Measles, Measles-Mumps-Rubella, and Varicella Vaccinations in Children with Egg Allergy

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ABSTRACT

Objective: Egg allergy is the second most common food allergy in infants and may cause urticaria, angioedema, anaphylaxis, and exacerbation of atopic dermatitis. Egg allergy is diagnosed by carefully examining a patient's clinical history, performing contributory skin prick tests, and assessing specific IgE levels to hen's egg. The administration of measles, measles-mumps-rubella (MMR), and varicella vaccinations to children with egg allergy remains controversial. These vaccines contain trace amounts of egg proteins as they are produced in chicken embryo fibroblast cultures. The incidence of anaphylaxis as a result of vaccinations is very low, and its cause (egg or gelatin) is not well known. Here we report our experience with the three vaccinations in 18 patients with egg allergy (34 dose).

Methods: Between 2013 and 2016, we retrospectively evaluated patients with egg allergy who presented to our allergy clinic for vaccinations. After performing the skin prick test for patients who were admitted to our clinic, vaccinations were administered by dividing the doses in equal two parts.

Results: All patients had a clinical history, and atopic dermatitis coexisted with egg allergy in three patients. The skin prick test results were positive in 12 (67%) patients. The specific IgE test was positive in 16 (89%) patients. There was a reaction in just one (2.9%) patient of 18 patients of 34 dose vaccinations.

Conclusion: Measles, MMR, and varicella vaccinations in children with egg allergy were found to be safe albeit small number of patients. We believe that egg allergy does not necessitate a delay or contraindication for vaccination.

Keywords: Allergy, egg, vaccination, measles, MMR, varicella

INTRODUCTION

Egg allergy is the second most common food allergy in infants (1). It may cause reactions, such as urticaria, angioedema, and anaphylaxis, due to immunoglobulin E (IgE)-induced type 1 reaction. In addition, reactions, such as atopic dermatitis and eosinophilic gastroenteropathy, may occur in mixed and non-IgE-mediated forms (1-4). Ovomucoid (Gad d 1), ovalbumin (Gad d 2), ovotransferrin (Gad d 3), lysozyme (Gad d 4), and ovomucin, which are the five major proteins found in egg white, cause more allergies (2). Although ovomucoid is the most allergic protein, the most commonly found protein is the ovalbumin. This protein is also thought to cause severe allergic reactions in the vaccines of measles, measles-mumps-rubella (MMR), and chickenpox. Egg allergies are diagnosed with a careful patient history (clinical history) and a skin prick test and specific IgEs that support it. A double-blind, placebo-controlled oral food provocation test is still the gold standard for the diagnosis of food allergies (3-5). Despite the limited number of studies in the literature, measles, MMR, and chickenpox vaccinations are considered safe in children with egg allergy although disputes continue. Contraindications for the usual MMR vaccination are anaphylaxis after the first dose of the MMR vaccine, severe allergic reaction to neomycin or gelatin, pregnancy, immunodeficiency, bone marrow and lymphatic system diseases, and systemic immunosuppression. Egg allergy is not included in these reasons (6-10).

Due to the refugee problem and epidemic concerns, measles vaccine administration was initiated again in the ninth month in our country. The MMR vaccine is administered at the end of the twelfth month and in the first year of primary school. Chickenpox vaccine is routinely administered at the end of the twelfth month. The aforementioned 3 vaccines are live and attenuated. The measles vaccine contains Edmonston-Enders (Moraten) strain. The mumps vaccine contains Jeryl–Lynn strain, the rubella vaccine contains Wistar RA 27/3 strain, and the chickenpox vaccine contains Oka strain (11). Since the measles, mumps, and chickenpox vaccines are produced in chicken embryo fibroblast culture, they may contain trace amounts (picogram-nanogram) of egg proteins (ovalbumin) (12-14). These vaccinations are important because of the possible side effects that may develop into anaphylaxis after administration in people with egg allergy. The rate of anaphylaxis due to these vaccinations is very low; it is seen one in a million (15). Since the vaccine can be safely administered even in those with severe egg allergies, the reason of anaphylaxis in these patients is controversial in literature. Although it has recently been considered to be caused by the gelatin that

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exists in the MMR and chickenpox vaccines at high amounts, this has not been confirmed (12-14). In this study, we present 18 cases (36 doses) of egg allergy diagnosed through clinical history and/or laboratory tests and in whom 3 types of vaccination were administered.

METHODS

We retrospectively evaluated 18 patients who applied for vaccination from May 2013 to May 2016 with a suspicion of egg allergy owing to a family complaint and tests in our child allergy polyclinic in Sakarya. Although patients provided written informed consent, ethics committee approval was not received due to the retrospective nature of this study. Our work has been conducted and written in accordance with the Helsinki Declaration. Five patients applied only for measles, 1 for chickenpox, 2 for MMR, 3 for MMR+chickenpox, 1 for measles+MMR, and 6 for measles+MMR+chickenpox vaccines. The patients who had more than one vaccine (measles+MMR+chickenpox) were those who applied to our clinic for the vaccination in around twelfth to fifteenth months after the measles vaccination was administered after ninth month.

