
Bronchial reactivity in schoolchildren allergic to food

Aneta Krogulska, MD, PhD; Jarosław Dynowski, MD, PhD; and Krystyna Wasowska-Królikowska, MD, PhD

Background: Food allergy (FA) is associated with an increased risk of asthma.

Objective: To evaluate whether bronchial hyperreactivity (BHR) occurs in children with FA depending on the presence of respiratory symptoms.

Methods: Fifty-four children with FA and 62 without FA were studied for BHR, defined as a provocation concentration of methacholine that caused a decrease in forced expiratory volume in 1 second of 20% (PC₂₀). The diagnosis of FA was established using questionnaires, clinical criteria, skin prick tests, serum specific IgE antibodies, and a double-blind placebo-controlled food challenge.

Results: Among nonasthmatic children, BHR was diagnosed in 15 (47%) with FA and in 7 (17%) without FA ($P < .005$); BHR was demonstrated in 7 children (41%) with FA alone. All the patients with asthma with or without FA had BHR. The mean (SD) PC₂₀ in children with FA alone was 2.8 [1.38] mg/mL and was significantly higher than that in children with asthma alone (0.88 [1.01] mg/mL) or with asthma and FA (0.96 [0.83] mg/mL) ($P < .001$). BHR was detected in 5 children (36%) with a mild anaphylactic reaction provoked by food, in 23 (74%) with a moderate reaction, and in all the children with a severe reaction.

Conclusions: Children with FA had increased BHR independent of respiratory symptoms. Although BHR occurs in asymptomatic children with FA, its course is milder than that in children with FA and asthma. Factors that determine BHR prevalence in children with FA are similar to those in children without FA.

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INTRODUCTION

Studies^{1–6} that have evaluated the relationship between food allergy (FA) and respiratory disorders, such as asthma or allergic rhinitis (AR), indicate that FA may be more frequent in patients with respiratory complaints or, conversely, that respiratory manifestations are more common in individuals with FA. It has been demonstrated that experimental gastrointestinal allergy primes for responses to allergens in the respiratory tract, enhancing airway inflammation and bronchial hyperreactivity (BHR).^{7,8}

It is estimated that 2% to 9% of asthmatic patients (children and adults) have a concomitant FA, provoking exacerbations in the respiratory tract.^{9,10} In some patients with asthma, reactivity of the respiratory tract to food challenge has been shown to increase without distinct symptoms of dyspnea.^{10,11} On the other hand, some studies demonstrated that patients with asthma have subclinical inflammatory

changes in digestive tract mucosa^{12,13} or a marked presence of cells implicated in allergic inflammation in macroscopically normal mucosa.¹⁴ Lamblin et al¹⁵ reported an airway-like inflammation in the gut of asthmatic patients. Conversely, previous studies^{16–18} suggest an association between subclinical involvement of bronchial mucosa and gut mucosa in inflammatory diseases, such as ulcerative colitis, Crohn disease, and irritable bowel syndrome. Because food allergens can cause an asymptomatic increase in BHR in patients with asthma or inflammatory bowel diseases, perhaps they can also affect BHR in patients with FA. Thaminy et al¹⁹ reported an increased prevalence of nonspecific BHR in adults with FA. To our knowledge, no similar study has been conducted in children with FA.

Nonspecific BHR can occur not only in patients with existing FA but also in patients with past FA. Priftis et al²⁰ reported that children allergic to egg or fish in infancy demonstrate at school age an increased risk of BHR. Moreover, many studies^{21–23} have suggested that food allergen sensitization is a risk factor for asthma. It is not clear why patients with FA and no history of asthma may develop bronchoconstriction during an allergic reaction to food. We hypothesized that perhaps BHR is the link between FA and asthma.

Based on these considerations, the aim of the present study was to determine (1) whether BHR occurs in children with FA depending on the presence of respiratory symptoms, (2) whether there are any differences in the degree of BHR severity between the groups studied, and (3) what factors increase the risk of BHR in some children with FA.

Affiliations: Department of Pediatric Allergology, Gastroenterology, and Nutrition, Medical University of Lodz, Lodz, Poland.

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METHODS

The initial study group consisted of 558 school-aged children. They were admitted to the Department of Pediatric Allergology, Gastroenterology, and Nutrition of the Medical University of Lodz under a suspicion of FA. Of these 558 children, 192 had positive skin prick test (SPT) reactions or specific IgE antibodies to food allergens. The FA was confirmed in 63 children. Only patients who could adequately perform pulmonary function testing were enrolled in the study between October 1, 2006, and August 31, 2009. Lack of data or cooperation resulted in the exclusion of 9 children. Therefore, 54 children (mean [SD] age, 10.9 [2.6] years) were subjected to further investigations. The study group consisted of 17 children with FA without respiratory symptoms, 22 with FA and concomitant asthma, and 15 with FA and AR. The control group comprised 62 children without FA (mean [SD] age, 10.9 [2.7] years): 25 healthy children, 20 with asthma, and 17 with AR. The patients' parents signed informed consent forms for participation in the investigations, and the study was approved by the institutional ethics committee of the Medical University of Lodz.

