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Prevalence and Clinical Impact of IgE-Mediated Food Allergy in School Children With Asthma: A Double-Blind Placebo-Controlled Food Challenge Study

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Purpose: Recent studies indirectly suggest a possible link between food allergy (FA) and asthma. Most of them have evaluated the occurrence of FA in asthmatic children, especially in the first year of life, using questionnaire-based studies or specific IgE (sIgE) assay. The aim of this study was to evaluate the prevalence and clinical impact of IgE-mediated FA in school children with asthma using a double-blind placebo-controlled food challenge (DBPCFC). **Methods:** The study group consisted of school children with atopic asthma who were admitted to the Department of Pediatric Allergology, Gastroenterology and Nutrition, Medical University of Lodz, for the evaluation of food hypersensitivity. The diagnosis of FA was established using questionnaires, sIgE analysis, and the DBPCFC. Asthma severity and asthma control state were also assessed. **Results:** A relationship between consumed food and complaints was reported in 180 children (49.7%). Seventy children (19.3%) were sensitized to food allergens. IgE-mediated FA was confirmed in 24 children (6.6%), while 11 children (3%) demonstrated respiratory symptoms. Food-induced asthma exacerbations were observed in 9 patients (2.5%). Statistically significant differences in the prevalence of atopic dermatitis ($P<0.002$), urticaria ($P<0.03$), digestive symptoms ($P<0.03$), rhinitis ($P<0.02$), sIgE level ($P<0.001$), positive family history of atopy ($P<0.001$), and FA in history ($P<0.001$) were found between asthmatic children with FA and those without. Children with food-induced asthma exacerbations demonstrated significantly greater severity, poorer controls, and worse morbidity compared to those without. **Conclusions:** Although food-induced respiratory reactions in children with asthma were rare, they were classified as severe and associated with worse morbidity, greater severity, and poorer control. As the most commonly observed symptoms were coughing and rhinitis, which can be easily misdiagnosed, a proper diagnosis is essential for improving the management of both clinical conditions.

Key Words: Food allergy; asthma; children; double-blind placebo-controlled food challenge

INTRODUCTION

Epidemiological data indicates that asthma and food allergy (FA) are widespread, that their frequency of occurrence is increasing, and that a possible relationship might exist between them.[1-3] Accumulating evidence confirms a relationship between FA and the occurrence of asthma. Children are more likely to present with asthma if they also manifest FA.[4] Sensitization to food allergens in early childhood is a risk factor for sensitization to inhaled allergens and development of asthma in later life.[5-7] Sensitization to food allergens is more likely to occur in patients with asthma.[8] Asthma and bronchial hyperreactivity are observed significantly more often in patients with specific serum IgE (sIgE) to food allergens.[9] Wang *et al.*[10] reported that food allergen sensitivity may be a marker of asthma severity. Patients with asthma are 5 times more likely to report adverse reactions to food than the general population.[11-13] FA has been found to contribute to severe courses of asthma and frequent hospitalization,[14-16] and is a risk factor for unstable asthma.[8,17,18] Asthma, in turn, poses a serious hazard factor for severe allergic reactions to food.[19] Moreover, recent studies indicate that food sensitization must be assessed to fully understand inflammation patterns in

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asthma.[20]

However, no current studies objectively ascertain the prevalence of FA in patients with asthma. While it is known that FA can coexist with asthma, the impact of FA on its course has not yet been fully explained. It is estimated that 2% to 73% of asthmatic patients might be affected by food-induced exacerbations.[11,13,21-24]

Together with the growing incidence of allergic diseases, the difficulty in controlling asthma, the possibility of life-threatening exacerbations, and prolonged time of acquiring tolerance to food allergens, the above data represent a clear need for the role of food allergens to be identified in asthmatic children, not only in infancy but also in later life. Therefore, the aim of this study was to evaluate the prevalence and clinical impact of IgE-dependent FA in school children with asthma using a double-blind placebo-controlled food challenge (DBPCFC). Little has been published concerning this issue, and hence this study is the first of its kind to be conducted in Poland.

MATERIALS AND METHODS

Study subjects

Four hundred and thirty children with physician-diagnosed asthma between February 2007 and March 2012 were enrolled in the study. All were patients of the Department of Paediatric Allergology, Gastroenterology and Nutrition, Medical University of Lodz, and Allergology Outpatient Clinics. Inclusion criteria were as follows: age between 6 and 18 years, the presence of atopic asthma diagnosed according to the GINA criteria,[25] and ability to cooperate while performing spirometric examination. Asthma was diagnosed on the basis of symptoms (*i.e.* recurrent dyspnea, wheezing, cough, chest tightness, and shortness of breath), the results of the physical examination of the respiratory system, and a ≥12% improvement in forced expiratory volume in 1 second (FEV1) after administration of salbutamol (400 μg). Exclusion criteria were as follows: the presence of other diseases than FA that could increase the risk of asthma exacerbation or influence the procedure of the study, and inability to complete study procedures. Based on these criteria, 76 children (15%) were excluded from the study. Complete sets of data were gathered from the parents of 362 children. The design of the study is shown in Fig. 1, and the profile of the study groups is presented in Table 1.

