

The Impact of Food Allergens on Airway Responsiveness in Schoolchildren With Asthma: A DBPCFC Study

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Summary. Background and Objective: Despite the growing evidence of a possible link between asthma and food allergy (FA), so far, the involvement of food in inducing respiratory symptoms has not been fully evaluated. The objective of this study was to evaluate the impact of food allergens on respiratory symptoms and bronchial reactivity (BHR) in schoolchildren with asthma. Methods: The initial study group consisted of 362 children with asthma. In the end, 22 children with concomitant FA, and 18 without FA, were selected to participate in the study. Spirometry and Methacholine Inhalation Challenge (MIC) were conducted prior to and after the completion of a double blind placebo control food challenge (DBPCFC). Results: The food-induced asthmatic reactions were observed in nine (2.5%) out of all 362 children with asthma. Mean FEV₁ prior to and after allergen or placebo challenge did not differ between the groups studied. Increase of BHR after DBPCFC was seen in 17 (4.7%) children with asthma. The mean PC₂₀ value in children with FA was 1.41 ± 1.12 mg/ml prior to the allergen challenge and 0.86 ± 0.71 mg/ml ($P = 0.002$) after the test, whereas these values were 1.93 ± 1.68 mg/ml and 2.02 ± 1.75 mg/ml, respectively, in children without FA ($P > 0.05$). Significant differences were noted after the allergen provocation in children with FA as compared to children without FA ($P = 0.007$). Conclusions: Although food allergens are a rare trigger of food-induced asthmatic reactions in schoolchildren with asthma, they could enhance BHR, despite a lack of evident clinical respiratory signs and decreased in FEV₁ values after food challenge. **Pediatr Pulmonol.** © 2016 Wiley Periodicals, Inc.

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INTRODUCTION

Contrary to inhaled allergens, which cause clinical exacerbation in patients with asthma, the involvement of food allergens in inducing allergic response within the respiratory system is unclear. Recent studies show that food sensitization must be assessed to fully understand inflammation patterns in asthma and affects both local and systemic markers of inflammation in asthma.^{1,2} Typically, the impact of food allergens is associated with such diseases as atopic dermatitis (AD), urticaria, vasomotor edema, anaphylactic reactions, or digestive complaints. However, many years' experience in performing oral food challenges (OFC) in children with AD suggests that each part of the respiratory system may be an effector of food-induced allergic reactions. James et al.³ reported the presence of nasal, laryngeal, and pulmonary symptoms in 70%, 48%, and 27% of children with AD and positive results of OFC, respectively. Businco et al.⁴ observed induction of asthma symptoms in 27% of children with AD and food allergy (FA) during a double blind placebo control food challenge (DBPCFC). Although FA is thought to be a factor rarely triggering asthma

exacerbation, situations in which this is the case usually involve younger children. The prevalence of food-induced asthma in infancy is estimated at 7–29%.^{5–8} In addition, asthma could be one of the life-threatening systemic symptoms of anaphylactic reactions to food.^{6,9} Sampson et al.¹⁰ described severe anaphylactic reactions to occasionally ingested food products in asthmatic

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children. Although food-induced respiratory symptoms occur sporadically, children and adults with FA tend to exhibit increased asthma morbidity.^{11,12} Despite the fact that food allergens are rarely responsible for clinically evident asthmatic symptoms, they could enhance airway hyper-reactivity without inducing evident dyspnea.^{13,14}

The findings discussed above, along with the difficulties in asthma control as well as possibility of life-threatening exacerbations and higher morbidity, justify further research on the impact of food allergens on asthma course not only in infants but also in older children. Additionally, the conclusions in many studies were based on indirect (non-provocative) methods, so mostly they concluded that food allergy increased the number of hospitalization, used of GCS, increase asthma morbidity, and severity, could be an under-recognized risk factor for problematic asthma. The objective of this study was to directly evaluate the impact of food allergens on respiratory symptoms and bronchial reactivity (BHR) in schoolchildren with asthma, using spirometry and non-specific bronchial hyper-responsiveness testing before and after DBPCFC. There has been no data in recent literature on the methods that could objectively evaluate the impact of food allergens on asthma in school-age children.