The diagnosis of FA was established using questionnaires, clinical criteria, SPTs to specific food allergens, serum specific IgE antibodies directed against the food allergens, and a double-blind placebo-controlled food challenge. The allergens responsible for positive results in the food challenge were egg in 21 children, milk in 8, wheat flour in 1, celery in 7, nuts in 3, and apple in 6. In 8 children (3 allergic to apple, 3 to peanuts, 1 to fish, and 1 to celery), the double-blind placebo-controlled food challenge was not performed because of a well-documented history of reaction and reported anaphylactic reactions. Exclusion of FA was confirmed by questionnaires, SPTs to specific food allergens, and food challenge. Moreover, all the parents of the children were asked about previous symptoms and sensitization to food and airborne allergens during the first 3 years of life.

Skin Prick Testing

Standardization of the method was in line with the position papers of the European Academy of Allergy and Clinical Immunology.²⁴ Standard allergen extracts were provided by Allergopharma (Reinbek, Germany). The food allergens included milk, egg, cereals (wheat flour and rye flour), fish, soy, cocoa, sesame, peanut, hazelnut, fruits (apple, peach, and orange), and vegetables (celery, carrot, potato, and tomato), and the inhaled allergens included mites, molds, pollen, and pets. Positivity on SPT was defined as a wheal at least 3 mm larger than the negative control. Data were excluded if the saline control was 3 mm or larger, the histamine control was less than 3 mm, or the difference between histamine and saline was less than 3 mm.

Serum Specific IgE Antibodies

Specific IgE for milk, egg, wheat and rye flour, fish, shrimp, soy, cocoa, sesame, peanut, hazelnut, fruits (apple, peach, and orange), and vegetables (celery, carrot, potato, and tomato)

were measured using the UniCAP 100 (Pharmacia Diagnostics AB, Uppsala, Sweden).

Food Challenge

The oral challenge tests were performed using the double-blind placebo-controlled food challenge method. The trials were conducted in hospitalized patients according to European Academy of Allergy and Clinical Immunology recommendations after a minimum 2-week elimination diet.²⁵ Systemic corticosteroids were contraindicated, and systemic antihistamines were withdrawn according to their half-life. The use of topical corticosteroids for the airways was no reason to discontinue testing; topical corticosteroids for skin complaints were tapered to the minimum dose and were kept constant throughout the challenge procedure. β_2 -Adrenergic agonists and theophylline were avoided for 48 hours before the challenge. Native food was used. In the provocation procedures, the following food allergens were used: egg, milk, wheat flour, celery, apple, and peanuts. The patients were observed for at least 48 hours. The food challenge results were scored as negative, mild to moderate, or severe using a clinical reference table adapted from Sampson²⁶ and Benhamou et al.²⁷

The respiratory evaluation (ie, SPT to aeroallergens, spirometric measurements, and methacholine challenge) was conducted in stable patients with no exacerbations for at least the previous 8 weeks, at least 6 months after diagnosis of FA, and at least 2 months after the last manifestations of FA. The study exclusion criteria were respiratory tract and gastrointestinal infections in the previous 8 weeks, forced expiratory volume in 1 second (FEV₁) less than 70% of predicted, treatment with inhaled β_2 -agonists or leukotriene modifiers (for 24–48 hours), oral theophylline use (for 48 hours), antihistamine use (for 48 hours), and oral corticosteroid therapy in the 4 months before the study.

Pulmonary Function Tests

Baseline pulmonary function testing was performed using spirometry software (Lungtest 1000; MES, Krakow, Poland) by adequately trained personnel. Only the best curve was used for further analysis. All the data are expressed in absolute values and in percentage of predicted normal values.²⁸

Methacholine Inhalation Challenge

The methacholine inhalation challenge was performed using methacholine (MP Biomedicals, Solon, Ohio) and the Inhalation Allergology Challenge System (MES). A pressure inhalator (PARI LC PLUS; PARI Respiratory Equipment Inc, Midlothian, Virginia) with 0.0054 mL/s of output was used for nebulization. The study was performed in compliance with American Thoracic Society recommendations by means of the continuous Cockcroft method starting with a 0.03-mg/mL concentration. Patients inhaled the diluent solution for 2 minutes of tidal breathing followed by doubling concentrations of methacholine at 5-minute intervals. The procedure was discontinued if the FEV₁ decreased by more than 20% from baseline values or when a concentration of 16

