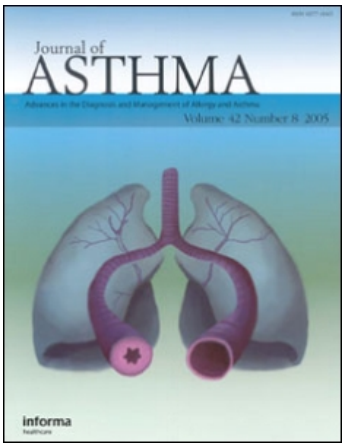

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Kostas N. Priftis [a]; Despina Mermiri [a]; Athina Papadopoulou [a]; Marios Papadopoulos [a]; Andrew Fretzayas [b]; Evagelia Lagona [c]
[a] Department of Allergy-Pneumonology, Penteli Children's Hospital, Athens, Greece [b] Third Department of Pediatrics, Attikon Hospital, Athens University Medical School, Athens, Greece [c] First Department of Pediatrics, "Aghia Sophia" Children's Hospital, Athens University Medical School, Athens, Greece

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ORIGINAL ARTICLE

Asthma Symptoms and Bronchial Reactivity in School Children Sensitized to Food Allergens in Infancy

KOSTAS N. PRIFTIS,[1] DESPINA MERMIRI,[1] ATHINA PAPADOPOULOU,[1] MARIOS PAPADOPOULOS,[1] ANDREW FRETZAYAS,[2] AND EVAGELIA LAGONA[3]

[1]*Department of Allergy-Pneumonology, Penteli Children's Hospital, Athens, Greece*
[2]*Third Department of Pediatrics, Attikon Hospital, Athens University Medical School, Athens, Greece*
[3]*First Department of Pediatrics, "Aghia Sophia" Children's Hospital, Athens University Medical School, Athens, Greece*

Food allergy in infancy usually disappears but is followed primarily by respiratory allergy. We hypothesized that children allergic to common food allergens in infancy are at increased risk of wheezing illness and bronchial hyperresponsiveness during school age. In a case-control study 69 children 7.2 to 13.3 years of age allergic to egg (N = 60) and/or fish (N = 29) in early life (first 3 years) who attended our allergy outpatient clinic were recruited. They received follow-up for 1 year and were evaluated by parental questionnaire, skin prick testing, spirometry, and metacholine bronchial challenge. Another 154 children (70 sensitized to inhaled allergens) recruited selectively from a general population sample with no history of food allergy during their first 3 years served as control subjects. Twenty-three children (38.3%) maintained their sensitization to egg and 19 (65.5%) to fish; the prevalence of sensitization to ≥1 inhaled allergen(s) increased from 59.4% to 71% during childhood. Current asthma symptoms were reported more frequently in the study group than in either control groups, sensitized to inhaled allergens and non-sensitized. Children of the study group showed a significantly increased frequency of positive response to metacholine bronchial challenge compared to the control group as a whole; the difference was statistically indicative when study groups separately were compared to the sensitized control subjects. Multivariate logistic regression analysis showed that bronchial hyperresponsiveness, as well as reported current asthma symptoms were associated with early wheezing and early sensitization to inhaled allergens but not with atopic dermatitis in infancy or persistence of egg or fish allergy. Children allergic to egg or fish in infancy are at increased risk for wheezing illness and hyperactive airways in school age; asthma and bronchial hyperresponsiveness development is mostly determined by wheezing and senzitization to inhaled allergens in early life regardless of atopic dermatitis in infancy or retention of food allergy.

Keywords allergic march, asthma, atopic dermatitis, bronchial hyperresponsiveness, food allergy, inhaled allergens

INTRODUCTION

During the last few decades, a worldwide phenomenon of increase in the prevalence of asthma in parallel to other allergic conditions such as food allergy, rhinitis, and eczema has been consistently observed (1, 2). Atopic dermatitis and food allergy often begin in infancy and there appears to be an onward trend that leads to asthma and allergic rhinitis in school age or early adulthood (3). Prevention strategies have mainly targeted the interruption of the allergic trend (4); therefore, knowledge of specific predictors in early infancy is a prerequisite if preventive intervention is being considered.

