

Allergen-Specific Immunoglobulin E Antibodies in Wheezing Infants: The Risk for Asthma in Later Childhood

Anne Kotaniemi-Syrjänen, MD*; Tiina M. Reijonen, MD*; Jarkko Romppanen, MD‡; Kaj Korhonen, MD*; Kari Savolainen, PhD‡; and Matti Korppi, MD*

ABSTRACT. *Objective.* To evaluate whether the measurement of specific immunoglobulin E (IgE) antibodies to food and/or inhalant allergens in infants who are hospitalized for wheezing can be used to predict later asthma.

Methods. Eighty-two children who were hospitalized for wheezing at <2 years of age were followed prospectively until early school age. The baseline data and the characteristics of infancy had been collected at enrollment. At school age, the children were evaluated for asthma and allergic manifestations, including skin prick tests to common inhalant allergens. Frozen serum samples obtained during the index episode of wheezing were available for 80 children for determination of food and inhalant allergen-specific serum IgE antibodies by fluoroenzyme-immunometric assay, UniCAP, applying the Phadiatop Combi allergen panel.

Results. Asthma was present in 32 (40%) children at school age. Food-specific IgE antibodies of ≥ 0.35 kU/L were found in 37 (46%) wheezing infants, but only specific IgE to wheat and to egg white at the level of ≥ 0.35 kU/L were significantly associated with later asthma. In regard to specific IgE to the mixture of food allergens, the cutoff level of ≥ 0.70 proved to be significant. Inhalant allergen-specific IgE of ≥ 0.35 kU/L was found only in 14 cases (18%), but when present, it was significantly predictive of asthma. Elevated levels of specific IgE antibodies to food or inhalant allergens were significantly associated with allergic rhinitis and skin-test reactivity at school age.

Conclusions. When present in wheezing infants, specific IgE of ≥ 0.35 kU/L to wheat, egg white, or inhalant allergens are predictive of later childhood asthma. Consequently, detection of those specific IgE antibodies in wheezing infants may facilitate the early diagnosis of asthma, especially in cases with no clinically evident atopic manifestations. *Pediatrics* 2003;111:e255-e261. URL: <http://www.pediatrics.org/cgi/content/full/111/3/e255>; asthma, infant, follow-up study, sensitization, specific IgE antibodies, wheezing.

ABBREVIATIONS: IgE, immunoglobulin E; ECP, eosinophil cationic protein; SPT, skin prick test; RAST, radioallergosorbent test; RSV, respiratory syncytial virus; FEV₁, forced expiratory volume in 1 second; OR, odds ratio; CI, confidence interval; PV+, positive

From the Departments of *Pediatrics and ‡Clinical Chemistry, Kuopio University Hospital, Kuopio, Finland.

Presented in part at the International Paediatric Respiratory and Allergy Congress, April 1–4, 2001; Prague, Czech Republic.

Received for publication Oct 2, 2001; accepted Oct 8, 2002.

Reprint requests to (A.K.-S.) Department of Pediatrics, Kuopio University Hospital, PO Box 1777, FIN-70211 Kuopio, Finland. E-mail: kotaniem@hytti.uku.fi

PEDIATRICS (ISSN 0031 4005). Copyright © 2003 by the American Academy of Pediatrics.

predictive value; LR+, positive likelihood ratio; ROC, receiver operating characteristic.

Approximately 20% of all children experience wheezing in infancy,¹ and these children are at increased risk for asthma in later childhood. On the basis of recent prospective follow-up data, up to 40% of them experience asthma at school age.² The majority of children with asthma have clinically evident atopic manifestations in later childhood, although allergies may not be apparent in infancy.^{2,3} Total serum immunoglobulin E (IgE),² blood eosinophilia,² and serum eosinophil cationic protein (ECP)⁴ are markers that are often used to determine subclinical atopy and susceptibility to respiratory allergy. However, these markers are non-specific, and to point out the allergen-specific responses, skin prick tests (SPTs) or radioallergosorbent tests (RAST) thus far have had to be performed. Both of these tests are qualitative, and for technical reasons, only a restricted number of allergens are applicable in SPTs in young children. These tests may also be susceptible to technical errors and variations as a result of either nonstandardized or non-automated methods. Consequently, new approaches are needed to screen those prone to atopy or allergen-induced asthma among the large group of wheezing infants.