MATERIALS

The study group consisted of 22 children with asthma and food allergy, while the control group comprised 18 children with asthma but without food allergy. The patients were selected from 430 children with atopic asthma, aged 6–18 years, who were admitted to the Department of Pediatric Allergology, Gastroenterology, and Nutrition of the Medical University of Lodz and Outpatient Clinic for the evaluation of food hypersensitivity. The following outline the applicable eligibility criteria: atopic asthma (according to the GINA criteria¹⁵), IgE-dependent FA (in compliance with the EAACI and AAAAI recommendations^{16,17}), at least a 2-week elimination diet prior to the experiment and the ability to cooperate while performing spirometric examination. Alternatively, the exclusion criteria were as follows: asthma exacerbation within the last 6 weeks, patients in the active phase of the disease and the use of immunotherapy and drugs such as β -adrenolytics, antihistamines, oral steroids. The flow chart depicting steps involved in patient selection and tests was described in our previous study.¹⁸ There were no significant differences between asthma controllers used by children from the study and control group. Characteristics of the patients are shown in Table 1. The institutional ethics committee approved the study and informed consent was obtained before enrollment (RNN 42/03/KE).

METHODS

Oral Food Challenges

The oral challenge tests were performed using the DBPCFC method in hospitalized patients, according to the EAACI/AAAAI recommendations, after a minimum 2-week eliminating diet.^{16,17} The DBPCFC were performed using foods suspected from history and specific IgE (sIgE). Systemic corticosteroids were contraindicated, and systemic antihistamines were withdrawn according to their half-life. The use of topical corticosteroids for the airways was continued without change, while, topical corticosteroids for skin complaints were tapered to the minimum dose and kept constant throughout the challenge procedure. In addition, the β_2 -adrenergic agonists and theophylline were avoided for 48 hr prior to the challenge. In the provocative procedures, the following allergens were used: milk, egg, peanuts, wheat and celery. The patients were observed for at least 24 hr after the completion of the final challenge. Objective skin (rash, urticaria, pruritus, angioedema, AD exacerbation), digestive (oral pruritus, vomiting, diarrhea), and respiratory signs (dyspnea, throat or chest tightness, wheezing, cough, rhinitis) that appeared after the provocation preceded by the asymptomatic time were regarded as a positive result of the test.

Pulmonary Function Tests

Spirometry was performed prior to and after the completion of the OFC. Baseline pulmonary function was measured by the use of Lungtest 1000 spirometry software (MES) and adequately trained personnel. The measurements were recorded at least three times. Only the best curve was used for further analysis. All data were expressed in absolute values and as percentage of predicted normal values (% pred), as standardized residuals (SR) or standard deviation score (SDS).^{19,20} In compliance with ERS and ATS, the values between 3 and 97 percentiles (-1.96 SR; $+1.96$ SR) were regarded as appropriate.^{20–21}

Methacholine Inhalation Challenge (MIC)

MIC was performed using methacholine (MP Bio-medicals) and the Inhalation Allergology Challenge System (MES), on the day preceding the food challenge test and 4 hr after its completion, at a previously established time of the day. A pressure inhalator PARI LC PLUS of 0.0054 ml/sec output was used for nebulization. The study was performed in compliance with ATS recommendations, by means of the continuous Cockcroft method, starting with 0.03 mg/ml concentration.²² All dilutions of methacholine were made fresh at least every 4 weeks. Subjects refrained from using asthma and allergy medication for 24 hr before the study. The