Methods

The study was approved by the institutional ethics committee,

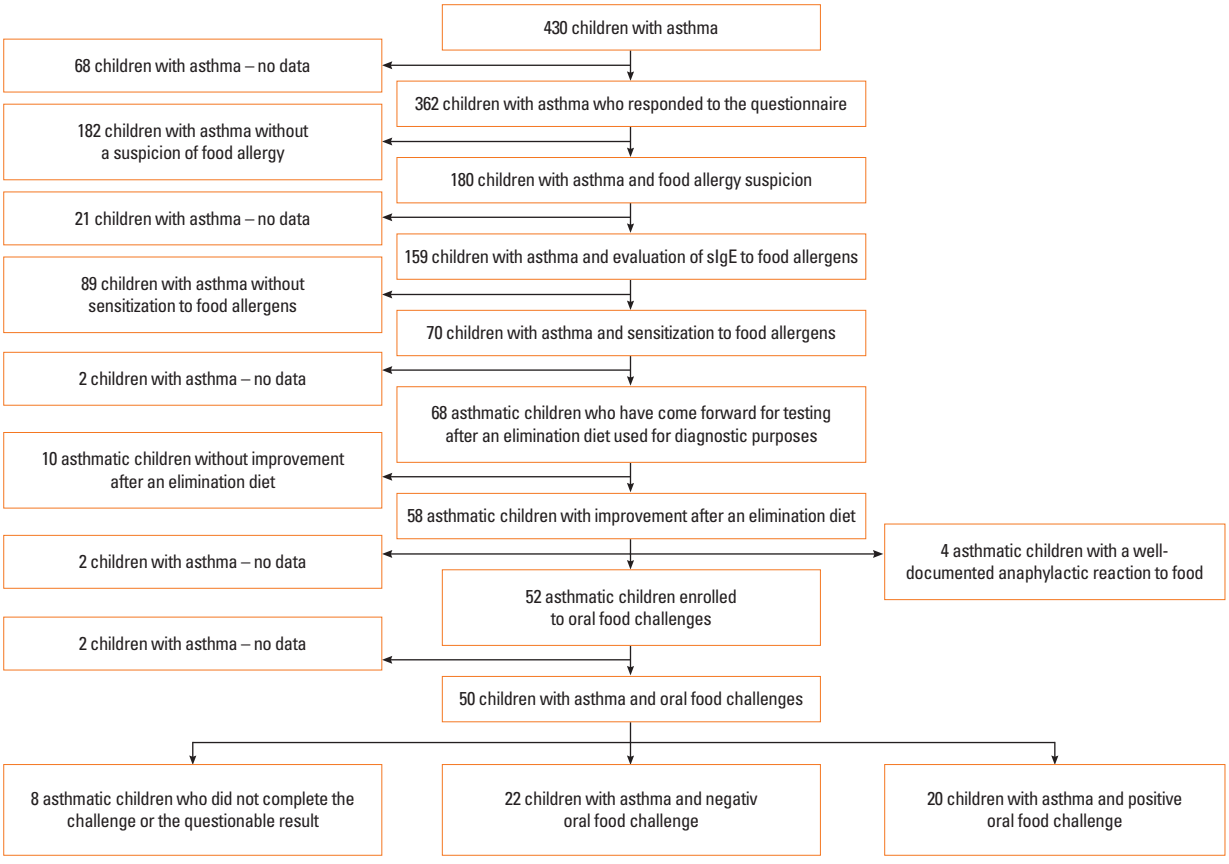

Fig. 1. Study design. Flow chart depicting steps involved in patient selection and tests in this study.

and informed consent was obtained before enrollment.

History

The subjects were screened for FA using a detailed questionnaire. The degree of asthma severity was evaluated using criteria recommended by GINA,[25] and the degree of control was assessed on the basis of the C-ACT and ACT control tests.[26,27] The patients were also evaluated for the markers of morbidity, such as the number of hospitalizations and courses of systemic steroids.