We have followed up prospectively a group of children who were hospitalized for wheezing at <2 years of age from 1992–1993 onward.⁵ In 1999–2000, the children were examined for asthma, and the allergen-specific IgE antibodies were measured from frozen sera obtained during the hospitalization for wheezing in infancy. The aim of the present study was to evaluate whether specific IgE antibodies to food and/or inhalant allergens in wheezing infants are predictive of later asthma.

METHODS

In 1992–1993, 100 children, aged 1 to 23 months, were recruited into this study. All of the children had infection-related wheezing resulting in hospital treatment in the Department of Pediatrics, Kuopio University Hospital. The baseline data were charted by using a structured questionnaire at enrollment, including the history of earlier episodes of wheezing, the history of atopic dermatitis, pet contacts in infancy, and the family history of asthma and atopy.⁶ More details are presented in Table 1. In addition, total serum IgE and ECP concentrations and blood eosinophil counts were determined. The IgE concentration of ≥ 60 kU/L,⁷ the ECP concentration of ≥ 16 μ g/L,⁸ and the eosinophil count of $\geq 0.45 \times 10^9$ cells/L⁹ were considered as elevated. Seven common respiratory viruses were studied by antibody and antigen assays; there

TABLE 1. Baseline Data and Characteristics of Infants During the Index Episode of Wheezing

Baseline Data	Children (n = 80; %)
Boys	59 (74)
Age ≥12 mo	31 (39)
History of an earlier episode of wheezing	11 (14)
Atopic dermatitis*	23 (29)
Family history of atopy†	45 (56)
Family history of asthma‡	15 (19)
Pet contacts in infancy§	25 (31)
Blood eosinophils of $\geq 0.45 \times 10^9$ cells/L	26/78 (33)
IgE of ≥ 60 kU/L	17/77 (22)
ECP of ≥ 16 $\mu\text{g/L}$	15 (19)
RSV identification	20 (25)

* Cases diagnosed by a physician.

† Allergic rhinitis or atopic dermatitis in parents or siblings, diagnosed by a physician.

‡ Asthma in parents or siblings, diagnosed by a physician.

§ Furry pets at home or at day care.

were 25 respiratory syncytial virus (RSV) and 18 other viral identifications.¹⁰

The children were followed up prospectively, and in 1999, 82 children, 61 boys and 21 girls, participated in the follow-up visit. The age of the children varied from 5.6 to 8.8 years (median: 7.2 years), and the time from enrollment (the index episode of wheezing) ranged from 5.3 to 7.2 years (median: 6.3 years). Frozen serum samples, which were obtained during the index episode of wheezing at <2 years of age (median: 0.9 years), were available for allergen-specific IgE antibody determinations in 80 children, who form the subjects of the present study.

In the follow-up study from January to March 1999, a structured questionnaire was used to record the symptoms suggestive of asthma associated with exercise, infections, or allergens. In addition, physician-diagnosed allergic rhinitis and atopic dermatitis were recorded. Allergic diseases were classified as current when there had been clinical manifestations during the preceding 12 months. The exercise challenge test was performed in all children. The baseline pulmonary function was examined by flow-volume spirometry (Medikro, Kuopio, Finland), and forced expiratory volume in 1 second (FEV₁) was the parameter used in challenge tests. First, the children were carefully instructed on how to perform the test. Thereafter, the measurements were repeated at least 3 times and accepted when the FEV₁ variation was <5% and when the printed graphic curves were appropriate and equal in shape. The highest FEV₁ value was used in later comparisons. The baseline pulmonary testing was followed by exercise that consisted of free running outdoors for 8 minutes at the heart rate of 80% or more of the predicted maximum. The heart rate was monitored by telemetry (Polar Sport Tester; Polar Elektro Ltd, Kempele, Finland) at 1-minute intervals. Flow-volume spirometry was performed 10 minutes after the exercise. FEV₁ changes were calculated as follows: [(preexercise FEV₁ - postexercise FEV₁)/preexercise FEV₁] × 100%.