TABLE 1—Characteristics of Asthmatic Children With and Without Food Allergy

	Children with asthma and FA	Children with asthma without FA	<i>P</i>
Children, n	22	18	
Age, years	9.4 ± 3.3	10.1 ± 3.1	>0.05
Mean ± SD (min–max)	6–18	6–18	
Males, n (%)	13 (59.1)	11 (61.1)	>0.05
Sensitisation to inhalant allergens, n (%)			
Dust mite	18 (81.8)	15 (83.3)	>0.05
Pollen	7 (31.8)	5 (27.8)	>0.05
Mould	8 (36.4)	6 (33.3)	>0.05
Animals	5 (22.7)	4 (22.2)	>0.05
Sensitisation to food allergens, n (%)			
Egg	19 (86.4)	3 (16.7)	<0.001
Milk	12 (54.5)	3 (16.7)	<0.04
Peanut	8 (36.4)	2 (11.1)	>0.05
Celery	7 (31.8)	2 (11.1)	>0.05
Wheat	10 (45.5)	7 (38.9)	>0.05
Others	9 (40.9)	2 (11.1)	>0.05
Clinical symptoms in history, n (%)			
AD in anamnesis	14 (63.6)	10 (55.5)	>0.05
AD recently	18 (81.8)	6 (33.3)	<0.01
Urticaria	10 (45.4)	1 (5.6)	<0.02
Vasomotor edema	2 (9.1)	0 (0)	>0.05
Digestive symptoms	14 (63.6)	9 (50)	>0.05
FA in history	19 (86.4)	16 (78.9)	>0.05
Family history of allergic diseases, n (%)	17 (77.3)	10 (55.6)	>0.05
Asthma severity, n (%)			
Mild	9 (40.9)	10 (55.6)	>0.05
Moderate	11 (50)	8 (44.4)	>0.05
Severe	2 (9.1)	0 (0)	>0.05
Asthma control, n (%)			
Controlled	4 (18.2)	8 (44.4)	>0.05
Partially controlled	12 (54.5)	9 (50)	>0.05
Non-controlled	6 (27.3)	1 (5.6)	>0.05
ICS treatment in the past 6 months N (%)	17 (77.3)	13 (72.2)	>0.05
tIgE, IU/ml (mean ± SD)	592.2 ± 304.4	418.5 ± 211.7	<0.04

FEV₁ and FVC were measured 90 sec after inhalation of each concentration, and the largest of triplicate FEV₁ or FVC values were used for the analysis. The procedure was terminated when the FEV₁ decreased by more than 20% of the post-saline value or when the highest methacholine concentration (25 mg/ml) was reached. The percentage decline of the FEV₁ from the post-saline value was plotted against the log concentration of inhaled methacholine. The provocative concentration (PC₂₀) of methacholine producing a 20% fall in FEV₁ was calculated by interpolating between two adjacent data points.

Statistical Analysis

The arithmetic means, minimum and maximum ranges as well as standard deviations for measurable variables were calculated. The distribution of quantitative variables was assessed by the Shapiro–Wilk test and homoscedasticity was tested with the F-Snedecor. To compare the values of measurable features in two different groups the test for two independent challenges, the Cochran–Cox test or the Mann–Whitney test were applied appropriately

to variables' distribution and their variance. The difference test or the Wilcoxon matched-pairs rank test were used for time-matched measurements appropriately to variables' distribution and their variance. For non-measurable features, the percentages within particular categories were calculated. The statistical analysis was performed with the independent χ^2 test, χ^2 with Yates modification or Fisher's exact test. The value of $P \leq 0.05$ was regarded as significant. The program STATISTICA 8.0 (StatSoft, Tulsa, OK) was used for calculations.

RESULTS

The patients were selected from 430 school-age children with atopic asthma. Complete sets of data were gathered from the parents of 362 children. Food complaints were reported in 180 (49.7%) children, of which 70 (19.3%) tested positive to food (sIgE). After analysis of the questionnaires, sIgE and results of elimination diet using for diagnostic purposes, on 50 children with IgE-dependent FA suspicion, DBPCFC was performed. A positive result of the DBPCFC was

observed in 20/50 (40%) of the patients studied. Medical documentation confirmed an anaphylactic reaction to food in four children (hypotension with flushing and pruritus in two and urticaria, angioedema and diarrhea in the other two). Based upon their medical history as well as sIgE and DBPCFC results, 24 children with asthma and IgE-dependent FA were identified. Ultimately, 22 children participated in the study, whereas, the control group comprised of 18 asthmatic children without FA. Allergens responsible for positive results of the challenge included: egg (12 children), milk (five children), wheat (one child), celery (one child), and peanuts (three children).