Table 1. Characteristics of the Study Groups

	Children with FA (n = 54)				Children without FA (n = 62)			
	FA alone (n = 17)	FA + asthma (n = 22)	FA + AR (n = 15)	Total (N = 54)	Healthy (n = 25)	Asthma (n = 20)	AR (n = 17)	Total (N = 62)
Age, mean (SD) [range], y	10.9 (2.4) [7–15]	10.0 (2.5) [7–18] ^a	12.3 (2.7) [8.9–18]	10.9 (2.6) [7–18]	10.5 (2.3) [8–18]	10.9 (2.8) [7.5–17.7]	12.8 (2.1) [8.3–18]	10.9 (2.7) [8–18]
Male sex, No. (%)	7 (41)	13 (59)	8 (53)	28 (52)	13 (52)	14 (70)	8 (47)	35 (56)
Atopic family history, No. (%)	7 (41) ^b	17 (77)	8 (53)	32 (59) ^c	4 (16)	11 (55)	6 (35)	21 (34)
Total IgE, mean (SD), kU/L	396 (197) ^b	592 (304)	427 (177)	449.7 (212) ^c	91 (38)	426 (153) ^d	382 (203)	289.7 (130)
Sensitization to food allergens, No. (%)	17 (100)	22 (100)	15 (100)	54 (100) ^c	3 (12)	4 (20) ^d	4 (24) ^e	11 (18)
Milk	5 (29)	8 (36) ^a	1 (7)	14 (26)	0	0 ^d	0	0
Egg	7 (41) ^b	16 (73) ^a	3 (20)	26 (48)	0	1 (5) ^d	0	1 (2)
Cereals	4 (24)	3 (14)	5 (33)	12 (22)	1 (4)	2 (10)	3 (18)	6 (10)
Fish	1 (6)	1 (5)	0	2 (4)	0	0	0	0
Nuts	4 (24)	5 (23)	6 (40)	15 (28)	1 (4)	0	2 (12)	3 (5)
Fruits	9 (53)	7 (32) ^a	10 (67)	26 (48)	1 (4)	2 (10)	2 (12) ^e	5 (8)
Vegetables	6 (35)	9 (41)	8 (53)	23 (43)	1 (4)	2 (10)	0 ^e	3 (5)
Sensitization to inhaled allergens, No. (%)	12 (71) ^b	22 (100)	15 (100) ^f	49 (91) ^c	3 (12)	20 (100)	17 (100)	40 (65)
Mites	2 (12) ^b	17 (77)	8 (53) ^f	27 (50)	1 (4)	18 (90)	12 (71)	31 (50)
Molds	2 (12)	4 (18)	2 (13)	8 (15)	0	6 (30)	3 (18)	9 (15)
Pollen	11 (65)	12 (55)	8 (53)	31 (57)	3 (12)	8 (40)	11 (65)	22 (35)
Pets	0	2 (9)	3 (20)	5 (9)	1 (4)	2 (10)	4 (24)	7 (11)

Abbreviations: AR, allergic rhinitis; FA, food allergy.

^a $P < .05$, FA + asthma vs FA + AR.

^b $P < .05$, FA alone vs FA + asthma.

^c $P < .05$, total with FA vs total without FA.

^d $P < .05$, FA + asthma vs asthma.

^e $P < .05$, FA + AR vs AR.

^f $P < .05$, FA alone vs FA + AR.

Table 2. Functional Characteristics and MIC Results of Nonasthmatic Patients With or Without FA

	Children with FA (n = 32)			Children without FA (n = 42)		
	FA alone (n = 17)	FA + AR (n = 15)	Total (N = 32)	Healthy (n = 25)	AR (n = 17)	Total (N = 42)
FEV ₁ , mean (SD), % of predicted	96.2 (7.1)	95.6 (5.5)	95.9 (8.6)	95.4 (9.8)	100.4 (11.3)	96.7 (9.8)
FVC, mean (SD), % of predicted	98.8 (9.3)	97.7 (8.9)	98.2 (9.1)	99.1 (7.6)	99.2 (7.9)	99.1 (7.3)
Positive methacholine challenge test result, No. (%)	7 (41) ^a	8 (53) ^b	15 (47) ^c	0	7 (41)	7 (17)
PC ₂₀ , mean (SD), mg/mL ^d	2.8 (1.38)	1.85 (1.62)	2.3 (1.5)	NA	1.98 (1.64)	1.98 (1.64)

Abbreviations: AR, allergic rhinitis; FA, food allergy; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; MIC, methacholine inhalation challenge; NA, not applicable; PC₂₀, provocation concentration of methacholine that caused a decrease in FEV₁ of 20%.

^a $P < .001$, FA alone vs healthy.

^b $P < .001$, FA + AR vs healthy.

^c $P < .005$, total with FA vs total without FA.

