

Sensitization (IgE antibody) to food allergens in wheezing infants and children

G. Weyman Price, MD,^{a, b} Angela D. Hogan, MD,^c A. Holly Farris, BA,^a
A. Wesley Burks, MD,^c Thomas A. E. Platts-Mills, MD, PhD,^b and
Peter W. Heymann, MD^a Charlottesville, Va., and Little Rock, Ark.

Abbreviations used

AD: Atopic dermatitis
RSV: Respiratory syncytial virus

Immediate hypersensitivity to food allergens in children develops early in life and is most often associated with symptoms of atopic dermatitis (AD).^{1, 2} However, the relationship between IgE-mediated food hypersensitivity and symptoms of wheezing in young children is not well defined, and there are few guidelines about the use of tests for food sensitization in evaluating these children. In a recent study we reported the prevalence of viral infections, IgE antibody to inhaled allergens, and exposure to tobacco smoke in children treated for acute attacks of wheezing in an emergency department.³ The aim of this study was to assess the prevalence of IgE antibodies to common food allergens in the same nonselected population.

METHODS

Subjects

The study population included 163 children who were seen in the University of Virginia Pediatric Emergency Department. Ninety-seven children were given a diagnosis of bronchiolitis or asthma (ages 2 months to 16 years) and were treated with at least a β_2 -agonist. Sixty-six patients (ages 6 months to 16 years) with no symptoms of respiratory tract infection

and no previous history of wheezing were enrolled as control subjects. In addition, 60 children (ages 6 months to 13 years) who were seen in the dermatology clinic because of moderate to severe AD were included in this analysis. The diagnosis of AD was made on the basis of criteria established by Hanifin and Rajka.⁴ The study was approved by the human investigation committee at the University of Virginia, and informed written consent was obtained from patients or their parents.

Immunoassays

Sera from patients were analyzed for IgE antibodies to egg white, cow's milk, soy, and peanut allergens. In keeping with other reports, positive skin test responses to one or more of these foods are observed in more than 90% of children judged to have food allergy in our clinic.⁴ Starting materials for the preparation of extracts included crude dried egg white (Sigma Chemical Co., St. Louis, Mo.), β -lactoglobulins A and B (Sigma), isolated soy proteins (Ralston-Purina, St. Louis, Mo.), and peanut proteins (defatted Florunner variety). IgE antibodies were measured by RAST as previously described.³ The concordances between the results of RAST assays and skin tests in 52 patients from our clinic with positive skin prick test results were 89%, 82%, 86%, and 85% for egg, milk, soy, and peanut, respectively. Sera from eight patients who had negative skin test responses and two patients who had positive skin test responses to the allergen tested served as controls in each assay. All sera (diluted 1:4) were assayed in duplicate, and sera from patients with high total IgE levels were diluted further so that the total IgE level was less than 1000 IU/ml. In addition, two sera with elevated total IgE, but without specific IgE antibodies to the food allergens tested, were included in each assay. Measurements of total serum IgE were performed by ELISA as described previously.³

Statistical analysis

To compare differences between the percentages of wheezing patients, control subjects, and patients with AD who had positive RAST responses to food, chi square analyses were used. When samples were small, we relied on Fisher's exact test. Continuous responses were compared with two-sample *t* tests. All hypothesis testing was based on two-sided tests of significance.

From ^aDepartment of Pediatrics, University of Virginia Health Sciences Center; ^bDepartment of Internal Medicine, University of Virginia Health Sciences Center; and ^cDepartment of Pediatrics, University of Arkansas for Medical Sciences.

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Reprint requests: Peter W. Heymann, MD, Department of Pediatrics, Building MR-4, Room 5061, University of Virginia Health Sciences Center, Charlottesville, VA 22908.