Of 22 asthmatic children with positive DBPCFC, 11 (50.0%) children developed respiratory symptoms, 13 (59.1%) gastric symptoms, and 15 (68.18%) skin lesions. The study also showed that isolated respiratory symptoms appeared in 2/22 (9.09%) children, whereas in 9/22 (40.9%) children they were diagnosed as one of the systemic reactions to food, accompanied by skin and gastrointestinal symptoms.

Mean FEV₁ value in children with asthma and concomitant FA was 1.89 ± 0.7 L prior to the OFC, 1.81 ± 0.77 L immediately after the test, and 1.78 ± 0.69 L 4 hr after the challenge (Table 2). Mean standardized FEV₁ values in this group prior to, immediately after, and 4 hr after the food challenge are illustrated in Figure 1. Immediately after the allergen provocation, a >20% decrease in FEV₁ was observed in 3/22 children (13.6%) one of whom reported dyspnea. FEV₁ values measured 4 hr after the challenge test were within normal limits in all children. The mean FEV₁ value was 1.93 ± 0.64 L (-0.4 ± 1.83 SDS) in children with asthma and FA before the placebo provocation, 1.79 ± 0.72 L (-0.54 ± 1.61 SDS) immediately after the test and 1.83 ± 0.63 L (-0.8 ± 1.55 SDS) 4 hr after the challenge. With the exception of one child, no decrease in FEV₁ value was observed after the placebo provocation.

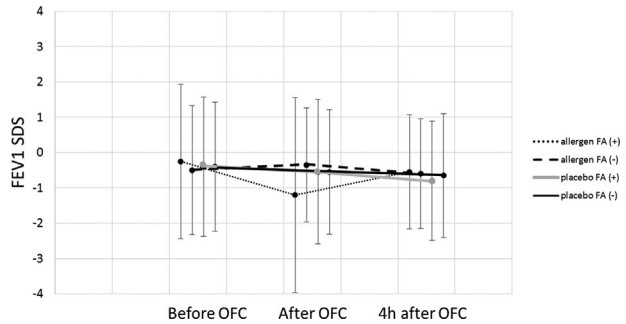


Fig. 1. FEV₁ SDS before, immediately and 4 hr after the oral food challenge (OFC) with verum and placebo in asthmatic children with and without food allergy (mean and standard deviation values were showed).

The mean FEV₁ and mean standardized FEV₁ values in asthmatic children without FA prior to, immediately after the allergen and placebo challenge and 4 hr after the test are shown in Table 2 and Figure 1. No child demonstrated a significant decrease in FEV₁ value, 4 hr after the food allergen or placebo provocation.

Mean FEV₁ values among those children suffering from asthma and FA prior to and after allergen or placebo challenge did not differ from patients with asthma but without FA ($P > 0.05$).

BHR was observed in all asthmatic children with FA, which was similar to those without FA (in two children, the values were questionable). There were no significant differences in the degree of BHR severity between the groups studied ($P > 0.05$). Prior to the challenge, 9/22 (40.9%) of the children with asthma and FA exhibited severe or moderate BHR and 13/22 (59.1%) displayed mild BHR. Among the group of children suffering from asthma without FA, severe or moderate BHR was recorded in 6/18 (33.3%) children, mild BHR in 10/18 children (55.5%) children and for two others (11.2%), the values were borderline.