^d Calculated for patients with bronchial hyperreactivity.

mg/mL was administered. The degree of airway responsiveness to methacholine was categorized as positive BHR if the provocation concentration of methacholine that caused a decrease in FEV₁ of 20% (PC₂₀) was less than 4 mg/mL, borderline BHR if the PC₂₀ was at least 4 mg/mL but not greater than 16 mg/mL, and negative BHR if the PC₂₀ was greater than 16 mg/mL.²⁹ Asymptomatic BHR was defined as a PC₂₀ less than 4 mg/mL in the absence of symptoms suggestive of asthma (wheeze, recurrent cough, chest tightness, and dyspnea). All the patients were following an elimination diet during methacholine inhalation challenge and beyond a season in the case of seasonal allergy.

Statistical Analysis

The mean values of measurable features (arithmetic means and medians), variable ranges (minimum to maximum), and standard deviations were calculated. To compare mean values, analysis of variance or nonparametric analysis of variance (Kruskal-Wallis test) was used with post hoc testing using the Mann-Whitney test (with Bonferroni correction or the Tukey Honestly Significant Difference test) or the *t* test. The χ^2 test or the χ^2 test with Yates correction or the Fisher exact test was performed for comparison of data frequency. Odds ratios with 95% confidence intervals were calculated using univariate logistic regression analysis. Logistic regression analysis was applied to assess the effects of various risk factors on BHR. A $P < .05$ was considered statistically significant. The programs Statgraphics Plus 5.1 (Statpoint Technologies Inc, Warrenton, Virginia) and Statistica 5.0 (StatSoft Inc, Tulsa, Oklahoma) were used for calculations.

RESULTS

The characteristics of the study and control groups are given in Table 1. There was no significant difference in age and sex besides the fact that children with FA and AR were older than children with FA and asthma ($P < .05$). To answer the question of whether BHR occurs in children with FA depending on the presence of respiratory symptoms, we divided the group of food-allergic children into nonasthmatic and asthmatic children. The physiologic data and results of metha-

choline inhalation challenge in nonasthmatic children with or without FA are displayed in Table 2. The baseline FEV₁ and forced vital capacity values were within their respective reference ranges. Among nonasthmatic children, BHR was revealed in 15 (47%) with FA and in 7 (17%) without FA ($P < .005$). Also, BHR was demonstrated in children with FA alone and in children with FA and AR ($P > .05$). The differences were significant compared with healthy children ($P < .001$) but not compared with children with AR. There were no significant differences in the mean PC₂₀ in nonasthmatic children with or without FA. To explain whether there are any differences between the severity of BHR in nonasthmatic children with FA and asthmatic children with or without FA, we compared the methacholine inhalation challenge results in the studied groups (Table 3). BHR was revealed in all the children with asthma. The mean PC₂₀ in nonasthmatic children with FA was significantly higher than that in children with asthma with or without associated FA.

Respiratory symptoms appeared as the result of food challenge in 14 children with FA (26%). In all the children with FA alone, no respiratory symptoms were observed during the food challenge test; nevertheless, BHR was found in 7 of them (41%). BHR occurred in all the children with asthma and FA, but respiratory complaints during the provocation

Table 3. Bronchial Hyperreactivity in Nonasthmatic Patients With FA vs Asthmatic Patients With or Without FA

	Nonasthmatic + FA (n = 32)	Asthmatic + FA (n = 22)	Asthmatic (n = 20)
Positive methacholine inhalation challenge test result, No. (%)	15 (47) ^a	22 (100)	20 (100)
PC ₂₀ , mean (SD), mg/mL ^b	2.3 (1.5) ^a	0.96 (0.83)	0.88 (1.01)

Abbreviations: FA, food allergy; PC₂₀, provocation concentration of methacholine that caused a decrease in FEV₁ of 20%.

^a $P < .001$, nonasthmatic + FA vs asthmatic + FA and vs asthmatic.

^b Calculated for patients with bronchial hyperreactivity.

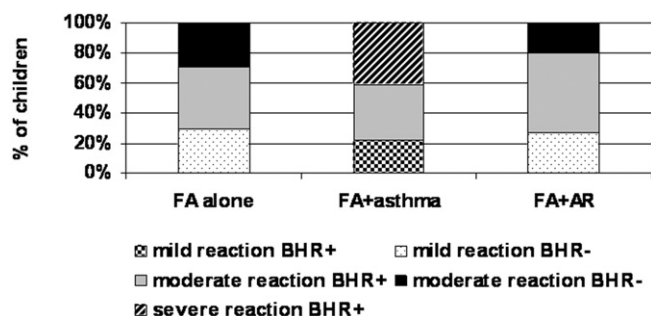


Figure 1. Bronchial hyperreactivity (BHR) and the severity of the anaphylactic reaction to food in the study group. AR indicates allergic rhinitis; and FA, food allergy.

test were observed only in 8 (36%). On the other hand, in the group with FA and AR, nasal symptoms (ie, rhinitis) were stated in 6 children (40%), all of whom had BHR. Two children with FA and AR revealed BHR without nasal symptoms.