The children's lungs were auscultated before the baseline lung function testing and immediately after the exercise. Symptoms and auscultatory findings, when present, were recorded. The exercise challenge test was regarded as positive when there was auscultatory wheezing present after the exercise and/or a $\geq 15\%$ fall in FEV₁.¹¹ Asthma was considered to be present when 1) the patient was on continuous maintenance medication for asthma or when 2) she or he had had repeated (≥ 2) episodes of wheezing and/or prolonged (≥ 4 weeks) cough apart from infection during the preceding 12 months and the exercise challenge test was regarded as positive.¹²

The allergens tested by SPTs were (the outdoor allergens) birch, common alder, timothy grass, meadow grass, and mugwort pollens and spores of *Cladosporium herbarum*; and (the indoor allergens) cat and dog epithelial dander and home dust mites *Dermatophagoides pteronyssinus* and *D farinae*. The concentration of a nonstandardized extract of *C herbarum* spores was 1:20 wt/vol. Other allergen extracts were standardized, the concentrations being 10 histamine equivalent points. Histamine hydrochloride (10 mg/mL) was used as a positive and 50% glycerol as a negative

control. Wheals with a mean diameter of at least 3 mm were regarded as positive,¹³ and no reactions were allowed in negative controls.

In 2000, allergen-specific IgE antibodies (Phadiatop Combi) were determined from frozen serum samples, which had been obtained at enrollment into the study in 1992–1993, by the fluoroenzyme-immunometric assay, UniCAP (Pharmacia, Uppsala, Sweden).³ First, the presence of IgE antibodies to the mixtures of inhalant and food allergens was screened, the concentrations of ≥ 0.35 kU/L being detectable in both assays. On occasions with detectable antibodies, additional determinations were performed to assess individual allergen-specific IgE antibody concentrations. The detection limit was the same (0.35 kU/L) as for the allergen mixtures. The other cutoff concentrations proposed by the manufacturer (≥ 0.70 kU/L and ≥ 3.50 kU/L) were also explored in the present analyses. Phadiatop Combi panel for food allergens included egg white, cow milk, fish, wheat, peanut, and soy bean and for inhalant allergens timothy grass pollen, birch pollen, mugwort pollen, cat dander, dog dander, horse dander, house dust mite *D pteronyssinus*, and spores of the mold *C herbarum*.

The data were analyzed using SPSS/PC + 9.0 software (SPSS Inc, Chicago, IL). Statistical significances of the differences between the groups were assessed by the χ^2 test for proportions. The Fisher exact test was used when the expected frequency for any cell was <5. The logistic regression analysis was used to calculate the adjusted odds ratios (ORs) and the related 95% confidence intervals (CIs). Two-tailed tests were used in all analyses. $P < .05$ was regarded as statistically significant. The κ statistics was applied to compare agreement between allergen-specific IgE and other markers and characteristics of atopy. $\kappa > 0.80$ indicates good agreement, 0.61 to 0.80 indicates substantial agreement, 0.41 to 0.60 indicates moderate agreement, 0.21 to 0.40 indicates fair agreement, and ≤ 0.20 indicates poor agreement.¹⁴ Sensitivity, specificity, positive predictive values (PV+), and positive likelihood ratios (LR+) were calculated by using routine equations. LR+ values of ≥ 3 are considered to have moderate effects on pretest probability, and LR+ values of ≥ 10 (or of ≥ 5) significant effects.¹⁵ The receiver operating characteristic (ROC) curves were applied to evaluate the optimal cutoff concentrations for specific IgE antibodies, maximizing true-positives (sensitivity) and minimizing false-positive cases (1-specificity).

The study was approved by the Research Ethics Committee of Kuopio University Hospital. Informed written consent was obtained from the parents of the children.