Sensitization to hen's egg in early life has been proposed as a predictor of subsequent sensitization to inhalant allergens that in itself constitutes a strong determinant of asthma (5, 6). Early onset of immunoglobulin (IgE)-mediated food allergy, especially if associated with atopic dermatitis, indicates a Th_2 dominant lymphocytic response pattern and a cytokine profile that facilitates an IgE response to environmental inhaled antigens; respiratory allergy is the consequence of the interaction between these inhaled allergens and high-risk genetic background (7).

Allergy to common food allergens, such as cow's milk, egg, and fish, begins predominantly before the second year of life demonstrating a clear temporal relationship with the introduction of these foods into the children's diet. Over time, most food allergy is lost, although the possibility of such loss depends on the individual child and the specific food allergen. In contrast to cow's milk and egg, allergies to fish are usually not outgrown (8). It is not clear if infants who present with food allergies with different natural history would tend differently to develop asthma at school age.

The mechanisms that predispose children with food allergy to develop asthma at a later age remain poorly understood. It is speculated that the immunologic basis of specific organ syndromes such as allergic rhinitis and asthma actually results from a systemic dysregulation of immunity (9, 10); eczema and at a later age hyperreactive airways could be manifestations of different target organs within the frame of the same systemic disease. Most studies that address this issue are observational and focus on the so-called "allergic march," i.e., the clinical expression of atopy that begins with eczema and sensitization to foods and evolves into asthma and allergic rhinitis in association with sensitization to airborne allergens (11). Few studies have focused on bronchial hyperresponsiveness (BHR) that does not always parallel the clinical expression of atopy and may remain latent (12, 13).

We hypothesized that children allergic to common food allergens in infancy are at increased risk of wheezing illness and BHR during school age; sensitization to food allergens with different natural histories may tend differently to develop asthma or hyperreactive airways at school age.

Corresponding author: Kostas N. Priftis, Allergy-Pneumonology Department, Penteli Children' Hospital, 152 36 P. Penteli, Greece; E-mail: kpriftis@otenet.gr

TABLE 1.—General characteristics of the study population (study group and two control groups).

	Study group N = 69	Sensitised controls N = 70	Non-sesnsitised controls N = 84
Male (%)	52 (75.4)	44 (62.8)	50 (59.5)
Median age, years (range)	9.9 (7.2–13.3)	10.3 (8.0–13.5)	10.0 (7.5–13.1)
Atopic family history (%)	41 (59.4)*	35 (50.0)¶	21 (25.0)
Passive smoking (%)	45 (65.2)	46 (65.7)	56 (66.7)
Central house heating (%)	59 (85.5)	56 (80.0)	67 (79.8)
Lifetime asthma symptoms (%)	38 (55.1)*#	20 (28.5)¶	9 (10.7)
Current asthma symptoms (%)	30 (43.5)*#	17 (24.3)¶	5 (5.9)
Lifetime chronic rhinitis (%)	27 (39.1)§	23 (32.8)	19 (22.6)
Current chronic rhinitis (%)	20 (29.0)§	21 (30.0)§	13 (15.5)
Lifetime atopic dermatitis (%)	38 (55.1)*#	20 (28.5)	13 (15.5)
Current atopic dermatitis (%)	7 (10.1)#	19 (27.1)	8 (9.5)

*In comparison to non-sensitised controls: $p < 0.001$.
#In comparison to sensitised controls: $p < 0.01$.
¶In comparison to non-sensitised controls: $p < 0.01$.
§In comparison to non-sensitised controls: $p < 0.05$.

PATIENTS AND METHODS

Study population

The present case-control study evaluated three groups of children (Table 1). The study group consisted of 69 school age children who presented to our outpatient allergy clinic during the first 3 years of life for a variety of symptoms from January 1995 until the end of 1998. The diagnosis of food allergy was based on a positive skin prick test (SPT) result or a positive serum-specific IgE test to hen's egg or/and fish (>0.35 IU/mL), a well-documented history of reaction to relevant food(s), and, in 13 cases, on immediate symptoms after open challenge with suspected food. Sixty children were allergic to hen's egg (egg white and yolk) and 29 to fish (20 were sensitized to both). Open food challenges were also performed when appropriate to investigate development of tolerance (14, 15).