We also examined the relationship between BHR and the severity of the anaphylactic reaction to food (Fig 1). BHR was detected in 5 of 14 children (36%) with a mild anaphylactic reaction, in 23 of 31 (74%) with a moderate reaction, and in all 9 with a severe reaction. The mean (SD) PC_{20} for children with a mild anaphylactic reaction to food was 1.88 (0.59) mg/mL, for those with a moderate reaction was 1.85 (1.44) mg/mL, and for children with a severe reaction was 0.39 (0.32) mg/mL. Statistically significant differences concerned children with a mild reaction compared with those with a severe one ($P = .002$) and the moderate group compared with those with a severe reaction ($P < .001$) (Fig 2).

Moreover, we tried to evaluate the risk of BHR. The results of univariate logistic regression analysis between BHR in children with vs without FA are given in Table 4. The risk of BHR was 6-fold higher in children with a positive family history of atopy in the groups of children with ($P = .005$) and without ($P = .003$) FA. The highest risk of BHR in the group with FA was found in children with atopic dermatitis (AD) and in those with allergy to mites occurring at the time of the examination and reported in the history.

DISCUSSION

BHR is a hallmark of asthma and a risk factor for asthma in patients with AR. This finding emphasizes the significance of BHR in patients with FA. This study is the first, to our knowledge, to demonstrate an increased prevalence of non-specific BHR in nonasthmatic children with FA. It is consistent with previous studies concerning adults.^{12,19,30} We demonstrated that BHR was detected in 47% of nonasthmatic children with FA. Thaminy et al¹⁹ found asymptomatic BHR in 53% of nonasthmatic adults with FA. The present results are also similar to those of Kivity et al,³¹ who reported that approximately 50% of patients with FA had BHR without having any symptoms of asthma. Increased BHR was found

in all of their patients with asthma regardless of whether they had FA and in 55% of patients with FA and nasal symptoms. We demonstrated that BHR was detected in all the children with FA and concomitant asthma and in 53% of children with FA and AR. Only 36% of children with asthma and FA had respiratory symptoms during food challenge. So even in asthmatic patients with FA, food does not always clinically manifest its effect in the respiratory tract, ie, causing dyspnea, cough, or wheezing during the provocation test but can provoke only an increase of BHR.¹¹ However, it is still unclear why some children with BHR manifest symptoms and others remain asymptomatic. Moreover, it is still unclear whether asymptomatic BHR in children with FA predisposes to asthma in the future. It was demonstrated that the presence of BHR and concomitant atopic manifestations in childhood increase the risk of asthma in adulthood.³² van den Nieuwenhof et al³³ stated that screening for asymptomatic airway hyperresponsiveness in adolescence does not identify individuals at risk for asthma, but conversely, the presence of allergy in adolescence does seem to be a risk factor for asthma. It is known that BHR exists in diseases with and without respiratory manifestation.^{16–18} Twenty-eight percent to 61% of children with AR were diagnosed as having BHR.³⁴ Epidemiologic surveys^{35,36} have confirmed the existence of asymptomatic BHR in various healthy populations with a prevalence of 8% to 13%. Although bronchopulmonary manifestations are rare, BHR was found in 41% of patients with inflammatory bowel disease. It has been suggested that latent inflammation of the bronchial mucosa, secondary to inflammation of the intestinal mucosa, may lead to increased BHR.¹⁷ The recent experimental study by Ozdemir et al⁸ found that $CD4^+$ T cells from mesenteric lymph nodes of mice with allergen-induced immediate-type hypersensitivity reactions in the gut can trigger airway hyperreactivity and eosinophilic airway inflammation (ie, transfer the phenotype of experimental asthma).

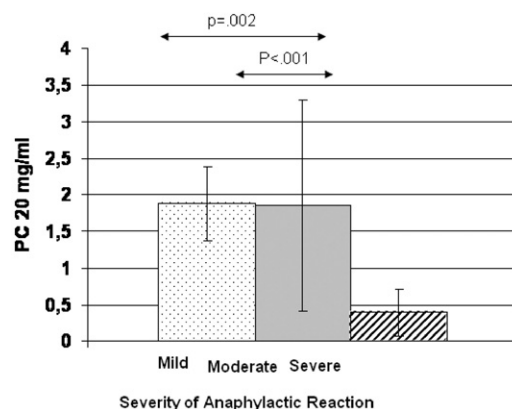


Figure 2. Mean provocation concentration of methacholine that caused a decrease in forced expiratory volume in 1 second of 20% (PC_{20}) in correlation with the severity of the anaphylactic reaction to food. Error bars represent SD.