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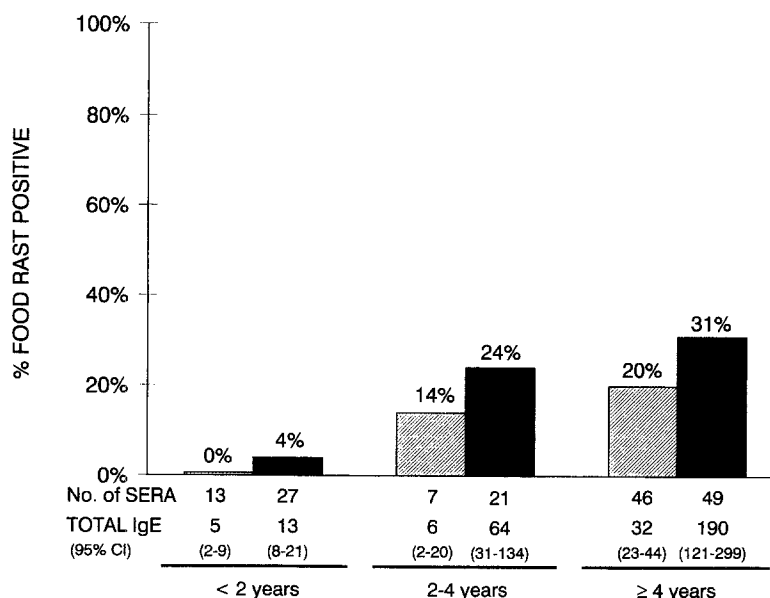


FIG. 1. The percentage of sera with positive test responses to one or more food allergens (i.e., food RAST positive) are shown for wheezing patients (black bars) and control subjects (hatched bars). The geometric mean of total IgE is reported for each group in international units per milliliter. The 95% confidence intervals are noted underneath in parentheses.

RESULTS

Only one wheezing patient (4%) and no control subjects under the age of 2 years had specific IgE antibodies to the food allergens tested (Fig. 1). Total IgE levels in the majority of these children were also low. After the age of 2 years, the percentage of sera that showed positive RAST responses to one or more food allergens increased; however, the percentages of RAST-positive sera from wheezing patients and control subjects were not significantly different. In contrast, geometric mean levels of total IgE were significantly higher among wheezing patients compared with control subjects for children ages 2 to 4 years ($p < 0.05$) and for children over the age of 4 years ($p < 0.001$). Among the children with AD, the prevalence of food sensitization under the age of 2 years was very high (84%) and remained significantly higher in the patients with AD than in wheezing patients and control subjects who were over the age of 2 years (Table I). In addition, the titers of antibody to individual food allergens (except those to milk) were significantly higher in sera from patients with AD than in sera from wheezing patients for egg, soy, and peanut ($p < 0.001$), whereas the titers measured in sera from wheezing patients and control subjects were very similar (Fig. 2).

Measurements of IgE antibodies to five inhalant allergens (mite, cat, cockroach, ryegrass, and ragweed) were reported for both the wheezing and

control patients in a previous study.³ Positive RAST responses to food and inhalant allergens are summarized for wheezing patients in Table II. Most wheezing children under the age of 2 years lacked IgE antibodies to both food and inhalant allergens. Among children ages 2 to 4 years, 43% were sensitized to food, inhalant allergens, or both. The percentage of wheezing children with IgE antibodies to food allergens in this age group was approximately the same as the percentage with IgE antibodies to inhalant allergens (24% and 29%, respectively). In addition, one third of the children with positive RAST results were only sensitized to foods. After the age of 4 years, the percentage of wheezing children with positive RAST responses to food allergens did not increase significantly. In contrast, the prevalence of aeroallergen sensitization (69%) did increase substantially compared with the prevalence observed in wheezing children ages 2 to 4 years ($p < 0.05$).

DISCUSSION

This is the first report of the prevalence of sensitization (IgE antibodies) to common food allergens in a nonselected population of wheezing children. In this study the prevalence of IgE antibodies to food allergens was low among children treated for wheezing before the age of 2 years. Although RASTs can be less sensitive

TABLE I. Patient characteristics

	Children <2 yr			Children ≥2 yr		
	Wheezing	Control	AD	Wheezing	Control	AD
No. of patients	27	13	19	70	53	40
Mean age (yr)	0.9	1.2	1.1	7.0	9.9	5.6
Age range	0.3-1.8	0.5-1.8	0.5-1.9	2.0-15.4	2.3-16.1	2.0-13.0
Male (%)	56	27	84	66	64	52
Race: Black (%)	67	45	53	51	33	53
Family history (%) [*]	56	82	88	83	47	94
Total IgE (IU/ml) [†]	15	4	109	166	27	541
95% CI	9-26	2-10	47-253	110-251	18-42	288-912
Food RAST positive [‡]	4%	0%	84%	28%	19%	68%

CI, Confidence interval.