TABLE 2—FEV₁ Before, Immediately and 4 hr After the Oral Food Challenge (OFC) With Verum and Placebo in Asthmatic Children With and Without Food Allergy

Spirometry testing time in correlation to OFC	Asthmatic children with food allergy (n = 22)	Asthmatic children without food allergy (n = 18)	P
	FEV ₁ liters mean $\pm$ SD (min–max)	FEV ₁ liters mean $\pm$ SD (min–max)	
Allergen			
Before	1.89 ± 0.71 (1.04–3.52)	1.51 ± 0.40 (1.22–4.14) ^a	>0.05
After	1.81 ± 0.77 (0.92–3.64)	1.62 ± 0.61 (1.21–3.93)	>0.05
4 hr after	1.78 ± 0.69 (1.22–3.81)	1.55 ± 0.64 (0.97–3.86) ^b	>0.05
Placebo			
Before	1.93 ± 0.64 (0.96–3.22)	1.69 ± 0.51 (1.03–3.46) ^c	>0.05
After	1.79 ± 0.72 (1.12–3.97)	1.72 ± 0.64 (1.22–3.77)	>0.05
4 hr after	1.83 ± 0.63 (1.21–4.13)	1.52 ± 0.71 (1.13–3.96) ^d	>0.05

FEV₁ before allergen challenge ^a $P > 0.05$; after allergen challenge, ^b $P > 0.05$; before placebo challenge, ^c $P > 0.05$; and after placebo challenge, ^d $P > 0.05$.

The mean PC₂₀ value in children with FA was 1.41 ± 1.12 prior to the allergen challenge, and 0.86 ± 0.71 mg/ml ($P = 0.002$) after the test, whereas these values were 1.93 ± 1.68 and 2.02 ± 1.75 mg/ml, respectively, in children without FA ($P > 0.05$). The comparison of mean PC₂₀ values before the OFC in both groups showed no statistically significant differences ($P > 0.05$), however, significant differences were noted after the allergen provocation in children with FA as compared to children without FA ($P = 0.007$; Fig. 2).

The mean PC₂₀ value in children with FA was 1.37 ± 1.08 before the placebo challenge and 1.42 ± 1.1 ($P = 0.05$) after the provocation, while in children without FA these values were 2.29 ± 2.98 and 2.34 ± 2.96 mg/ml, respectively, and did not show a statistically significant difference ($P > 0.05$).

In 15/22 (68.2%) asthmatic children with FA, BHR increased after the food allergen provocation but not after the placebo. In 80% of them (12/15), PC₂₀ values decreased after the food challenge, however, without corresponding changes in FEV₁ values immediately after OFC. Eleven of 22 (50%) children with asthma and FA (all with BHR increased after the food allergen provocation) developed respiratory symptoms after the food challenge. The symptoms exhibited were as follows: rhinitis in 31.8% (7/22) children, throat tightness in 18.2% (4/22) children, and symptoms of asthma exacerbation in 40.9% (9/22): cough in 27.2% (6/22) children, wheezing in 9.1% (2/22) children, and dyspnea in only one case (4.5%; 1/22). Additionally, six children (27%) had an increase in BHR without symptoms typical for asthma exacerbation after allergen provocation.

The mean PC₂₀ value in children with FA and respiratory symptoms was 0.97 ± 0.69 prior to the food challenge, and 0.47 ± 0.46 mg/ml ($P = 0.007$) after the provocation. In asthmatic children with FA but without the respiratory symptoms, the value was 1.77 ± 1.3 prior to the challenge and 1.18 ± 0.73 mg/ml ($P = 0.04$) after

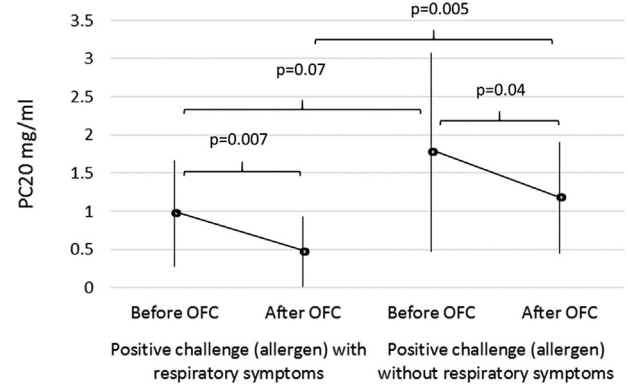


Fig. 3. PC₂₀ in asthmatic children with food allergy (FA) before and after food challenge versus respiratory symptoms.