Table 1. Patient characteristics

Analyzed variable	Children with asthma	
	n	%
Number	362	100
Male sex	211	58.4
Age (year), mean±SD (min-max)	11.7±3.8 (6-18)	na
Age at onset of asthma (year), mean±SD (min-max)	5.2±4.1 (0.6-13.5)	na
Spirometric parameters (% predicted), mean±SD		
FEV1	94.5±21.9	na
FVC	99.7±19.3	
FEV1/FVC	85.8±9.2	
tIgE (IU/mL), mean±SD	568.4±225.7	na
Sensitization to:		
Mite	296	81.8
Pollen	199	54.9
Mould	119	32.8
Furry animal	76	20.9
Family history of atopy	133	36.7
History of food allergy	204	56.3
AD in the past	160	44.2
Current AD	95	26.2
Urticaria, rash	83	22.9
Vasomotor edema	31	17.2
Pruritus of skin	85	23.5
Itching, redness in mouth, throat	43	11.8
Rhinorrhea, sneezing, blocked nose	188	51.9
Anaphylaxis: light headedness, hypotension	2	0.5
Digestive symptoms recently:	137	37.8
Abdominal pain	115	31.8
Constipation	56	15.5
Diarrhoea	43	11.8
Vomiting, nausea	28	7.7
Bloating, belching	32	8.8
Asthma severity		
Mild	250	69
Moderate	110	30.4
Severe	2	0.6
Asthma control		
Controlled	137	37.9
Partially controlled	180	49.7
Non-controlled	45	12.4

SD, standard deviation; na, not applicable; AD, atopic dermatitis.

Pulmonary function tests

Flow-volume curves were obtained using a Lungtest 1000 spirometer (MES, Poland, Krakow). Subjects underwent 3 technically acceptable trials according to the ERS recommendations,[28] and the highest values for forced expiratory volume (FVC) and FEV1 were recorded.

Measurement of sIgE

The sIgE levels were measured using the UniCAP 100 (Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden). The detection level was 0.35 kU/L. The results were analyzed in 5 different allergen categories: mite (*Dermatophagoides pteronyssinus* and *D. farinae*), mold (*Alternaria alternata*/*Alternaria tenuis* and *Cladosporium herbarum*), furry animal (cat and dog), pollen (grasses, grain, trees, and weeds), and food allergens, such as hen's egg, cow's milk, wheat, fruits (apple and peach), vegetables (carrot, potato, celery, and tomato), peanuts, hazelnuts, and others (soy, shrimp, cod, and sesame).

Oral food challenges

Food challenges were carried out in patients showing a history of FA and elevated sIgE using the DBPCFC method. The trials were carried out in the hospital according to the recommendations of the EAACI/AAAAI.[29,30] Native forms of samples were applied. In the provocative procedures, the following food allergens were used: hen's egg, cow's milk, celery, and peanuts. Food challenge results were rated as negative, mild/moderate, or severe using a clinical reference table adapted from Sampson and Benhamou *et al.*[31,32] The test was considered positive when a patient manifested symptoms following provocation after a complaint-free period.

Statistical analysis

Arithmetic mean values, standard deviations, and ranges (min-max) were calculated for all parameters. The *F* test for equality of 2 variances (homoscedasticity) was used to compare mean values between the groups, followed by the test for 2 independent samples. The Shapiro-Wilk test was used to evaluate the distribution of variables. In the case of a distribution different from normal, the Mann-Whitney *U* test was used. The test of differences or, in the case of a non-normal distribution, the Wilcoxon paired difference test was applied to compare the mean values of a quantitative characteristic for the same group at 2 different time points. For non-measurable characteristics, the percentage of occurrence of particular categories was calculated. *P* levels less than 0.05 were considered statistically significant. The Statistica 10.0 package (Statsoft, Tulsa, OK, USA) was used for statistical analysis.

RESULTS

Evaluation of the prevalence of FA on the basis of history

Adverse reactions to food were reported by 180 children (49.7%). The type of "harmful food" was identified in 107 children (29.6%), these being chocolate in 56 children (15.5%), cow's milk in 42 children (11.6%), citrus fruit in 39 children (10.8%), hen's egg in 38 children (10.5%), strawberries in 34 children (9.4%), nuts in 29 children (8%), tomatoes in 27 children (7.5%), honey in 17 children (4.7%), gherkins in 11 children (3%), carrots in 5 children (1.4%), fish in 5 children (1.4%), potatoes in 1 child (0.3%), and other foods in 10 children (2.8%).

Reported symptoms that correlated with food consumption included skin lesions in 152 children (84.4%), digestive symptoms in 99 children (55%), angioedema in 23 children (12.8%), cough in 2 children (1.1%), and rhinitis in 1 child (0.6%), while 2 children (1.1%) demonstrated anaphylactic reactions (light headedness with hypotension). Although various complaints were reported, the connection between the complaints and food intake was not always realized. FA during infancy affected 204 children (56.3%) with asthma, and although an elimination diet was applied to 149 children (41.2%) in this period of life, it was actually used in 39 children (10.8%).

Results of sIgE

Seventy (19.3%) of the children studied were sensitized to at least 1 food allergen, with the sIgE level ranging from 0.35 to 100 kU/L. Ten children were sensitized to 1 allergen, 25 children to 2 allergens, 28 children to 3 allergens, and 7 children to more than 3 allergens. The highest mean sIgE levels were observed to hazelnuts, peanuts, hen's egg and wheat, while the lowest mean sIgE levels were observed to carrot and sesame (Table 2). Sensitization was observed to cow's milk in 25 asthmatic children (6.9%), to hen's egg in 31 asthmatic children (8.6%), to fruit in 29 asthmatic children (8%), to vegetables in 38 asthmatic children (10.5%), to wheat in 33 asthmatic children (9.1%), to hazelnuts in 21 asthmatic children (5.8%), to peanuts in 13 asthmatic children (3.6%), and to other foods in 19 asthmatic children (5.2%).