Study inclusion criteria were (1) symptomatic sensitization to hen's egg and/or fish during the first 3 years of life, (2) age on recruitment over 7 years, and (3) ability to perform reproducible spirometry according to the standards of the American Thoracic Society (16). Children with diagnosed or suspected cystic fibrosis, primary ciliary dyskinesia, myoskeletal abnormalities, immunodeficiency, and history of bronchopulmonary dysplasia were excluded.

Study Design

Follow-up and review of patients and controls were performed between February 2003 and September 2005. A detailed medical and social history, physical examination, SPTs, spirometry, methacholine challenge test (MCT) when feasible, and parental questionnaire completion were performed for study purposes. The questionnaire included the International Study of Asthma and Allergies in Children (ISAAC) core questions on symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema and questions related to the outcome of food allergy, family history of atopy, tobacco exposure, and housing characteristics.

Spirometry was performed according to the standards of the American Thoracic Society (16). Flow-volume curves were obtained using a computerized pneumotachograph (Vicatest P2a, Mijnhardt). Forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and forced expiratory flow at 50% FVC (FEF_{50}) were recorded. Spirometry was deferred if the child had a respiratory tract infection within 3 weeks or had used a bronchodilator within 12 hours of assessment for study purposes. Values were expressed as percentage of predicted for gender and height (17).

Assessment of BHR was performed only when FEV_1 values were more than 70% of the predicted value. Children underwent MCT according to the American Thoracic Society guidelines (18). The short protocol of five tidal breaths was performed. The procedure was discontinued if FEV_1 decreased by more than 20% of baseline values or when a 16 mg/mL concentration had been administered. Asthma medication such as short- and long-acting $beta_2$-agonists, leukotriene modifiers, or chromones were withheld for 24 to 48 hours before testing; anti-histamines were also discontinued for an appropriate period depending on the pharmacokinetic characteristics of the various medications. Inhaled corticosteroids were continued as prescribed. Spirometry and MCT were performed during asymptomatic periods (a minimum of 6 weeks after resolution of any acute respiratory symptomatology), between 9 A.M. and 1 P.M.

Atopic status was assessed by skin-prick testing (SPT). They were performed on the volar aspects of the forearm with eight common standardized inhaled allergen extracts such as house dust mites (*Dermatophagoides pteronyssinus, Dermatophagoides farinae*), *Alternaria alternata*, olive tree, mixed grasses and *Parietaria officinalis* pollens, cat and dog dander; another battery of five common food standardized allergen extracts, i.e., cow's milk, hen's egg, mixed cereals, fish, and mixed nuts, was tested (SoluprickTM, ALK, Hørsholm, Denmark). Histamine dihydrochloride 10 $mg.mL^{-1}$ was used as the positive and 50% glycerol as the negative control. The prick tests were performed according to the instructions of the European Academy of Allergy and Clinical Immunology (EAACI) (19). Children were considered to be sensitized if a palpable wheal reaction to any allergen, calculated as the sum of the longest and the midpoint orthogonal diameters divided by two, was ≥3 mm larger than the negative control.

Children that belonged to the study group were followed prospectively by clinical assessment every 4 months for a year to establish their respiratory and skin manifestations; at the third visit all children were evaluated by SPTs and spirometry, whereas 57 out of 69 underwent MCT to assess BHR; 4 refused and 8 were unable to cooperate.

Subjects, matched for age and sex with the study group, with a negative history of food allergy in the first 3 years of life were selected from a general population sample of Athenian schoolchildren and assigned to two control groups. One consisted of 70 children sensitized to inhaled allergens regardless of any current sensitization to food allergens, and the other consisted of 84, none of whom were sensitized to any of the allergens tested. All control subjects underwent MCT.

Ethical approval was obtained from the ethics committee of Penteli Children's Hospital. The parents or guardians of each participating subject provided written informed consent to participate in the study.

Statistical analysis

All analyses were performed using the statistical software SPSS 13.1 (SPSS Inc., Chicago, IL). Chi square or Fisher's

TABLE 2.—Clinical characteristics of study group in the first 3 years of life; the OR (95% CI) refers to sensitized only to egg and only to fish subjects.