the test. Children with FA and respiratory symptoms had statistically significantly higher BHR both before ($P = 0.07$) and after the provocation ($P = 0.005$) as compared to children with FA but without respiratory symptoms (Fig. 3).

An increase in BHR after the OFC was observed in 17/40 (42.5%) children suffering from asthma, including 15 with FA. In the remaining two asthmatic children, despite a negative result of the oral provocation, an increase in BHR occurred without changes in FEV₁ values after the food challenge. All children ($n = 17$) with decreased PC₂₀ value after the OFC had chronic asthma, which was mild in 23.5% (4/17) patients (two with FA, and two without FA), moderate in 64.7% (11/17) patients (all with FA), and severe in 11.8% (2/17) patients (all with FA). Asthma was controlled in 5.9% (1/17) child with increased BHR after the food challenge (child with FA), partially controlled in 52.9% (9/17; eight with FA), and non-controlled in 41.2% (7/17) children (six with FA; $P > 0.05$).

In all children with a confirmed food allergy ($n = 22$), an elimination diet was introduced and an assessment of

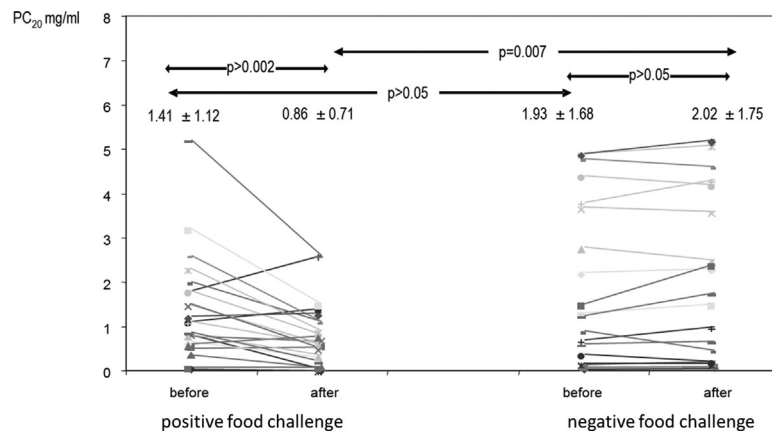


Fig. 2. PC₂₀ in asthmatic children with and without food allergy, before and after allergen oral food challenge.

asthma control was performed after a time period of 8 weeks. The results showed a decrease in the number of children with non-controlled asthma (from six to two) as well as those with partially controlled asthma (from 12–6), while the number of children with controlled asthma increased (from 4–14). The improvement of asthma control was observed in 54.5% (12/22) children (Table 3). The group of 12 children with improved asthma control after an elimination diet comprised of all 100% children (6/6) with increased BHR after food challenge without evident symptoms of asthma exacerbation, and 66.7% (6/9) children with increased BHR and exacerbation of asthma symptoms after food challenge.

DISCUSSION

The present study showed that isolated respiratory symptoms in the course of DBPCFC in children with asthma occur rarely (i.e., 9.09% [2/22] children with asthma and FA; 0.5% [2/362] children with asthma). The most common respiratory symptoms observed due to food challenge were cough and rhinitis. Although cough or rhinitis are typical symptoms in children with asthma, they are seldom associated with food intake.^{23–27} Similarly, asthma is rarely an isolated symptom of FA, however, it is most often one of the systemic symptoms of anaphylactic reaction to food.²⁸ Asthmatic symptoms usually occur in combination with cutaneous and/or digestive symptoms,^{5,6,28} which have also been observed in the children studied. It is worth emphasizing that not all children with asthma and concomitant FA experienced respiratory reactions after food challenge. The frequency of food-induced asthmatic reactions in the studied children with asthma and FA, was 40.9% (9/22), that is, 2.5% (9/362) children with asthma. However, in 68.2%

(15/22) of children with asthma and FA, that is, 4.7% (17/362) of children with asthma, an increase in BHR was observed as a result of DBPCFC.