Evaluation of the prevalence of IgE–mediated FA on the basis of history, results of sIgE, and the DBPCFC

After analysis of the questionnaires and sIgE results, an elimination diet was introduced for diagnostic purposes in 70 chil-

Table 2. Prevalence and level of sensitization toward airborne and food allergens in asthmatic children

		Asthma (n=362)					
		Prevalence of allergen specific IgE		Level of allergen specific IgE (kU/L)			
		Number (%)	95% CI	Mean±SD	95%CI	Min-max	Geometrical mean
Aeroallergens	Mite	296 (81.8)	77.8-85.8	11.1±18.7	8.2-14.0	0.35-100	4.1
	Pollen	199 (54.9)	49.8-60.0	12.9±23.2	9.3-16.5	0.39-100	4.6
	Mould	119 (32.8)	28.0-37.6	21.6±29.1	17.1-16.1	0.7-100	9.4
	Furry animal	76 (20.9)	16.7-25.1	10±21.8	6.6-13.4	0.35-100	2.4
Food allergens	Hen's egg	31 (8.6)	5.7-11.5	21.6±34.9	16.2-27.0	0.35-100	4.6
	Cow's milk	25 (6.9)	4.3-9.5	4.3±6.3	3.3-5.3	0.36-28.9	2.03
	Wheat	33 (9.1)	6.1-12.1	9.02±21	5.8-12.3	0.35-100	2.4
	Fruits:	29 (8)	5.2-10.8	6.2±18.6	3.3-9.1	0.35-100	1.06
	Apple	20 (5.5)	3.2-7.8	8.4±22.1	5.0-11.8	0.36-100	2.1
	Peach	9 (2.5)	0.9-4.1	1.3±1.1	1.1-1.4	0.35-2.9	0.9
	Vegetables:	38 (10.5)	7.3-13.7	6.4±20.6	3.2-9.6	0.35-100	1.2
	Tomato	7 (1.9)	0.5-3.3	1.3±1.1	1.1-1.5	0.36-3.2	1
	Celery	15 (4.1)	2.1-6.1	13.5±31.9	8.5-18.5	0.36-100	2.05
	Carrot	7 (1.9)	0.5-3.3	0.9±1.1	0.7-1.1	0.35-3.4	0.6
	Potato	9 (2.5)	0.9-4.1	2.7±5.6	1.8-3.6	0.35-17.5	0.9
	Peanuts	13 (3.6)	1.7-5.5	23.6±40.7	17.3-29.9	0.36-100	2.6
	Hazelnuts	21 (5.8)	3.4-8.2	25.4±37.8	19.5-37.8	0.36-100	3.5
	Others:	19 (5.2)	2.9-7.5	1.1±0.8	1.0-1.2	0.36-3.5	0.8
	Cod	4 (1.1)	0.03-2.2	1.3±1.4	1.1-1.5	0.58-3.4	0.8
	Soy	8 (2.2)	0.7-3.7	0.8±0.5	0.7-0.9	0.38-1.9	0.7
	Sesame	7 (1.9)	0.5-3.3	1.4±1.3	1.2-1.6	0.36-3.5	0.9

CI, confidence interval.

dren with asthma and suspected FA. Fifty-eight children improved after the elimination diet was introduced. The presence of anaphylactic reactions to food was confirmed by convincing history and sIgE results in 4 children: light-headedness and hypotension in one pair, and urticaria, angioedema, and diarrhoea in the other. Finally, DBPCFC tests were performed on 50 children with asthma (Fig. 1). In total, 116 provocation tests were conducted: 67 tests with verum and 49 tests with a placebo (Table 3). Positive results of the oral provocation test were observed in 20 (5.5%) of the patients studied. An early reaction was noted in 14 children (70%), while 6 children (30%) displayed a mixed reaction. The DBPCFC results, including those of 4 children with a well-documented history of FA, are presented in Table 4. Digestive symptoms included oral pruritus, oral tingling, lip swelling, nausea, vomiting, and diarrhea; skin symptoms included flushing, urticaria, pruritus, angioedema, and exacerbation of atopic dermatitis (AD). Finally, the following respiratory symptoms were observed: nasal congestion, sneezing, rhinorrhea, throat tightness, cough, dyspnea, and wheezing. The most common symptoms observed during oral provocation tests involved the respiratory tract (36.6%) and skin (36.6%), while the least frequent symptoms involved the gastrointestinal tract (26.8%). Four of 11 children demonstrated respiratory symptoms after the OFC and manifested symptoms exclusively from the respiratory system, whereas in 7 children respiratory symptoms were accompanied by symptoms from the