	Total N = 69*	Sensitised only to egg N = 40	Sensitised only to fish N = 9	OR (95% CI)
Mean age at diagnosis of sensitisation (mo)	20.6 ± 10.3	19.5 ± 10.5	21.2 ± 3.6	0.97 (0.89–1.05)
Mean age at first clinical presentation (mo)	10.7 ± 4.3	10.1 ± 5.2	12.4 ± 3.6	1.15 (0.97–1.37)
Presenting symptoms (%)				
Urticaria/anaphylaxis	46 (66.6)	29 (74.4)	7 (77.8)	0.77 (0.14–4.07)
Atopic dermatitis	30 (43.5)	16 (40.0)	2 (22.2)	0.48 (0.07–3.32)
Gastrointestinal symptoms	12 (17.3)	5 (12.5)	4 (44.4)	5.83 (1.0–33.77)¶
Respiratory distress	7 (10.3)	3 (7.5)	2 (22.2)	1.52 (0.11–20.76)
Sensitisation to other food allergens (%)	43 (62.3)	15 (37.5)	8 (88.9)¶	13.9 (1.48–131.17)
Milk	11 (15.9)	6 (15.0)	1 (11.1)	0.45 (0.02–8.34)
Nuts	16 (23.2)	4 (10.0)	6 (66.5)#	66 (3.89–1146.47)
Cereals	12 (17.4)	4 (10.0)	1 (11.1)	1.07 (0.08–13.41)
Shellfish	8 (11.6)	1 (2.5)	4 (44.4)#	43 (2.84–674.90)
Fruits	9 (13.0)	2 (5.0)	2 (22.2)	4 (0.32–42.83)
Vegetables	6 (8.7)	3 (7.5)	1 (11.1)	1.08 (0.07–15.65)
Sensitisation to inhaled allergens (%)	41(59.4)	20 (50.0)	4 (44.4)	0.81 (0.13–4.94)
Mites	18 (26.1)	8 (20.0)	0	NA
Molds	10 (14.5)	5 (12.5)	0	NA
Pollen	28 (40.5)	13 (32.5)	4 (44.4)	1.9 (0.26–14.82)
Pets	13 (18.8)	12 (30.0)	1 (11.1)	0.22 (0.02–2.74)

*20 cases were sensitized to both egg and fish protein; NA=non applicable.
¶$p < 0.05$; #$p < 0.01$.

exact test was performed for categorical variables; Student's *t* or Mann-Whitney U tests were suitable for continuous parametric and non-parametric variable. The characteristics of children of the primary study group, i.e., sensitized to hen's egg versus fish protein at presentation, were compared separately and odds ratios with 95% confidence interval (CI) were calculated. Logistic regression analysis was used to assess the independent effects of various risk factors (maternal smoking, atopic family history, wheezing in infancy, sensitization to inhaled or food allergens allergens, current or lifetime asthma symptoms, chronic rhinitis, and atopic dermatitis) on BHR. Significance was two tailed and set at $p \leq 0.05$.

RESULTS

The main characteristics of the study population (study group, controls) are presented in Table 1. Atopic family history, lifetime asthma symptoms, lifetime-current chronic rhinitis and lifetime atopic dermatitis reported by study group differed significantly from non-sensitized controls; current asthma symptoms were reported significantly more frequently in the study group than in either control groups. Current atopic dermatitis was found to be more frequent in sensitized *versus* study group and non-sensitized controls. Seventeen (56.7%) current asthmatics of study group and 4 (23.5%) of sensitized controls were on maintenance anti-asthma treatment (OR 0.23, 95%CI 0.06-0.89, $p = 0.04$).

The presenting symptoms were reactions to relevant food in 45 (65.2%) children of the study group. The clinical characteristics of the 69 children in the first 3 years of life are shown in Table 2. Sixty-two (89.8%) presented with skin manifestations (atopic dermatitis and/or urticaria) and 29 (42.0%) reported wheezing before 3 years of age, which was associated to sensitization to inhaled allergens by that time ($p = 0.001$).