Table 4. Risk of Bronchial Hyperreactivity in Children With and Without FA

	Children with FA (n = 54)		Children without FA (n = 62)	
	OR (95% CI)	P value	OR (95% CI)	P value
Atopic family history	6.48 (1.76–23.80)	.005	6.04 (1.85–19.77)	.003
Current symptoms				
Urticaria	0.19 (0.05–0.71)	.01	3.75 (0.64–21.84)	
Gastrointestinal	0.06 (0.01–0.37)	.002	4.13 (1.19–14.31)	.02
AD	23.33 (4.28–127.10)	<.001	4.71 (0.84–26.49)	
Respiratory	6.12 (1.67–22.44)	.007	5.16 (1.78–23.68)	.006
Current sensitization to food allergens				
Milk	1.25 (0.32–4.92)		NA	
Egg	1.07 (0.33–3.46)		NA	
Cereals	1.50 (0.34–6.66)		7.73 (0.81–73.95)	
Nuts	1.38 (0.35–5.33)		0.63 (0.05–7.77)	
Fruits	1.51 (0.46–5.25)		2.06 (0.31–13.83)	
Vegetables	1.56 (0.46–5.25)		2.72 (0.22–33.33)	
Current sensitization to inhaled allergens				
Mites	5.34 (1.41–20.27)	.01	19.41 (5.03–74.87)	<.001
Molds	0.73 (0.15–3.61)		14.32 (1.59–128.91)	.02
Pollen	1.85 (0.56–6.07)		2.68 (0.90–7.99)	
Pets	0.66 (0.10–4.58)		0.97 (0.19–4.91)	
Symptoms in the first 3 y of life				
AD	7.67 (1.80–32.57)	.007	4.80 (1.39–16.56)	.01
Gastrointestinal	0.74 (0.23–2.43)		0.54 (0.19–2.89)	
Respiratory	6.00 (1.57–22.90)	.009	2.12 (0.74–6.01)	
Urticaria, rashes	0.86 (0.26–2.79)		0.32 (0.06–1.74)	
Sensitization in the first 3 y of life to food allergens				
Milk	1.94 (0.57–6.51)		2.87 (0.47–17.63)	
Egg	0.60 (0.18–1.96)		2.42 (0.51–11.56)	
Cereals	5.14 (0.57–46.73)		0.97 (0.19–4.89)	
Nuts	1.75 (0.31–9.87)		3.75 (0.64–21.84)	
Fruits	1.75 (0.31–9.87)		3.75 (0.64–21.84)	
Vegetables	0.73 (0.15–3.61)		5.91 (0.59–59.02)	
Sensitization in the first 3 y of life to inhaled allergens				
Mites	X		9.90 (2.36–41.50)	.002
Molds	1.94 (0.19–19.84)		1.86 (0.37–9.40)	
Pollen	2.53 (0.59–10.79)		3.05 (0.67–13.96)	
Pets	NA		1.32 (0.17–10.46)	

Abbreviations: AD, atopic dermatitis; CI, confidence interval; FA, food allergy; NA, nonapplicable; OR, odds ratio; X, all children sensitized to mites had bronchial hyperreactivity.

Similar to other studies,^{16,17} the present study demonstrating BHR in asymptomatic children with FA suggests the presence of a subclinical inflammatory process in the bronchi. The mechanisms responsible for airway inflammation in patients with FA are likely multifactorial. Wallaert et al³⁰ showed a high neutrophil count, without activation in induced sputum from adults with FA, which can explain, at least in part, why these patients had airway neutrophil inflammation but did not exhibit clinical respiratory symptoms. Another study³¹ reported high eosinophil levels in the sputum of patients with FA, which might predict respiratory involvement. A potential limitation of the present study may be that we have not evaluated some special features of suggested bronchial inflammation through assessing, for example, induced sputum; however, additional investigative techniques

would hinder already difficult and troublesome methods for children in our research.

BHR is often called a marker for the severity of asthma.³⁷ Evaluation of BHR according to the severity of the anaphylactic reaction to food demonstrated that with a higher degree of anaphylactic reaction, BHR was more often recognized. Considering that severe anaphylactic reaction is related to concerns of the respiratory system,^{26,27} the observed regularity seems to be correct. It was also proved that the lowest PC₂₀ was affecting children with severe anaphylactic reactions to food, and these concerned only asthmatic children. These data confirm the results of recent studies indicating a higher risk of severe anaphylactic reactions in asthmatic children with concomitant FA.³⁸ FA is an independent risk factor for potentially fatal childhood asthma. Although BHR

appears in nonasthmatic children with FA, its course is milder than that in children with FA and asthma.