Table 3. Results of oral food challenges

Oral provocation test	Children with asthma and oral food challenges			
	Positiv N=20	Negativ N=22	Ambiguous or incomplete N=8	Total N=50
Provocation with 1 allergen	9	16	6	31
Provocation with 2 allergens	11	6	1	18
Number of oral provocation tests	51	50	15	116
V	V 31	V 28	V 8	V 67
P	P 20	P 22	P 7	P 49
Number and kinds of oral provocation tests				
Milk	10	12	3	25
Positiv	5	0		
Negativ	5*	12		
Egg	16	12	3	31
Positiv	12†	0		
Negativ	4	12		
Peanut	4	4	1	9
Positiv	2‡	0		
Negativ	2	4		
Celery	1	0	1	2
Positiv	1§			
Negativ	0			

Food allergy was confirmed: *milk allergy in 5 children; †egg allergy in 12 children; ‡peanut allergy in 2 children; §celery allergy in 1 child.
V, verum; P, placebo.

Table 4. Symptoms of food allergy in this study

Food allergen	One organ system involved (n=10)			≥2 organ system involved (n=14)				Total n (%)
	Skin, n	Gastrointestinal, n	Respiratory, n	Skin +gastrointestinal, n	Gastrointestinal +respiratory, n	Skin +respiratory, n	Shock, n	
Cow's Milk	1	2	1	0	0	1	0	5 (20.8)
Hen's Egg	2	1	2	3	2	3	0	13 (54.1)
Peanut	0	0	1	1	0	1	1	4 (16.7)
Celery	0	0	0	1	0	0	0	1 (4.2)
Fish	0	0	0	0	0	0	1	1 (4.2)
Total n (%)	3 (12.5)	3 (12.6)	4 (16.7)	5 (20.8)	2 (8.3)	5 (20.8)	2 (8.3)	24 (100)

Table 5. Comparison of asthmatic children with and without IgE-mediated food allergy, including asthmatic children with IgE-mediated food allergy and with food-induced respiratory reactions