At school age, 38 (63.3%) cases had developed tolerance to egg and were able to consume it freely; the one child that retained positive SPT for egg was also able to consume it freely as well. The median age of egg tolerance was 2.1 (1.0-7.4) years. Ten out of 29 (34.5%) children lost their sensitization to fish but only 5 (17.2%) of these children developed tolerance; however, tolerance to fish occurred at a significantly older age as compared to egg, i.e., 5.0 (2.5–8.2) years ($p = 0.004$).

The prevalence of sensitization to inhaled and food allergens during school age in the study group and sensitized controls is shown in Table 3. Sensitization to molds was detected

TABLE 3.—Sensitization to inhaled and/or food allergens at school-age in study group and sensitized controls.

	Study group				Sensitised controls	
	Sensitized only to egg N = 40	Sensitized only to fish N = 9	OR (95% CI)	Total N = 69*	N = 70	OR (95% CI)
Inhaled allergens (%)	28 (70.0)	5 (55.6)	0.46 (0.08–2.48)	49 (71.0)	70 (100)	
Mites	10 (25.0)	0	NA	18 (26.1)	31 (44.3)	2.31 (0.96–4.22)
Molds	11 (27.5)	2 (22.2)	0.63 (0.08–4.72)	24 (34.8)#	7 (10.0)	0.23 (0.07–0.51)
Pollen	24 (60.0)	4 (44.4)	0.69 (0.12–3.91)	39 (56.5)	47 (67.1)	1.50 (0.73–3.45)
Pets	6 (15.0)	3 (33.3)	8.69 (0.72–95)	11(15.9)	21 (30.0)	2.06 (0.88–4.76)
Food allergens (%)	40 (100)	9 (100)	NA	69 (100)	0	NA
Milk	2 (5.0)	0	NA	4 (5.7)	0	NA
Egg	13 (32.5)	0	NA	23 (33.3)	0	NA
Mixed cereals	4 (10.0)	1 (11.1)	0.96 (0.14–26.8)	9 (13.0)	0	NA
Fish	0	9 (100)	NA	19 (65.5)	0	NA
Mixed nuts	9 (22.5)	6 (66.6)	8.0 (1.47–43.6)	20 (29.0)	3 (4.2)	0.10 (0.02–0.37)#

*20 cases were sensitised to both egg and fish; #p =0.001; ¶$p = 0.01$; NA = non applicable.

TABLE 4.—Spirometry (mean ± SD) and BHR in the three groups of the study.

	Study group N = 69*	Sensitised controls N = 70	Non-sensitised controls N = 84
FVC (% predicted)	94.5 ± 8.2	96.2 ± 9.1	99 ± 6.6
FEV_1 (% predicted)	98.4 ± 8.3	99.3 ± 7.2	97.7 ± 7.1
FEF_{50} (% predicted)	87.7 ± 16.9	75.9 ± 16.5	83 ± 10.6
Positive metacholine challenge test (%)	31 (54.4)#	28 (40.0)#	8 (9.5)

*Methacholine bronchial challenge test performed in 57 out of 69 children.

¶ In comparison to either study group or non-sensitized controls: $p < 0.01$.

#In comparison to non-sensitized controls: $p < 0.001$.

more frequently in the study group than among sensitized controls.

All children of the study group exhibited normal pulmonary function tests (Table 4). A significant decrease of MEF_{50} values was detected among controls sensitized to inhaled allergens as compared to the study group. Multivariate analysis of spirometric indices and specific sensitization revealed an independent association of sensitisation to mites with MEF_{50} values (OR: 0.97, 95%CI: 0.95-1.0, $p = 0.04$).

Study group showed a significantly increased frequency of positive response to MCT when compared with the controls as a whole (OR: 0.26, 95%CI: 0.13-0.49, $p < 0.001$); the difference was statistically insignificant when study groups separately were compared with the sensitized control subjects (OR: 0.56, 95%CI: 0.28–1.12, $p = 0.07$).

