patients who were followed up in their clinics due to egg allergy and administered MMR vaccine [13]. Çöğürlü *et al.* performed the SPT with egg yolk, egg white, and gelatin, SPT and intradermal test with MMR vaccine on 62 patients with IgE-mediated egg allergy before MMR vaccine. The tests performed with gelatin and vaccine were negative in all patients, the vaccine was administered in a single dose to all patients, macular rash occurred in 1 patient 30 min after the vaccine, and no reaction was observed in the other patients, which regressed spontaneously [14]. In our study, we found a negative SPT in all patients with the vaccine.

Studies have shown that most of the allergic reactions with MMR vaccines are due to vaccine components such as gelatin and neomycin. In a 17-year-old patient who had anaphylaxis after MMR vaccination, the SPTs performed with gelatin and MMR vaccine and specific IgE testing were positive for both gelatin and vaccine. And they found that anaphylaxis after oral provocation with gelatin, the post-vaccine reaction was decided to be due to gelatin, a vaccine component [15]. The World Allergy Organization (WAO), in its international consensus article for allergic reactions to vaccines, recommends the development of an alternative to gelatin as a stabilizer in measles and varicella vaccines in research priorities for immunization-related allergic reactions and states that the MMR vaccine can be safely administered to patients with egg allergy [16]. In addition, studies have shown that vaccination against SARS-CoV-2, which caused a worldwide pandemic and affected millions of people, is safe in allergic patients [17].

CONCLUSIONS

In our study, no serious allergic reaction developed after MMR vaccination in cases with egg allergy. The limitation of our study is that no sample size calculation was made to calculate the Standardized Incidence Ratio (SIR). We think that there is no harm in administering the MMR vaccine to these patients in centers where other vaccines are applied, without testing with the vaccine and without the need for divided doses. Cases with a history of anaphylaxis and/or an allergic reaction to the previous vac-

cine should be referred to the allergy center. In addition, in all centers where vaccines are administered, precautions should be taken in terms of anaphylaxis reactions that may develop due to any content in the vaccine.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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