It is noteworthy that the present patients had BHR during an elimination diet, so we cannot say that BHR was directly due to food allergen intake. Thaminy et al¹⁹ suggests that nonspecific BHR in FA is not induced by long-term allergen intake. It has been demonstrated that food allergen can increase BHR in food-allergic patients with asthma.¹¹ Considering that BHR can increase due to exposure to an allergen to which the patient is sensitive, establishment of a proper diet for patients with concomitant FA is important.

Some studies^{2,3,19} indicate that the prevalence of BHR in patients with FA is similar in those with positive as well as negative SPT reactions to aeroallergens, which suggests that sensitization to aeroallergens is not the sole factor that determines the development of BHR associated with FA. Note that nonasthmatic children with FA in the present study were mostly sensitive to pollens, and not to mites, whereas mite allergy was detected in approximately 90% of children with FA and asthma. Mite sensitivity is known to be the most important factor in developing airway disease.³⁹ Factors that determine the risk of BHR in children with FA are similar to those in children without FA.

In conclusion, this study, for the first time, to our knowledge, showed increased BHR in children with FA irrespective of the presence of respiratory symptoms and suggests that FA favors by itself the development of BHR. The evaluation of BHR in children with FA seems to be worth emphasizing.

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REFERENCES

- Schäfer T, Böhler E, Ruhdorfer S, et al. Epidemiology of food allergy/food intolerance in adults: associations with other manifestations of atopy. *Allergy*. 2001;56:1172–1179.
- Schroeder A, Kumar R, Pongracic JA, et al. Food allergy is associated with an increased risk of asthma. *Clin Exp Allergy*. 2009;39:261–270.
- Pénard-Morand C, Raherison C, Kopferschmitt C, et al. Prevalence of food allergy and its relationship to asthma and allergic rhinitis in schoolchildren. *Allergy*. 2005;60:1165–1171.
- Spergel JM, Fiedler J. Food allergy and additives: triggers in asthma. *Immunol Allergy Clin North Am*. 2005;25:149–167.
- Baena-Cagnani CE, Teijeiro A. Role of food allergy in asthma in childhood. *Curr Opin Allergy Clin Immunol*. 2001;1:145–149.
- Huang SW. Follow-up of children with rhinitis and cough associated with milk allergy. *Pediatr Allergy Immunol*. 2007;18:81–85.
- Brandt EB, Scribner TA, Akei HS, Rothenberg ME. Experimental gastrointestinal allergy enhances pulmonary responses to specific and unrelated allergens. *J Allergy Clin Immunol*. 2006;118:420–427.
- Ozdemir C, Sel S, Schöll I, et al. CD4+ T cells from mice with intestinal immediate-type hypersensitivity induce airway hyperreactivity. *Clin Exp Allergy*. 2007;37:1419–1426.
- Roberts G, Patel N, Levi-Schaffer F, Habibi P, Lack G. Food allergy as a risk factor for life-threatening asthma in childhood: a case-controlled study. *J Allergy Clin Immunol*. 2003;112:168–174.
- James JM. Respiratory manifestations of food allergy. *Pediatrics*. 2003;111:1625–1630.
- James JM, Eigenmann PA, Eggleston PA, Sampson HA. Airway reactivity changes in asthmatic patients undergoing blinded food challenges. *Am J Respir Crit Care Med*. 1996;153:597–603.
- Wallaert B, Desreumaux P, Copin MC, et al. Immunoreactivity for interleukin 3 and 5 and granulocyte/macrophage colony-stimulating factor of intestinal mucosa in bronchial asthma. *J Exp Med*. 1995;182:1897–1904.
- von Wattenwyl F, Zimmermann A, Netzer P. Synchronous first manifestation of an idiopathic eosinophilic gastroenteritis and bronchial asthma. *Eur J Gastroenterol Hepatol*. 2001;13:721–725.
- Pires GV, Souza HS, Elia CC, et al. Small bowel of patients with asthma and allergic rhinitis: absence of inflammation despite the presence of major cellular components of allergic inflammation. *Allergy Asthma Proc*. 2004;25:253–259.
- Lamblin C, Desreumaux P, Colombel JF, Tonnel AB, Wallaert B. Overexpression of IL-10 mRNA in gut mucosa of patients with allergic asthma. *J Allergy Clin Immunol*. 2001;107:739–741.
- Kanazawa H, Yoshikawa J. A case-control study of bronchial asthma associated with ulcerative colitis: role of airway microvascular permeability. *Clin Exp Allergy*. 2005;35:1432–1436.
- Mansi A, Cucchiara S, Greco L, et al. Bronchial hyperresponsiveness in children and adolescents with Crohn's disease. *Am J Respir Crit Care Med*. 2000;161:1051–1054.
- Yazar A, Atis S, Konca K, et al. Respiratory symptoms and pulmonary functional changes in patients with irritable bowel syndrome. *Am J Gastroenterol*. 2001;96:1511–1516.
- Thaminy A, Lamblin C, Perez T, Bergoin C, Tonnel AB, Wallaert B. Increased frequency of asymptomatic bronchial hyperresponsiveness in nonasthmatic patients with food allergy. *Eur Respir J*. 2000;16:1091–1094.
- Priftis KN, Mermiri D, Papadopoulou A, Papadopoulos M, Fretzayas A, Lagona E. Asthma symptoms and bronchial reactivity in school children sensitized to food allergens in infancy. *J Asthma*. 2008;45:590–595.
- Leung TF, Lam CW, Chan IH, Li AM, Tang NL. Sensitization to common food allergens is a risk factor for asthma in young Chinese children in Hong Kong. *J Asthma*. 2002;39:523–529.
- Nickel R, Kulig M, Forster J, et al. Sensitization to hen's egg at the age of twelve months is predictive for allergic sensitization to common indoor and outdoor allergens at the age of three years. *J Allergy Clin Immunol*. 1997;99:613–617.
- Kulig M, Bergmann R, Tacke U, Wahn U, Guggenmoos-Holzmann I. Long-lasting sensitization to food during the first two years precedes allergic airway disease: the MAS Study Group, Germany. *Pediatr Allergy Immunol*. 1998;9:61–67.
- Dreborg S, Frew A. Position paper: allergen standardization and skin tests: the European Academy of Allergology and Clinical Immunology. *Allergy*. 1993;48(suppl 14):49–54.
- Bindslev-Jensen C, Ballmer-Weber BK, Bengtsson U, et al. Standardization of food challenges in patients with immediate reactions to foods: position paper from the European Academy of Allergology and Clinical Immunology. *Allergy*. 2004;59:690–697.
- Sampson HA. Anaphylaxis and emergency treatment. *Pediatrics*. 2003;111:1601–1608.
- Benhamou AH, Zamora SA, Eigenmann PA. Correlation between specific immunoglobulin E levels and the severity of reactions in egg allergic patients. *Pediatr Allergy Immunol*. 2008;19:173–179.
- Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows: report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal: official statement of the European Respiratory Society. *Eur Respir J*. 1993;16:5–40.
- Crapo RO, Casaburi R, Coates AL, et al. Guidelines for methacholine and exercise challenge testing—1999. *Am J Respir Crit Care Med*. 2000;161:309–329.
- Wallaert B, Gosset P, Lamblin C, Garcia G, Perez T, Tonnel AB. Airway neutrophil inflammation in nonasthmatic patients with food allergy. *Allergy*. 2002;57:405–410.