Analyzed variable	Children with asthma and IgE-mediated food allergy	Children with asthma and IgE-mediated food allergy		Children with asthma and without IgE-mediated food allergy	OR* (95% CI)	OR† (95% CI)
		with respiratory reactions	without respiratory reactions			
Number of patients	24	9	15	338		
Age (year), mean ± SD	9.5 ± 3.3	9.61 ± 3.1	9.48 ± 2.9	10.2 ± 3.2	na	na
Range	6-18	6-18	6-18	6-18		
Male sex, N (%)	15 (62.5)	5 (55.6)	10 (66.7)	192 (56.8)	na	na
Data from history:						
AD in the past, N (%)	18 (75)	7 (77.8)	11 (73.3)	142 (42.0)	4.14 (1.60-10.73)‡	4.58 (0.93-22.46)
CURRENT AD, N (%)	16 (66.7)	5 (55.6)	11 (73.3)	79 (23.4)	6.56 (2.70-15.94)‡	5.93 (1.45-24.33)§
Urticaria, rash, N (%)	10 (41.6)	4 (44.4)	6 (40)	73 (21.6	2.59 (1.10-6.10)§	2.77 (0.72-10.63)
Vasomotor edema, N (%)	3 (12.5)	0	3 (20)	28 (8.3)	1.79 (0.50-6.44)	-
Digestive symptoms N (%)	14 (58.3)	5 (55.6)	9 (60)	123 (36.4)	2.45 (1.05-5.69)§	2.09 (0.55-7.97)
Itching of the skin N (%)	16 (66.7)	5 (55.6)	11 (73.3)	69 (20.4)	7.80 (3.2-19.02)‡	4.27 (1.11-16.34)§
Rhinorrhea, sneezing, itchy, blocked nose N (%)	18 (75)	9 (100)	9 (60)	170 (50.3)	2.96 (1.14-7.68)§	-
Anaphylactic shock N (%)	2	0	2 (13.3)	0	-	-
FA in history N (%)	20 (83.3)	7 (77.8)	13 (86.7)	184 (54.4)	4.18 (1.4-12.55)§	2.77 (0.56-13.62)
Itching, redness in mouth and throat N (%)	7 (29.2)	2 (22.2)	5 (33.3)	36 (10.6)	3.45 (1.34-8.92)§	2.17 (0.43-10.87)
Family history of atopy N (%)	17 (77.3)	7 (77.8)	10 (66.7)	105 (31.1)	5.40 (2.16-13.43)‡	7.24 (1.47-35.68)§
FEV1 % predicted, mean ± SD	97.3 ± 19.1	96.9 ± 19.8	98.1 ± 18.9	99.9 ± 21.8	na	na
FVC % predicted, mean ± SD	93.9 ± 18.7	92.8 ± 17.9	94.2 ± 18.9	97.2 ± 17.9	na	na
FEV1/FVC, mean ± SD	0.847 ± 0.079	0.812 ± 0.085	0.851 ± 0.072	0.892 ± 0.081	na	na
tIgE (IU/ML) mean ± SD	742.2 ± 412.4	739.1 ± 389.3	745.3 ± 423.5	426.1 ± 313.5	na	na
sIgE (IU/ML) mean ± SD						
Cow's milk	13 ± 10.5	17.6	11.9 ± 11.7	1.25 ± 1.16	na	na
Hen's egg	48.8 ± 40.7	59.04 ± 42.8	42.3 ± 40.8	1.03 ± 0.89	na	na
Peanut	74.8 ± 39.9	91.5 ± 12.0	58.05 ± 59.32	0.87 ± 0.92	na	na
Asthma severity:						
Mild, N (%)	14 (58.3)	2 (22.2)	12 (80)	236 (69.8)	0.60 (0.26-1.41)	0.12 (0.02-0.60)§
Moderate, N (%)	9 (37.5)	6 (66.7)	3 (20)	101 (29.9)	1.41 (0.59-3.33)	4.79 (1.17-19.60)§
Severe, N (%)	1 (4.2)	1 (11.1)	0	1 (0.3)	14.6 (0.88-244.12)	44.0 (2.50-774.84)§
Asthma control:						
Controlled N (%)	7 (29.2)	2 (22.2)	5 (33.3)	130 (38.5)	0.66 (0.27-1.64)	0.46 (0.09-2.27)
Partially controlled N (%)	11 (45.8)	3 (33.3)	8 (53.3)	169 (50)	0.85 (0.37-1.95)	0.50 (0.12-2.03)
Non-controlled N (%)	6 (25)	4 (44.4)	2 (13.3)	39 (11.5)	2.56 (0.95-6.84)	6.09 (1.56-23.70)§
Emergency Department visit for asthma, past 12 months N (%)	9 (37.5)	7 (77.8)	2 (13.3)	135 (39.9)	0.84 (0.36-1.69)	5.52 (1.12-27.10)§
Hospitalization, lifetime N (%)	13 (54.2)	9 (100)	4 (26.7)	112 (36.1)	2.38 (1.04-5.51)§	-
Hospitalization, past 12 months N (%)	6 (25)	6 (66.7)	0	67 (19.8)	1.35 (0.51-3.54)	8.53 (2.07-35.18)‡
Hospitalization for asthma, past 12 months N (%)	5 (20.8)	5 (55.6)	0	32 (9.4)	2.52 (0.88-7.22)	12.54 (3.19-49.28)‡
Systemic corticosteroids treatment due to asthma N (%)	5 (20.8)	4 (44.4)	1 (6.7)	84 (24.9)	0.80 (0.29-2.20)	2.52 (0.66-9.65)
ICS treatment in the past 6 months N (%)	19 (79.2)	7 (77.8)	12 (80)	240 (71)	1.55 (0.56-4.29)	1.40 (0.29-6.90)

*Children with asthma and IgE-mediated food allergy vs children with asthma and without IgE-mediated food allergy; †Children with asthma and IgE-mediated food allergy with respiratory reactions vs children with asthma and without; IgE-mediated food allergy; ‡$P<0.01$; §$P<0.05$.

SD, standard deviation; AD, atopic dermatitis; FA, food allergy; FEV1, the forced expiratory volume in 1 second; FVC, the forced vital capacity; tIgE, total IgE; sIgE, specific IgE; OR, the odds ratio; ICS, inhaled corticosteroids; CI, confidence interval; na, not applicable.

