



Does Food Allergy Require Any Change in Measles-Mumps-Rubella Vaccination?

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Abstract

Objectives To determine the allergic reactions that develop after Measles and Measles-Mumps-Rubella (MMR) vaccination, and whether any delay in the timing of vaccination occurs in children with food allergy.

Methods Children with food allergy who were admitted to the Şişli Hamidiye Etfal Training and Research Hospital Healthy Child Clinic between 1st January 2015 and 30th June 2018 for Measles or MMR vaccination were studied retrospectively. Their age, delayed days of vaccination, the types of allergic food, the results of the specific IgE and skin tests, and any reaction after the vaccination were recorded.

Results During the study period, 159 patients were vaccinated and 170 doses of Measles or MMR vaccine were administered. Children allergic to egg were 50.3%, allergic to egg and milk were 25.8%, and 13.2% had multiple food allergy including egg. The rate of post-vaccination reactions in the patients with food allergy was 1.76%. Minor reaction was observed in three patients and no anaphylaxis was seen in any patient. Delayed days of vaccination in the patients referred by another center were greater than followed-up by present clinic ($p < 0.001$).

Conclusions Any serious allergic reaction was not observed in this study. Food allergy does not necessitate modification of routine vaccination. Anaphylaxis may develop in any vaccinated child regardless of whether he/she has food allergy or not. Therefore, vaccines should be administered in a healthcare facility that can treat anaphylaxis.

Keywords Allergy · Anaphylaxis · Child · Vaccination

Introduction

Vaccination is an important part of preventive health services to prevent infectious diseases and deaths caused by disease [1]. Vaccination at an early age has been associated with survival [2]. Allergic reactions to vaccines are very rarely observed [3–6]. Estimates of allergic reactions to vaccines including immediate hypersensitivity reactions, range from 1 in 50,000 to 1 in

1,000,000 doses [7–9]. Such allergic reactions can manifest themselves with varied clinical presentations of minor reactions involving a single system limited to redness and itching of the skin to major reactions involving the respiratory, gastrointestinal and cardiovascular systems that may result in anaphylaxis. Such early type, potentially life-threatening reactions associated with any component of a vaccine are mostly mediated by IgE [10]. Such reactions have been reported after Measles-Mumps-Rubella (MMR) vaccination included in the national vaccination program [11–13]. Measles vaccine may contain trace amounts of egg protein since it is grown in chicken embryo fibroblast culture. There are studies that attribute allergic reactions that may develop after vaccination in children with food allergy to this fact [12, 14]. Although the incidence of anaphylaxis associated with vaccination is quite low, both physicians and families are concerned about vaccination of children with food allergy [10, 15]. These concerns hinder timely vaccination of children and cause delayed vaccination.

With the present study, authors aimed to determine the allergic reactions that develop after Measles and MMR

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vaccination, and whether any delay in the timing of vaccination occurs in children with food allergy.

Material and Methods

Children with food allergy who were admitted to the Health Sciences University, Şişli Hamidiye Etfal Training and Research Hospital Healthy Child Outpatient Clinic between 1st January 2015 and 30th June 2018 for Measles or Measles-Mumps-Rubella (MMR) vaccination were included in the study. The medical records of the children were retrospectively reviewed. Their age, gender, the administered vaccines' names, their administration dates, the number of days of delay of vaccination, the types of food to which each subject was allergic, the diagnoses of food allergy, the results of the specific IgE and skin tests, and any reaction experienced after the vaccination were recorded. Approval was obtained from the Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee for the study (1045/2018).

The vaccination practice in authors' outpatient clinic is in accordance with the national vaccination program. In their country, the first dose of MMR vaccine is administered at the end of 12 mo of age [16]. However, vaccination against measles at the end of 9 mo of age had been added to the vaccination program between December 2014 and March 2017 due to the measles outbreaks affecting neighboring countries [17]. Therefore, patients admitted between these dates received measles vaccine (M-Vac) at the end of 9 mo of age and MMR vaccine (Priorix or MMR-II) at the end of 12 mo of age in accordance with the national vaccination program. Due to the end of the measles elimination program, MMR vaccine (Priorix or MMR-II) at the end of 12 mo of age was administered after March 2017.

Since this hospital is a tertiary care hospital, the Healthy Child Outpatient Clinic is a reference centre for patients with food allergy. Patients with food allergy who require vaccination are referred to this outpatient clinic by family health centers or pediatricians. Possible allergic reactions were explained in detail to the families before vaccination, and all patients were followed-up for one hour at the clinic after the vaccination. The observation period was extended to four hours for patients in whom allergic reaction was seen at the end of first hour. Those who did not have anaphylaxis in their history received the vaccination subcutaneously at full dose without test. For those who had experienced anaphylaxis with food, firstly prick testing was performed with the vaccine, then the vaccine was given at full dose without division to those with negative test results.