Some data indicate that the estimated frequency of FA-induced asthmatic reactions in different populations of children ranges from 2.0% to 29.0%, while in children with asthma it is between 5.7% and 8.0%.^{5,6,29,30} Less common occurrence of food-induced asthmatic reactions in our study may be due to the methods used. Contrary to populations examined in other analyses, the study group was comprised of children above the age of six and the study was based on the DBPCFC method.

Despite a decrease in FEV₁ values in three children immediately after the food challenge, no differences were highlighted by a comparison of mean FEV₁ values prior to, immediately after and again, 4 hr after the OFC in the group of children with and without FA. Therefore, it seems reasonable to conclude that in the majority of cases, neither clinical observation nor pulmonary function tests fully indicate the impact of food allergens on respiratory system in asthmatic children.

Non-specific BHR tests were found to be the best method to evaluate the effect of food allergens on the pulmonary function in asthmatic children with FA. It has been shown that food products may induce an asymptomatic increase in BHR in subjects with FA without asthma,³¹ thus they seem to be even more significant in asthmatic patients sensitized to food products. Bjornson et al.³² demonstrated a significantly more frequent occurrence of asthma and BHR in patients with sIgE toward food allergens than in subjects not sensitized to foods. Patelis et al.¹ indicated that exposure of the gastrointestinal tract to food allergens may drive inflammation in primed tissue in the airway mucosa in subjects sensitized to both aeroallergens and food

TABLE 3— The Degree of Asthma Control Before and After Elimination Diet in Children With Asthma and Food Allergy (FA) in Correlation With Asthma Symptoms and Bronchial Reactivity (BHR)

	Children with asthma and FA, n = 22 (100%)		Children with asthma and FA and increased BHR after OFC, n = 15 (100%)		Children with asthma and FA and increased BHR with asthma exacerbations after OFC, n = 9 (100%)		Children with asthma and FA and increased BHR without asthma exacerbations after OFC, n = 6 (100%)	
	Before elimination diet	After elimination diet	Before elimination diet	After elimination diet	Before elimination diet	After elimination diet	Before elimination diet	After elimination diet
Asthma control, n (%)								
Controlled	4 (18.2)	14 (63.6)	0	10 (66.7)	0	4 (44.4)	0	6 (100)
Partially controlled	12 (54.5)	6 (27.3)	9 (60)	3 (20.0)	5 (55.6)	3 (33.4)	4 (66.7)	0
Non-controlled	6 (27.3)	2 (9.09)	6 (40)	2 (13.3)	4 (44.4)	2 (22.2)	2 (33.3)	0

(i) In each group composition of an elimination diet was based on the results of DBPCFC; (ii) the evaluation of asthma control was done before and 8 weeks after including elimination diet. The patients are still under observation; and (iii) the composition of an elimination diet included after completion of DBPCFC was different from the diet which preceded the challenge in all children, except two.

allergens, however, they noted a weakness of their study in the lack of data on exposure to allergens, especially food allergens. The present study combines food allergen exposure with the DBPC method and BHR evaluation, which are very difficult and troublesome tasks, especially in children. The possible impact of food allergens on altered lung function and BHR has also been shown in experimental studies.^{33,34} Brandt et al.³⁴ demonstrated increased airway hyper-responsiveness after a single intranasal OVA challenge in mice with gastrointestinal allergy compared with that seen in control mice not subjected to gastrointestinal allergen challenge. Moreover they noted that gastrointestinal allergy primes for allergic responses to unrelated allergens, for example, HDM. The study by Forbes et al.³³ suggests that allergic inflammation of the gastrointestinal tract may alter bronchial reactivity in an eotaxin/eosinophil-dependent manner. Bihouée et al.³⁵ demonstrated that food sensitization to one allergen primes the immune system to build an amplified pulmonary inflammation associated with an exaggerated immune reaction in response to another, unrelated allergen.