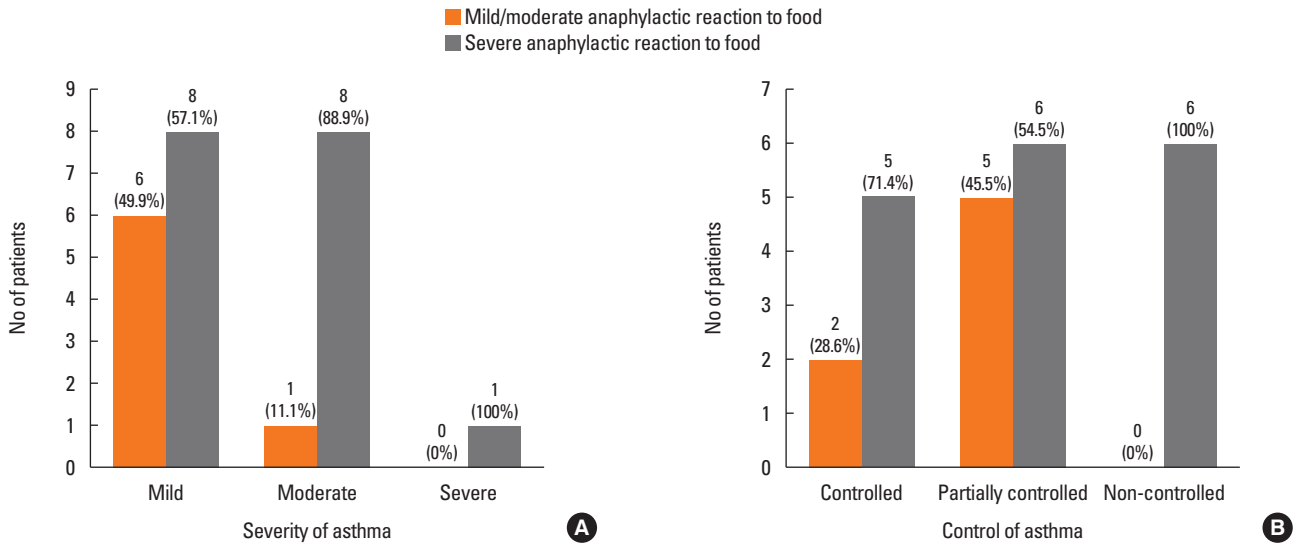

Fig. 2. Degrees of asthma severity (A) and control (B) in association with the degree of food reactions after the OFC in children with asthma and food allergy.

gastrointestinal tract or the skin. Respiratory symptoms included coughing in 6 children, wheezing in 2 children, dyspnea in 1 child, and nasal congestion, sneezing or rhinorrhea in 7 children. Asthma exacerbation as a consequence of food consumption was observed in 9 children (2.5%).

The allergens responsible for positive results from the challenge included the following: hen's egg in 12 children (3.3%), cow's milk in 5 children (1.4%), peanuts in 2 children (0.6%), and celery in 1 child (0.3%). The eliciting doses were 0.5-15 g for hen's egg (mean 5.2 g), 2-110 mL for cow's milk (mean 28.5 mL), 4.8 g for celery, and 0.0625-0.135 g for peanut.

Based on well-confirmed anaphylactic reactions in history, 4 children were excluded from the OFC. Therefore, IgE-mediated FA was confirmed in 24 children (6.6%) with asthma, which included 13 children (3.6%) who were allergic to hen's egg, 5 children (1.4%) to cow's milk, 4 children (1.1%) to peanuts, 1 child (0.3%) to celery, and 1 child (0.3%) to fish.

Seventeen children (70.8%) were found to display severe reactions following the OFC, while 7 children (29.2%) demonstrated mild/moderate reactions. In total, 36 reactions occurred in children with both asthma and confirmed FA. Seventeen reactions (47.2%) were classified as severe, 9 of these reactions being associated with the respiratory system. Another 19 reactions (52.8%) were mild/moderate, affecting mostly the skin (10 reactions) and gastrointestinal system (7 reactions).

The comparison of age, gender, prevalence of angioedema, mean FEV1, FVC, or FEV1/FVC value did not reveal any statistically significant differences between asthmatic children with IgE-mediated FA and those without (Table 5). However, there were significant differences in the prevalence of AD, urticaria, digestive symptoms, itching of the skin, rhinitis, swollen nose, sneezing, oral allergy syndrome (OAS), total and specific IgE level to food allergens, positive family history of atopy, and the presence of FA in anamnesis.

Although the risk of moderate or severe asthma, as well as partially controlled or non-controlled asthma, was greater in children with FA, these differences were not statistically significant. In addition, severe food reactions occurred mostly in children with moderate/severe or partially controlled or non-controlled asthma (Fig. 2), and asthmatic children with FA were more frequently hospitalized. Finally, significant differences in asthma severity, control, and morbidity were also found between children with food-induced respiratory reactions and those without.

DISCUSSION

Our findings indicate that almost half of the asthmatic children studied report food-related complaints. Similarly, other studies have found that 34% to 78% of asthmatic patients report food-related symptoms.[11,13,33,34] According to this study, the foods most commonly associated with patient complaints were those which are common in the area where the study was performed: chocolate, cow's milk, citrus fruit, hen's egg, and strawberries. Other studies have shown that fruit and vegetables (39.4%), seafood (23.2%), peanuts (14.8%), cow's milk (13.4%), hen's egg (10.6%), nuts (7%), and fish (7%) contribute the most to adverse reactions in school children.[4,35] The differences may have resulted from age, different tastes, and eating habits. Consumption of fruit, vegetables, fish, or seafood is not common in Poland, and particularly not in children.

The most common food-related symptoms reported in this study were, as noted by Caffarelli *et al.*,[36] skin lesions and digestive symptoms, with coughing and rhinitis being observed less

frequently. It is noteworthy that although complaints of the respiratory tract due to food consumption were only reported by 3 children, the DBPCFC results indicate that this problem affected 11 children, of which 9 had food-induced asthma exacerbations.

Sensitization to food allergens was observed in 19.3% of the children studied. Previous studies have indicated that the incidence of sensitization to food allergens in asthmatic children varies between 29.3% and 77%.[37-39] The lower sensitization rate noted in this study may be due to older age, less frequent occurrence, or the presence of another phenotype of FA in Poland.