^{*}After the age of 2 years, the prevalence of a positive history for asthma, allergic rhinitis, and eczema in the immediate family (patients and siblings) was significantly increased in both wheezing patients and patients with AD compared with control subjects ($p < 0.001$ and $p < 0.001$, respectively).

[†]Total IgE levels are expressed as geometric means, and the 95% confidence intervals for total IgE are noted underneath.

[‡]Serum IgE antibodies to egg, milk, soy, and peanut allergens were measured by RAST. Shown for each group are the percentage of sera testing positive to one or more of these allergens. The percentage of food RAST positive sera was significantly higher in patients with AD than in wheezing patients ($p < 0.001$) or in control subjects ($p < 0.001$) both under and over the age of 2 years.

than skin tests, it is likely that this finding reflects a low rate of atopy in this group. Collectively, these children also had low total IgE levels, a low prevalence of IgE antibodies to inhaled allergens, and a high rate of viral infection, especially respiratory syncytial virus (RSV).³ None of the infants had eczema. Two other investigations of infantile wheezing did include children with eczema.^{5,6} These studies concluded that children with bronchiolitis may have an increased risk for subsequent wheezing and atopy. This may not be surprising because young children with moderate to severe AD are frequently atopic and have been shown to have an increased risk for the development of allergic respiratory symptoms as they grow older.^{7,8} In keeping with this, the patients with AD who were older than 2 years in our study were previously observed to have a high prevalence of sensitization to aeroallergens, and 48% had a history of asthma.⁹

In agreement with our results, others have reported that atopy is not strongly associated with episodes of wheezing during early childhood.^{10,11} In addition, the majority of infants who wheeze are likely to outgrow their symptoms and do not develop asthma. Nevertheless, some of these infants (possibly up to 40%) may continue to wheeze as they grow older.¹¹ The process of identifying those who are at risk for subsequent wheezing, however, is still a problem. With respect to allergic mechanisms, IgE antibodies to viral antigens have been reported in nasopharyngeal secretions from

hospitalized children with RSV bronchiolitis.¹² When followed up prospectively, the infants with the highest titers of IgE to RSV continued to have recurrent episodes of wheezing.¹³ Others have shown that infants sensitized to food allergens may also have an increased risk for the development of allergic respiratory disease, even if they do not have eczema.¹⁴ In our study an increased prevalence of food sensitization was not observed among wheezing children until after age 2 years. Among wheezing children ages 2 to 4 years with positive RAST results, one third had IgE antibodies only to food allergens. At this age, it is possible that tests for food sensitization may enhance efforts to identify children with an allergic predisposition. Prospective studies will be needed to learn whether these children will develop IgE antibodies to aeroallergens and whether they will continue to have problems with wheezing. After the age of 4 years, most wheezing children had positive test results for inhalant allergens. Few had IgE antibodies to foods alone. In addition, the prevalence of food sensitization and titers of IgE antibodies to individual food allergens were not significantly different in the wheezing patients and control subjects. These results support recommendations that the evaluation of food hypersensitivity in older children with asthma should focus primarily on those who have a history of AD or food-induced wheezing.¹⁵

In conclusion, when results of tests for food sensitization are positive at any age, further evaluation