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31. Kivity S, Fireman E, Sade K. Bronchial hyperactivity, sputum analysis and skin prick test to inhalant allergens in patients with symptomatic food hypersensitivity. *Isr Med Assoc J*. 2005;7:781–784.
32. Porsbjerg C, von Linstow ML, Ulrik CS, Nepper-Christensen S, Backer V. Risk factors for onset of asthma: a 12-year prospective follow-up study. *Chest*. 2006;129:309–316.
33. van den Nieuwenhof L, Schermer T, Heijdra Y, et al. Are asymptomatic airway hyperresponsiveness and allergy risk factors for asthma? a longitudinal study. *Eur Respir J*. 2008;32:70–76.
34. Choi SH, Yoo Y, Yu J, Rhee CS, Min YG, Koh YY. Bronchial hyperresponsiveness in young children with allergic rhinitis and its risk factors. *Allergy*. 2007;62:1051–1056.
35. Sears MR, Jones DT, Holdaway MD, et al. Prevalence of bronchial reactivity to inhaled methacholine in New Zealand children. *Thorax*. 1986;41:283–289.
36. Salome CM, Peat JK, Britton WJ, Woolcock AJ. Bronchial hyperresponsiveness in two populations of Australian schoolchildren: relation to respiratory symptoms and diagnosed asthma. *Clin Allergy*. 1987;17:271–281.
37. Murray AB, Ferguson AC, Morrison B. Airway responsiveness to histamine as a test for overall severity of asthma in children. *J Allergy Clin Immunol*. 1981;68:119–124.
38. Vogel NM, Katz HT, Lopez R, Lang DM. Food allergy is associated with potentially fatal childhood asthma. *J Asthma*. 2008;45:862–866.
39. Milián E, Díaz AM. Allergy to house dust mites and asthma. *PR Health Sci J*. 2004;23:47–57.
- Requests for reprints should be addressed to:*
Krogulska Aneta, MD, PhD
Department of Pediatric Allergology, Gastroenterology, and Nutrition
Medical University of Lodz
Sporna 36/50
91-738 Lodz, Poland
E-mail: anetkrog@poczta.onet.pl
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