The types of food allergens to which children were sensitized were similar to those observed in the general population, except for sensitization to fruit and vegetables which occurred more frequently in the children studied (8% and 10.5%) than in the general population (0.1%-4.3%).[40,41] A possible explanation for this is the occurrence of cross reactivity. In total, 54.9% of the asthmatic children examined in this study were sensitized to pollen. Children were most frequently sensitized to vegetables, wheat, hen's egg, and fruit, but rarely to cow's milk, hazelnuts, and peanuts. In contrast, Calamelli *et al.*[38] reported that the most frequent food allergens were wheat and peanuts, while Patelis *et al.* reported that they were fruit and hazelnuts.[20]

Although at least 50% of asthmatic children reported food-related symptoms and almost 20% were sensitized to food allergens, IgE-mediated FA was confirmed in only 6.6%. Previous studies have shown that the incidences of FA in asthmatic children range from 4% to 44%.[4,34,36-39] A high incidence of FA in certain studies may result from methodological differences in diagnosis: FA was diagnosed only on the basis of results of the history or sIgE levels above a 95% positive predictive value, while in our study FA was diagnosed on the basis of DBPCFC results.

The food types which most frequently provided positive results in the DBPCFC were hen's egg and cow's milk, followed by peanuts, celery, and fish. According to Rance and Dutau[34] or Calamelli *et al.*,[38] the most common food allergen was peanut, followed by hen's egg and cow's milk.[34,38] Thus, our findings do not significantly differ from those obtained by other European authors. However, they are different from those of studies conducted in different geographical regions, for example, India where rice, mung beans, citrus fruit, and bananas were confirmed as the most common food allergens.[37]

Two-thirds of children with both asthma and FA demonstrate symptoms from multiple organs after the DBPCFC: respiratory symptoms occur in 36.6% of asthmatic children with FA. Our results were similar to those obtained by Calamelli *et al.*[38] Rance *et al.*[34] observed skin symptoms in 59% of asthmatic patients with FA, respiratory symptoms in 23.9%, and gastrointestinal symptoms in 11.5%. However, while the study of Calamelli *et al.*[38] referred to IgE-mediated FA, that of Rance *et al.*[34] was independent of pathomechanism. It can thus be concluded that the higher frequency of skin symptoms observed by Rance *et al.*[34] may have resulted from the inclusion of patients with non-IgE-mediated allergy in the study.

In this study, respiratory symptoms induced by food allergens occurred in 3% of the asthmatic children, but asthmatic symptoms were observed only in 2.5%. It is estimated that 2% to 9% of children and adults with asthma have concomitant FA, which is responsible for provoking exacerbations in the respiratory system.[17,23] Rance *et al.*[34] and Calamelli *et al.*[38] observed food-induced asthma exacerbations in 2.8% and 5.8% of asthmatic children, respectively. Our findings confirm the aforementioned results of previous studies and indicate that food allergens are rarely responsible for clinically evident asthmatic symptoms resulting from food intake during oral challenges in asthmatic school children.[42] However, it is noteworthy that the majority of food reactions after the DBPCFC are classified as severe due to respiratory reactions.

Food-induced respiratory symptoms are usually accompanied by other complaints and occur in patients with a more severe course of the disease. Recent studies have demonstrated that children with food allergy and asthma are more likely to have near-fatal or fatal allergic reactions to food.[17,19,43,44] The small number of serious anaphylactic reactions encountered in this study may have resulted from the application of appropriate procedures, the small size of our subjects study, or daily consumption of allergenic food. Cow's milk and hen's egg were found to be most responsible for inducing allergic reactions, which are commonly consumed in Poland.

Unlike the results of a study by Graif *et al.*,[45] no significant differences in asthma severity were observed between children with and without FA. However, children with food-induced respiratory reactions were found to have significantly greater risk of more severe and non-controlled asthma than those without. Both the results of previous studies and ours showed that the risk of being hospitalized in children with asthma is greater if the patients are allergic to food, especially in those with food-induced respiratory reactions.[14,15,46] Asthma exacerbations provoked by food occur in children with worse morbidity.

This study has contributed to an objective determination of the prevalence and significance of FA in children with asthma. As a consequence, the diets of asthmatic children with confirmed FA were modified: 13 children were introduced to an elimination diet, and 28 children returned to their regular diet. Our study has some limitations. Provocation tests were performed only on children who had both asthma and suspected FA. We also excluded sIgE-negative patients for the oral provocation test. In addition, this study was based on a relatively small number of patients, some of whom were referred to the clinic with suspected FA.

Although food-induced respiratory reactions in children with asthma were rare, they were classified as severe and associated with worse morbidity, greater severity, and poorer control.

Since the most commonly observed symptoms were coughing and rhinitis, which can be easily misdiagnosed, a proper diagnosis is essential for improving the management of both clinical conditions.

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