Patients who used a food elimination diet during vaccination due to food allergy and were admitted to the Healthy Child Outpatient Clinic for measles or MMR were included in the present study.

The statistical analysis for the study was conducted using the Statistical Package for the Social Sciences 16.0 for Windows (SPSS Inc.; Chicago, IL, US) software. The continuous variables for descriptive statistics were shown as mean $\pm$ standard deviation (SD), maximum and minimum. The frequency analyses were expressed as n (number) and percentage (%). The Student's *t* test was used to compare the independent groups. The statistical alpha significance level was considered at $p < 0.05$.

Results

During the study period, 159 patients with food allergy were vaccinated. Ninety five (59.7%) of the patients were boys and 64 (40.3%) of them were girls. Most of the cases (n:122, 76.8%) were children who had been referred to authors' outpatient clinic from another center because of food allergy. The number of the patients who had been followed-up for routine pediatric examinations and received the other childhood vaccines at authors' center was 37 (23.2%).

Eighty (50.3%) of the children were allergic to egg, 41 (25.8%) were allergic to egg and milk, and 21 (13.2%) had multiple food allergy including egg. Fourteen (8.8%) patients had allergy only to milk and had been referred from another center because of inability to vaccinate them due to food allergy. The types of food to which the patients were allergic are shown in Table 1.

When the food-related clinical findings were reviewed, it was seen that 102 (64.2%) had a history of atopic dermatitis, 25 (15.7%) had a history of gastrointestinal tract involvement (proctocolitis and/or reflux and/or vomiting), 24 (15.1%) had a history of atopic dermatitis and gastrointestinal tract involvement (proctocolitis and/or reflux and/or vomiting), five (3.1%) had a history of urticaria, and three (1.9%) had a history of food-related anaphylaxis (Table 1).

One hundred one of the patients were tested for specific IgE to diagnose and follow-up their allergic diseases, and 85 underwent skin prick testing with food. The distribution of the patients' laboratory data is shown in Table 2.

During the study period, 21 doses of Measles vaccine (M-Vac) and 149 doses of MMR vaccine (108 doses of Priorix- 41 doses of MMR-II) were administered to the patients with food allergy. Totally 472 doses of Measles vaccine (M-Vac) and 805 doses of MMR vaccine (625 doses of Priorix and 180 doses of MMR-II) were administered at the outpatient clinic during the same period. When the vaccination dates were looked at, the number of days of delay of vaccination in the patients referred by another center because of allergy were greater than those with allergy who were being followed-up by the present outpatient clinic ($p < 0.001$). The administered vaccines and the days delayed are shown in Table 3.

Table 1 Demographic data of patients and distribution of clinical findings related to food allergy

Characteristics	Number of patients n: 159 (%)
Gender	
Girl	64 (40.3)
Boy	95 (59.7)
Patients	
Followed-up by the present outpatient clinic	37 (23.2)
Referred by another center	122 (76.8)
Allergic to	
Egg	80 (50.3)
Egg + milk	41 (25.8)
Multiple types of food including egg	21 (13.2)
Milk	14 (8.8)
Egg+other*	3 (1.9)
Food allergy-related clinical finding	
Atopic dermatitis	102 (64.2)
Gastrointestinal tract finding (Proctocolitis, GER or vomiting)	25 (15.7)
Atopic dermatitis+gastrointestinal tract finding (Proctocolitis, GER or vomiting)	24 (15.1)
Urticaria	5 (3.1)
Anaphylaxis	3 (1.9)

*hazelnut, sesame. GER Gastroesophageal reflux

Three patients who described anaphylaxis after food intake underwent prick testing with MMR and found negative before vaccination. To these patients, the vaccine was given at full dose without division. The other patients received the vaccination at full dose without test. During this period, 170 doses of Measles or MMR vaccine were administered to children with food allergy and post-vaccination reaction was observed in three patients. One patient developed urticaria 15 min after

the vaccination. This patient had a history of anaphylaxis after intake of milk products. The patient's prick test performed before the MMR vaccination was negative. Several macular rashes were observed within half an hour after the vaccination in the other two patients (Table 4). There was no respiratory, gastrointestinal or cardiovascular involvement in any of the three patients who developed reaction after the vaccination. Their complaints improved after receiving an oral antihistamine (hydroxyzine dihydrochloride). No clinical manifestation suggesting anaphylaxis was observed. In the present study, the rate of post-vaccination reactions in the patients with food allergy was 1.76% (3/170).