Skin Prick Test: A skin prick test was performed by a specialist physician using a lancet and a whole egg allergen. Histamine phosphate at 10% was used as positive control and glycerin-saline as a negative control (Stallergenes, France). An endurance diameter sized ≥3 mm than the negative control after 15-20 min of the test was considered positive (16).

Specific IgE Test: Whole egg-specific IgE, egg white-specific IgE, and egg yolkspecific IgE were measured using a fluorescent enzyme immunoassay method (UniCAP, Phadia; Uppsala, Sweden). Results ≥0.35 KU/L were considered positive for egg (whole, white, and yolk)-specific IgE (17, 18).

Application Protocol of Vaccines: The skin prick test and specific IgE tests were evaluated in patients with egg allergy and/or with allergic disease. The patients were admitted to the pediatric service and a vascular access was opened in all patients for any intervention. Skin prick tests were performed without dilution with positive (histamine) and negative (saline) controls and the vaccine. Twenty minutes later, after the tests were evaluated and they were found to be negative, 2 separate doses of the vaccine were administered. First, one of the 2 vaccines was administered in a controlled manner; after 30 minutes, the other half of the vaccine was administered in the patients in whom no reaction developed. Patients were monitored for at least 4 hours and those without any reaction were discharged. If there was a suspicious rash, the patient was called in the following days and was followed up for 1–2 days. The vaccine application for those having egg allergy has been adapted from the protocol of influenza vaccination (2010 BSACI) in such patients (19).

Statistical Analysis

The statistical package program of IBM Statistical Package for the Social Sciences 22 (IBM SPSS Statistics; Armonk, New York, USA) was used. The correlation between the skin prick test and specific IgE values was assessed using the Pearson test. A $p<0.05$ was considered as significant.

RESULTS

The characteristics and vaccinations of the patients participating in the study are shown in Table 1. All the patients were found to have a clinical history or atopic dermatitis, which suggests egg allergy. As per the clinical history, there were complaints suggesting urticaria or rash and/or atopic dermatitis developing after food intake. In 3 patients, egg allergy was accompanied by atopic dermatitis (Table 1). There was no clinical history suggesting respiratory or gastrointestinal involvement or anaphylaxis. In the skin prick test, 8 patients were found to have a positivity (≥3+) equal to or greater than the histamine level, and four patient had a positivity lower than the histamine level; thus, positivity was found in a total of 12 (67%) patients. Class II or higher (+) specific IgE levels against whole egg, egg white, and egg yolk were determined in 14 patients. Two children had Class I or higher (+) specific IgE levels. In total, 16 (89%) patients had positive specific IgE value. No oral food provocation test was performed on any of our patients.

Of the 18 patients who participated in the study and received a total of 36 doses of vaccination, only 1 (2.9%) had a suspected macular rash during the 4-hour follow-up period after vaccination (after measles vaccination). The rash recovered without medication in the patient who was called to the control between 24–48 hours. The correlation between the egg skin prick tests and the specific IgE values ($r=0.44$, $p=0.033$, one-tailed) was between the whole egg prick test level and the egg white-specific IgE values.

In the studies using the ImmunoCAP system, the specific IgE≥2 kU/L value was defined as 95% positive predictive value (PPV) in egg allergies in children aged under 2 years of age (17, 18). Similar studies have been conducted for skin prick tests and the value of ≥5 mm was determined to be 95% PPV in children aged under 2 years (20, 21). The skin prick tests showed an endurance size of ≥5 mm in 9 of 18 patients aged under 2 years. The specific IgE values were ≥2 kU/L in 8 of 18 patients aged under 2 years. In 6 of 18 patients, both skin prick tests and specific IgE values were ≥95% PPV. While only 7 of the 18 (more than one third) patients did not have any of the limit values for this serious reaction, two-third of the patients had one of them.

DISCUSSION

In this study, we present our experience related to 18 patients diagnosed with egg allergy through clinical history and/or laboratory tests and applied with 3 types of vaccines (36 doses) in between the ninth and fifteenth months. Although the number of cases is inadequate, the details of our study in which measles, MMR, and chickenpox vaccinations were found safe in children with egg allergy are discussed.

Although two-third of our patients had egg allergy as severe as that seen clinically, 18 patients did not have any significant side effects after vaccination. In MMR vaccination, some authors suggested that there is usually no possibility of developing an IgE-mediated reaction, such as anaphylaxis, even if the person has severe egg allergy (22). Therefore, it has been reported that the vaccination can also be administered in egg-allergic patients af-

Table 1. The characteristics of our patients and the results of examination and vaccination