The results of multivariate logistic regression analysis between BHR and current asthma symptoms (dependent variables) in the index case group and relevant clinical characteristics of children during infancy and school age (independent variables) are presented in Table 5. BHR was associated with wheezing and sensitization to perennial allergens (mites, molds) in infancy as well as in school age; it was also associated with early sensitization to inhaled allergens (OR: 13.24, 95%CI: 1.76-85.20, $p < 0.01$). There was no association to anaphylaxis at presentation, persistence of sensitization to egg/fish or development of tolerance.

TABLE 5.—Multivariate logistic regression analysis (95% CI) between BHR and current asthma (dependent variables) and various characteristics of study group (independent variables).

Variables	BHR OR (95% CI)	Current asthma OR (95% CI)
Atopy family history	2.52 (0.34–21.47)	3.05 (0.57–15.89)
Passive smoking	0.21 (0.02–2.06)	2.86 (0.50–16.12)
Urticaria/anaphylaxis in infancy	0.65 (0.19–2.25)	0.40 (0.07–2.37)
Atopic dermatitis in infancy	1.57 (0.50–4.88)	2.10 (0.43–10.6)
Gastrointestinal manifestations in infancy	2.2 (0.50–0.56)	1.2 (0.28–5.7)
Wheezing in infancy	12 (1.40–103.63)*	15.18 (2.62–94.23)#
Current eczema	2.23 (0.11–44.37)	1.47 (0.11–19.35)
Current rhinitis	0.45 (0.04–4.33)	2.09 (0.44–9.83)
Lifetime asthma symptoms	0.41 (0.01–9.92)	23.27 (2.35–241.62)#
Current asthma symptoms	51.42 (2.34–1105.31)*	NA
Sensitization to perennial in infancy	13.3 (2.9–59.8)#	12.5 (2.6–60.2)#
Sensitization to pollen in infancy	3.0 (0.77–12.08)	7.2 (1.44–36.4)*
Sensitization to pets in infancy	0.51 (0.11–2.32)	0.50(0.10–2.56)
Current sensitization to perennial	15 (1.59–141.92)*	4.30 (0.66–28.19)
Current sensitization to pollen	0.61 (0.13–2.74)	1.55 (0.26–9.42)
Current sensitization to pets	0.83 (0.12–6.35)	1.22 (0.13–11.41)
Current sensitization to hen's egg	0.48 (0.07–3.21)	1.67 (0.16–16.56)
Current sensitization to fish	0.28 (0.07–1.15)	0.39 (0.10–1.52)

NA: non-applicable, * $p < 0.05$, # $p < 0.01$.

DISCUSSION

The present case control study of infants allergic to egg and/or fish followed to school age demonstrates that they are at increased risk of wheezing illness and BHR at school age. Diagnosis of childhood asthma and airway hyperreactivity is associated with early sensitization to inhaled allergens and late sensitization to mites and molds; conversely, they are not associated with atopic dermatitis of infancy or retention of food allergy into school age.

Our results confirm the transient character of egg allergy and are in agreement with the findings of others that sensitization to hen's egg in infancy is a marker of increased risk of sensitization to inhaled allergens and asthma symptoms later in life (6, 20). In the Isle of Wight birth cohort study, allergy to egg, whether during infancy or cumulative, correlated with respiratory allergic symptoms (asthma and/or rhinitis) and sensitization to aero-allergens at 4 years of age (6). In the German Multicenter Allergy Study (MAS) children with a long-lasting sensitization to food allergens developed allergic rhinitis or allergic asthma more often than children only transiently or never sensitized to food (20). In contrast to MAS we found that asthma symptoms as well as BHR were not associated with retention of egg or fish allergy. This difference could be due to methodological issues; the MAS study investigated sensitized children regardless of clinical expression and did not differentiate in its analysis between the various food allergens; thus its findings do not take into account differences in the natural history of allergic disease caused by different food allergens. However, these reports (6, 20) did not include follow-up into school age. It is of interest that when the MAS cohort was reviewed at 7 years of age, children with early atopic dermatitis and concomitant wheeze carried an almost threefold higher risk of having current wheeze; this effect was independent of concurrent sensitization to egg or milk (21).