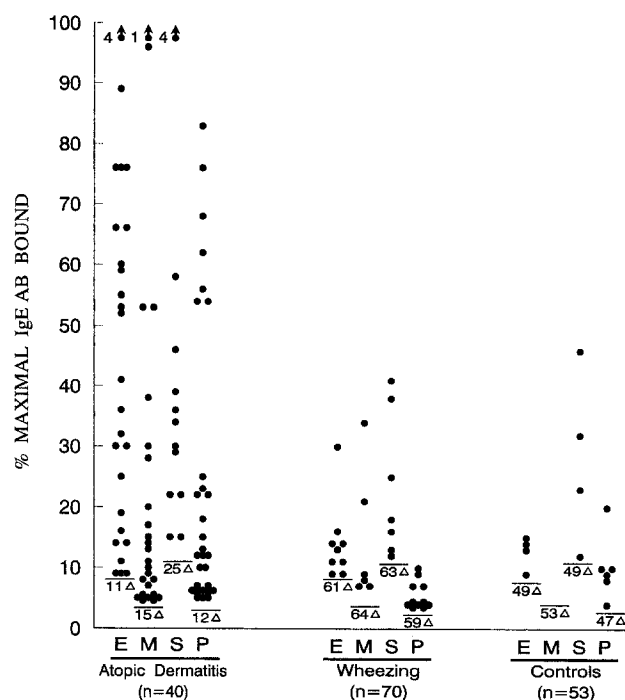


FIG. 2. Titers of IgE antibodies to egg (E), milk (M), soy (S), and peanut (P) were measured by RAST. The results in sera from patients with AD, wheezing patients, and control subjects are compared for children age 2 years and older. The titers are expressed as a percent of maximal counts bound of radiolabeled goat anti-human IgE by using a control curve established for each allergen. Solid circles (●) represent sera that were positive for IgE antibodies to each allergen. Numbers below the solid lines followed by an open triangle (Δ) represent the number of sera that tested below the sensitivity for each assay. Geometric means of IgE antibody titers to egg, milk, soy, and peanut allergens from patients with AD who had positive RAST results were 37%, 13%, 44%, and 16%, respectively. These values are significantly higher ($p < 0.001$) than the geometric mean of titers from wheezing patients for egg (13%), soy (20%), and peanut (5%), but not for milk (12%). The geometric means of titers from wheezing patients, however, were not significantly different from the values for control subjects, which were 13%, 25%, and 9% for egg, soy, and peanut, respectively ($p = \text{NS}$).

TABLE II. RAST responses to food and inhalant allergens in wheezing children

Sera with IgE antibodies to one or more:	Age <2 yr (n = 27)		Age 2-4 yr (n = 21)		Age ≥4 yr (n = 49)	
	Positive sera*	Total IgE†	Positive sera*	Total IgE†	Positive sera*	Total IgE†
Food allergens	1 (4%)	59	5 (24%)	140	15 (31%)	217
Inhalant allergens	2 (7%)	102	6 (29%)	155	29 (59%)	338
Any allergen	2 (7%)	102	9 (43%)	149	34 (69%)	259

*Sera from 97 wheezing patients were available for measurements of IgE antibodies to both food and inhalant allergens by RAST. The number of sera containing IgE antibodies to one or more food allergens, one or more inhalant allergens, or to any allergen tested (food or inhalant) are shown. In addition, the percentage of sera that were RAST-positive in each group are shown in parentheses.

†Total serum IgE levels are reported as geometric means in international units per milliliter.

(e.g., food challenge studies) is often needed to assess their clinical significance. The purpose of this study, however, was to determine whether tests for food sensitization would further our understanding about the relationship between early childhood wheezing

and atopy. The results showed that the prevalence of IgE antibodies to foods was low among wheezing children under the age of 2 years. However, there are subgroups of wheezing infants (e.g., infants who experience recurrent attacks of wheezing, who re-

quire hospitalization, and who have a history of asthma or allergy in the immediate family) who may have a greater risk for developing asthma. As a result, additional studies to examine the prevalence of IgE antibodies to foods in such children may be needed. Among toddlers seen because of wheezing in our study, tests for IgE antibodies to both foods and inhalants improved the assessment of atopy compared with tests for inhalants alone. After the age of 4 years, however, most of the allergen-specific IgE antibody responses among wheezing children were to aeroallergens, and it is not clear that routine tests for food sensitization will enhance their evaluation.

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Allergy to cheese produced from sheep's and goat's milk but not to cheese produced from cow's milk

Brunello Wüthrich, MD,^a and S. G. O. Johansson, MD,^b *Zurich, Switzerland, and Stockholm, Sweden*

Most adult patients with cow's milk allergy (CMA) are sensitized to cow's milk casein, as can be demonstrated by specific IgE determination

with the Pharmacia RAST or CAP system (Pharmacia, Uppsala, Sweden), and they do not tolerate sheep's or goat's milk or cheese made from sheep's or goat's milk because of the existence of cross-sensitivities among the different caseins (α , β , γ , κ)

From ^athe Allergy Unit of the Department of Dermatology, University Hospital, Zurich; and ^bthe Department of Clinical Immunology, Karolinska Hospital, Stockholm.

Reprint requests: Brunello Wüthrich, MD, Allergy Unit, Department of Dermatology, University Hospital, Gloriastrasse 31, CH-8091 Zurich, Switzerland.

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