Table 2 Distribution of the laboratory data found in the tests performed due to the patients' allergy to milk and egg

Patients tested for specific IgE	n:101
Distribution of the specific IgE results	
Tested with egg white	n:96
Egg white positive	63 (65.6%)
Tested with egg yolk	n:69
Egg yolk positive	31 (44.9%)
Tested with cow's milk	n:69
Cow's milk positive	25 (36.3%)
Patients underwent skin prick testing	n:85
The skin prick test results	
Tested with egg white	n:69
Egg white positive	46 (66.6%)
Tested with egg yolk	n:55
Egg yolk positive	28 (50.9%)
Tested with cow's milk	n:46
Cow's milk positive	22 (47.8%)

Discussion

During the present study, no major allergic reaction or anaphylaxis after the Measles and MMR vaccinations in patients with food allergy were observed. Only in three patients (1.76%) minor reactions involving a single system (limited to the skin) were observed. These skin lesions regressed after administration of oral antihistamines, and no serious allergic reaction was observed. Studies and guidelines state that measles and MMR vaccines can be safely administered to children with food allergy (including those allergic to egg)[18,19]. The results of the present study support these recommendations. Although the guidelines state that these vaccines can be safely administered to children with food allergy, physicians and families are still concerned about this. Physicians refer the

Table 3 Vaccines administered and evaluation of the days delayed

	Patients followed-up by present outpatient clinic	Patients referred by another center	<i>P</i>
Dose of vaccine administered			
Measles	12	9	
MMR	34	115	
The days delayed			
Mean $\pm$ standard deviation	5.67 $\pm$ 6.052	28.20 $\pm$ 33.17	<0.001
Minimum-maximum	0–23	0–206	

MMR Measles-Mumps-Rubella

children to advanced centers instead of vaccinating them at the centers where their routine vaccines are administered. About 75% of the children with food allergy in this study were those who were referred by another center without vaccination. Concerns of both physicians and families about vaccination lead to delays in the administration of routine vaccines. The mean time delay in vaccination was four times higher in the patients who were referred by another center due to allergy than those followed-up by authors' clinic. The more notable result was that the delay could be measured as months for some patients.

The frequency of allergic reactions reported with Measles and MMR vaccines has been very rare, though it is important because it can result in anaphylaxis. Many studies have reported that MMR vaccine can be safely administered to children with egg allergy. However, allergic reactions have been reported in patients with food allergy. Yavuz et al. reported that three subjects with egg and milk allergy, whose specific IgE tests for egg and milk were positive, developed anaphylaxis after administration of MMR vaccine [12]. Most of the children in present study had egg allergy and about two-thirds

underwent egg-specific IgE testing. Most of the patients who underwent specific IgE testing were positive for egg white and about half of them were egg yolk positive. About half of the patients were tested for cow's milk-specific IgE, and one-third of these were positive. They did not develop any major allergic reaction. The three patients in whom minor allergic reactions were observed, the one who developed urticaria was specific IgE positive for egg white, egg yolk and cow's milk. One of the patients who developed macular rash was specific IgE positive for egg white, egg yolk and milk, and the other had negative results for egg white- and egg yolk-specific IgE and positive result for cow's milk-specific IgE. However this patient's skin prick test result with egg white was positive. About half of the study group underwent prick testing with egg, and most of them were positive. One-third of the cases underwent prick testing with milk, and about half of these were positive. No serious allergic reaction was observed in patients who underwent skin prick testing with suspected types of food and were found positive. The results of present study suggest that prick testing and specific IgE testing against food has no predictive value with respect to development of

Table 4 Characteristics of the patients who developed post-vaccination reactions

Case number	Gender	Allergic to	Symptom associated with food allergy	Specific IgE	Prick	Vaccine administered	Reaction type
1	M	Egg+Milk	Anaphylaxis	Egg white: Positive (>100 kIU/L) Egg yolk: Positive (36.4 kIU/L) Cow's milk: Positive (8.91 kIU/L)	Milk: Positive (5 $\times$ 5 mm)	MMR (Priorix)	Urticaria
2	M	Egg+Milk	Atopic Dermatitis	Egg white: Negative (<0.10 kIU/L) Egg yolk: Negative (<0.10 kIU/L) Cow's milk: Positive (0.4 kIU/L)	Egg white: Positive (3 $\times$ 3 mm) Milk: Negative	MMR (MMR-II)	Macular rash
3	M	Egg	Atopic Dermatitis	Egg white: Positive (0.64 kIU/L) Egg yolk: Positive (0.4 kIU/L)	Egg white: Positive (3 $\times$ 3 mm) Egg yolk: Positive (3 $\times$ 3 mm) Milk: Negative	MMR (Priorix)	Macular rash