The study discussed here showed that a definite increase in BHR occurred after the OFC in children with asthma and FA as compared to children without FA. However, no differences in PC₂₀ values were observed in any of the groups studied after the placebo provocation. These observations are in line with the findings published by James et al.,³ but not with those noted by Zwetchkenbaum et al.,³⁶ who reported an increase in BHR in adults after both an allergen and placebo challenge using the same methods cited in this study. In Zwetchkenbaum's study, the MIC was performed later than in the present research, and moreover, patients were not hospitalized, which may imply the possibility of the effect of external factors on modulation of BHR.

It is worth emphasizing that an increase in BHR after OFC in the majority of children diagnosed with FA occurred without changes in FEV₁. Thus, it can be stated that MIC is a more effective method of evaluating the food allergen impact on pulmonary function than spirometry. Statistically significant differences in the range of PC₂₀ values were found in children, in whom respiratory symptoms occurred in the course of positive DBPCFC compared to negative results. Attention should be paid to the fact that an increase in BHR was also observed in children with FA in whom no respiratory symptoms were detected as well as in 2 of 18 children with negative results of DBPCFC, who are still under observation.

Particularly noteworthy is the observation that an increase in BHR after the food challenge mainly occurred in children with moderate asthma which was partially controlled or uncontrolled. Therefore, in the majority of cases, the risk of food induced respiratory symptoms involved children with less controlled and more severe

asthma, which aligns with data reported in other literature.^{37–41}

The use of complex diagnostic methods, that is, DBPCFC and MIC, allowed for the introduction of an elimination diet in 22 children with asthma, including six with increased BHR after OFC without asthma symptoms. This approach allowed the improvement of asthma control to be achieved. The improvement of asthma control concerned all children with an increase in BHR after food challenge, but without the typical symptoms of asthma exacerbation, as well as 66% of children with asthma exacerbation after food challenge. Such observation could indicate that complex diagnostic methods, that is, DBPCFC and MIC, allow a better control of asthma to be obtained. Additionally, such observation could be explained by the fact that it is easier to obtain better asthma control in children with milder courses of the disease, that is, without asthma exacerbations after OFC. In addition, a lack of total improvement after the use of an elimination diet could be due to the recommendations concerning the diet not being followed, or the impact of other factors triggering asthma exacerbations.

Limitations: our study has its weaknesses. We performed provocation tests only on children with asthma with suspicion of FA. Another weakness of our study was the relatively small number of patients and also the fact that some of the selected patients were referred to the clinic with suspicion of FA.

This DBPCFC study investigated impact of food allergens on respiratory symptoms, spirometry and BHR in school asthmatic children. The study results emphasizes the usefulness of MIC in considering FA in children with asthma, despite a lack of evident clinical respiratory signs after food intake. FA should be considered not only in children with acute life-threatening asthma exacerbations and in highly atopic children with severe persistent asthma resistant to medical management, but also in children with asthma exacerbations without identifiable triggers or children with partially or non-controlled asthma. Johnson et al.⁴² showed that young non-atopic asthmatics with perceived food hypersensitivity were characterized by poorer asthma control and asthma-related quality of life (perceived food hypersensitivity relates to poor asthma control and quality of life in young non-atopic asthmatics).

This approach can contribute to improved care for the asthmatic child, the course of their disease and their quality of life. Further studies are needed for improvement of asthma morbidity.

Conclusions: although food allergens are a rare trigger of food-induced asthmatic reactions in school-age children with asthma, they were able to increase BHR, despite a lack of evident clinical respiratory signs and decreased in FEV₁ values after food challenge.

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