Patient characteristics				Skin prick test (mm)			Specific IgE (KU/L)			Vaccination	
Patient (n)	Application age (month)	Gender	Clinical history	Whole egg	Positive control	Negative control	Whole egg	Egg yolk	Egg white	Type of vaccine	Reaction
1	9–12	M	+	4	4	0	0.58	0.64	0.97	Measles, MMR, chickenpox	Did not develop
2	10	F	+	0	10	0	0.26	0.56	1.50	Measles	Did not develop
3	9–13	M	+	3	8	0	0.33	0.43	0.66	Measles,	Did not develop
4	9–12	M	+	10	5	0	14.90	13.20	29.40	Measles, MMR, chickenpox	Macular rash
5	9–15	M	+	0	6	0	0.12	0.16	0.18	Measles, MMR, chickenpox	Did not develop
6	12	F	+	0	3	0	3.70	0.88	6.50	Chickenpox	Did not develop
7	9–12	F	+	5	5	0	0.12	3.60	4.70	Measles, MMR, chickenpox	Did not develop
8	9–13	M	+	0	5	0	1.94	0.71	0.50	Measles, MMR, chickenpox	Did not develop
9	10	M	+	0	5	0	0.17	0.17	0.23	Measles	Did not develop
10	12	M	+	10	5	0	0.35	0.35	0.35	MMR, chickenpox	Did not develop
11	12	M	+	8	5	0	0.57	0.38	1.50	MMR, chickenpox	Did not develop
12	12	M	+	9	4	0	10.90	10.8	18.90	MMR, chickenpox	Did not develop
13	12	F	+	0	5	0	0.48	0.72	0.60	MMR	Did not develop
14	9–13	M	+	7	3	0	7.30	8.80	15.00	Measles, MMR, chickenpox	Did not develop
15	9–12	M	+	4	9	0	10.90	10.80	18.90	Measles, MMR	Did not develop
16	9	M	+	6	7	0	6.70	12.80	12.10	Measles	Did not develop
17	12	M	+	11	9	0	0.51	0.49	0.78	MMR	Did not develop
18	9	M	+	5	9	0	2.90	1.60	5.50	Measles	Did not develop

ter the routine precautions are taken in a similar manner, as in case of non-allergic children. However, if there is an allergic disease, such as asthma in the patient, the threshold for anaphylaxis falls and the risk increases (22).

In literature, studies have shown that children with egg allergy are vaccinated in a single dose, in 2 divided doses, or with a graded dose increase (19). Mild exanthematous allergic reactions have also been reported in some cases in graded or

divided dose applications, wherein vaccinations are considered safer in patients with egg allergy (23, 24). Among those administered divided vaccination at equal doses, we found doubtful rashes in one patient who underwent only measles vaccination in our clinic, but we did not have any systemic findings.

The skin prick test or intradermal test with the vaccine before the vaccination is contradictive. Both the tests had conflicting results regarding the predictive role of post-vaccination allergic reactions in egg-allergic patients (25). Baxter (20) performed skin tests with the MMR vaccine in 200 patients with egg allergy, and the skin prick test results were found positive in five vaccinated patients. In 4 of these patients, the intradermal test was negative, and no reaction was observed after MMR vaccination. Only one patient had anaphylaxis after intradermal testing. For this reason, they argued that a skin allergy test should be performed with the vaccine before the MMR vaccination in egg-allergic patients. However, it was not been determined whether the patient has a reaction to the egg component or other components of the vaccine. In the same study, 15 patients who had a severe reaction to eggs were also vaccinated, and no reaction was observed after vaccination (20). In literature, children without egg allergy were observed to have anaphylactic reactions depending on measles, MMR, and chickenpox vaccination, and mostly, the gelatin in the vaccines was considered responsible (26). An intradermal test was not performed in our patients because of the risk of anaphylaxis in the test itself in addition to the difficulty in application compared to the skin prick test (invasive), the difficulty in obtaining approval from the family, and the false positivity rate of up to 15% (27).

In 366 children who had reaction to 0.2% gelatin-containing MMR vaccination, Nakayama et al (26) found anaphylaxis in 34, urticarial rash in 76, non-urticarial rash in 215, and local reaction in 41 children. The IgE antibody against gelatin was examined in the serum of 206 cases. Although antibodies were detected in 93% of those who had anaphylaxis, in 56% of the cases with urticarial, and in 9% of the cases with rash, no antibodies were detected in those who had local reactions. In this study, information was obtained about the vaccines of 202 cases and it was found out that DTaP vaccines containing gelatin were applied in 98% of them, indicating that sensitization developed previously. MMRII®, which is a MMR vaccine, contains 14.500 µg/0.5 mL dose of gelatin and Varivax®, a chickenpox vaccine, contains 12.500 µg/0.5 mL of gelatin (26). Sakaguchi et al. (28) detected specific IgE against gelatin in all 33 early allergic reactions that occurred with chickenpox vaccine containing gelatin.

CONCLUSION

Despite the significant clinical and laboratory findings of egg allergy in two-third of our patients, it was shown that 3 different vaccines (measles, MMR, and chickenpox) could be administered safely without any delay in the ninth to fifteenth months. Until the conflicting situation in literature is resolved, we believe that the vaccinations in egg-allergic patients should be performed in the hospital environment and after taking the necessary precautions against anaphylaxis.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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