MMR Measles-Mumps-Rubella

allergic reactions. Similarly, in previous studies, 54 children with egg allergy underwent prick testing with egg and were found positive; MMR vaccine was administered to these children and no allergic reaction was observed. Absence of serious allergic reactions despite the positive test results may most likely be attributed to the fact that even if these vaccines contain measurable amounts of ovalbumin or proteins exhibiting cross-reactivity, the reported amounts are too low to cause allergic reactions [18].

It is recommended to perform prick testing with the vaccine itself before vaccination in patients who have the potential to develop allergic reactions to the components of vaccines. However, controversial results were obtained from prick testing with MMR vaccine in studies. Baxter et al. performed prick testing with the vaccine before administration of MMR vaccine in 200 children with egg allergy of whom only five were found positive. These positive children underwent an intradermal test with the vaccine and four were found negative. One hundred ninety nine patients did not develop any allergic reaction after vaccination, and only the ones whose intradermal test was positive, developed anaphylaxis [14]. However it was not specified whether this reaction was to the egg components or other components of the vaccine. Aickin et al. obtained positive results from skin testing with the vaccine in five of 410 subjects they studied, however no reaction was observed after vaccination. However, they also reported that the four cases that were negative for the prick testing with the vaccine before vaccination, developed post-vaccination reactions (vomiting, peroral urticaria, flushing, transient wheezing) [20]. In the present study, three patients underwent prick testing with the MMR vaccine before vaccination because of their history of anaphylaxis after food intake. Although they showed negative results in the prick testing with the vaccine, one developed urticaria after vaccination. The other patients with food allergy who underwent prick testing with the vaccine did not show any reaction after administration of the MMR vaccine. It is considered that negative results of prick testing with vaccine do not rule out the risk of development of allergic reactions.

Studies note that subjects without egg allergy develop allergic reactions after administration of MMR vaccine [19, 21]. Therefore the other components of the vaccine, primarily gelatin, are accused of post-vaccination allergic reactions. Sakagucki et al. reported a relationship between gelatin antibodies and allergic reactions developing following administration of MMR vaccine [21, 22]. Another study conducted in Japan found that most of the cases who developed anaphylaxis after administration of MMR vaccine were positive for gelatin-specific IgE [23]. After this study, the gelatin-free form of measles vaccine or the hypoallergenic form of gelatin was started to be used in the vaccination against measles in Japan, and a dramatic reduction was observed in the reported rates of anaphylaxis. Similarly, Patja et al. demonstrated that of 36

subjects who developed anaphylaxis or allergic reactions after administration of MMR vaccine had gelatin allergy. They reported that gelatin-specific IgE positivity was associated with egg- and chicken-specific IgE. They found that four of the gelatin-positive subjects were positive for egg and chicken, two were positive for egg and two were positive for chicken. In the same study, four subjects were found positive for both gelatin- and milk-specific IgE [13]. Before this study, several studies noted a cross-reactivity between cow's milk and gelatin [24]. Any major allergic reaction did not develop in the present cases, but authors were not able to test the three cases with minor reactions for gelatin-specific IgE. This was the limitation of present study.

Conclusions

The cases with food allergy did not develop any serious allergic reaction such as anaphylaxis after the administration of MMR vaccine. The results of present study support the suggestions and recommendations previously reported on this issue. Food elimination diet applied to a child due to food allergy does not necessitate modification of routine MMR vaccination. Referral to an advanced center for this leads to delayed vaccination and concerned families. Anaphylaxis is a rare but life-threatening condition that may develop in any vaccinated child regardless of whether he/she has food allergy or not. Therefore all vaccinations should be performed at a healthcare facility with the ability of medical intervention should an anaphylaxis develops.

Authors' Contribution GKE: Prepared the concept of the study, designed the study, and wrote the manuscript; EÇ: Data collection, initial analysis and final submission of the manuscript; LB and AK: Design and revision of manuscript; TT: Data collection; AB and SU: Analysis, interpretation and supervised the study. AB will act as guarantor for this paper.

Compliance with Ethical Standards

Ethics Committee Approval This study was approved by the Şişli Hamidiye Etfal Education and Research Hospital Ethics Committee (1045/2018).

Conflict of Interest None.

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