According to our findings the prevalence of current asthma symptoms as well as BHR was higher in the index case group as compared to the control group; the difference in BHR did not reach significance when compared to controls sensitized to inhaled allergens, but there was an apparent trend towards higher prevalence in study group. However, control group as a whole is a general population sample with a negative history of food allergy in the first 3 years of life, enriched with children sensitized to inhaled allergens. Therefore, food allergy in early life predisposes to the development of asthma symptoms and BHR at school age. Such natural history was primarily found to be associated with early sensitization to inhaled allergens and early wheezing rather than early life food allergy. Based on a similar observation Illi et al. (21) suggested the existence of a phenotype incorporating early atopic dermatitis and concomitant wheeze. It appears that the so called "allergic march" is a matter of complex gene-environment interactions, and antenatal and early life

exposures to environmental factors are more likely to have a greater impact on the immature immune system and airways and the subsequent development of disease (22). Initial assault may be sensitization to food allergens, clinical manifestation of atopic dermatitis, wheezing illness, or even sensitization to inhaled allergens.

The earliest serologic marker for atopic immunoreactivity in infancy is the presence of IgE antibodies to egg, followed by milk (8), with an estimated point prevalence of allergy to egg of 1.6% in children 2.5 years of age (23). In a British population-based birth cohort study (ALSPAC) 0.4% of children skin prick tested at approximately 7.5 years were positive to egg (24). A strong association between sensitization to egg and sensitization to aeroallergens, such as grass or tree pollen and mites, was found in the ALSPAC study; unfortunately, no information on the clinical presentation of sensitized children was reported (24).

We found that development of BHR in symptomatic infants allergic to egg and/or fish in infancy is not associated with atopic dermatitis either in infancy or in school age. Most studies use the outcome of atopic dermatitis as the "entry point" of subsequent allergic disease that is often accompanied by food allergy (3, 11, 21, 25). However, there are data that support the hypothesis of two or more variants of eczema that carry different prognoses and disease associations (26–29). Our finding of an association between BHR and sensitization to inhaled allergens but not to atopic dermatitis supports this hypothesis. It seems that a genetic background that facilitates a specific immune response constitutes the main drive that determines the manifestations of the allergic march (11); this genetic background may not be present in all cases of the "atopic eczema/dermatitis syndrome."

We found different patterns in the natural history of egg as compared to fish allergy; however, sensitization to hen's egg or fish at school age did not constitute independent risk factors of BHR or current asthma symptoms in school age (Table 5). Specific sensitization to food depends on the specific allergen characteristics, degree of utilize, and host characteristics (30). Conversely, while the development of BHR is also related to exposure, adjuvant factors, and host characteristics (31, 32), our results suggest that it most likely is unrelated to the natural history of food allergy.

Lung function measurements revealed lower air flows at mid-FVC of controls sensitized to inhaled allergens as compared to the study group and non-sensitized controls; this could be the result of inhaled maintenance treatment of symptomatic children. Sensitization to mites was associated with lower FEF_{50} values. A negative association between FEV_1 or FEF_{50} and sensitization to house dust mite has been reported previously (33).

Although children of the study group were derived from a tertiary care allergy center, selection bias is not an issue as this is not a study of prevalence of sensitization but rather one examining the natural history of food allergy and the sequence of clinical signs of atopic disease. A potential limitation may be the fact that assessment of tolerance to egg or fish was based on open or single-blind and not double-blind placebo-controlled food challenges. We performed all of the challenges for clinical purposes; nevertheless, most of them were performed before 3 years of when double-blind, placebo-controlled food challenges are not indicated (14, 15). A negative history of food allergy by 3 years of age in control groups may be subject to recall bias. To minimize this possibility parents were interviewed personally by one of the study's physicians (A.P.); despite this limitation, the low prevalence of food allergy in the general population (34) makes it highly likely that such bias only minimally affected our results. Lastly, we recognize that a small number of children exclusively allergic to fish represent a limitation of the study but we were not able to obtain more cases monosensitized to fish up to 3 years of age.

In conclusion, the findings of our study show that children who had egg or fish allergy in infancy have an increased risk for asthma symptoms and hyperreactive airways in school age as compared to their non-allergic peers. Late wheezing or BHR is mostly determined by wheezing and sensitization to inhaled allergens in early life and is not associated with the manifestation of atopic dermatitis in infancy or persistence of egg or fish allergy until school age.

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