RESULTS

The baseline data of the 80 subjects of the present study, obtained at enrollment in 1992–1993, are shown in Table 1. The characteristics of early childhood in these 80 children did not significantly differ from those 20 with specific IgE antibody determinations or follow-up data not available (data not shown). At school age, asthma was present in 32 (40%) children. Twenty-nine (91%) children were on continuous maintenance medication for asthma, and 24 (83%) of them reported repeated wheezing (4 children) or prolonged cough (4 children) or both (16 children) during the preceding 12 months. The exercise challenge was positive in 7 (24%) children with maintenance medication and, based on the definition, in all 3 children now considered as having asthma present but having no maintenance medication for asthma. When the logistic regression analysis was done separately for each baseline characteristic with adjustment for gender and age at entry to the study, atopic dermatitis ($P = .008$; OR: 4.24; 95% CI: 1.47–12.27), total serum IgE of ≥ 60 kU/L ($P = .048$; OR: 3.36; 95% CI: 1.01–11.17), blood eosinophil count of $\geq 0.45 \times 10^9$ cells/L ($P < .001$; OR: 6.87; 95% CI: 2.20–21.37), and a history of an earlier episode of wheezing before the index episode at <2 years of age ($P = .043$; OR: 4.39; 95% CI: 1.04–18.43) were signif-

TABLE 2. Specific IgE Antibodies to Food and Inhalant Allergens in Wheezing Infants During the Index Episode of Wheezing

Specific IgE of ≥ 0.35 kU/L to	All (n = 80)	Age	
		<12 Months (n = 49)	≥ 12 Months (n = 31)
Food allergens	37 (46%)	17 (35%)	20 (65%)†
Egg white	31	13	18
Cow milk	22	9	13
Fish	5	1	4
Wheat	12	4	8
Peanut	14	4	10
Soy bean	4	2	2
Inhalant allergens	14 (18%)	1* (2%)	13 (42%)‡
Timothy grass	1	-	1
Birch	3	-	3
Mugwort	1	-	1
Cat	7	-	7
Dog	8	-	8
Horse	5	-	5
<i>D pteronyssinus</i>	2	-	2
<i>C herbarum</i>	0	-	0

* Individual inhalant allergen-specific IgE determinations not done because of an inadequate blood specimen.

† $P = .009$ vs <12-month-old children (the χ^2 test).

‡ $P < .001$ vs <12-month-old children (the χ^2 test).

icantly associated with school-age asthma. In addition, RSV identification during the index episode of wheezing was negatively associated with later asthma ($P = .034$; OR: 0.22; 95% CI: 0.06–0.89). The family history of asthma or atopy was not significantly predictive of school-age asthma. Accordingly, 16 children had both asthma and atopy in the family; in 7 (44%) of them, asthma was present at school age ($P = .482$; OR: 1.52; 95% CI: 0.47–4.90).

The results of the specific IgE antibody determinations are shown in Table 2. Almost half (46%) of the children were sensitized to food allergens, whereas only 18% were sensitized to inhalant allergens. All children, except 1 with specific IgE to inhalant allergens, were older than 12 months. Sensitization to food allergens was more evenly distributed: 35% of the children younger than and 65% of those older than 12 months were sensitized. Concerning food allergens, the sensitization was most frequent to egg white (39%), followed by cow milk (28%), peanut (18%), and wheat (15%), and concerning inhalant allergens to dog (10%) and cat (9%) dander. Sensitization to the house dust mite *D pteronyssinus* was

rare (3%), and no one was sensitized to the mold *C herbarum*. All except 2 children with specific IgE to inhalant allergens had specific IgE also to food allergens; the corresponding figure for specific IgE to inhalant allergens was 32% among the children who were positive for food allergen.

Specific IgE of ≥ 0.35 kU/L to the mixture of inhalant allergens but not to the mixture of food allergens was significantly associated with school-age asthma (Table 3). However, among individual food allergens, specific IgE of ≥ 0.35 kU/L to egg white and to wheat were associated with later asthma. In contrast, cases with cow milk-specific IgE of ≥ 0.35 kU/L were almost equally common in children both with and without later asthma, and, thus, association with asthma was not to be seen.

When a cutoff concentration of 0.70 kU/L was applied, specific IgE to the mixture of food allergens associated significantly with school-age asthma independent of age and gender ($P = .031$; OR: 2.97; 95% CI: 1.10–7.97). Furthermore, at the level of 3.5 kU/L, the respective OR was even higher (4.23; 95% CI: 1.16–15.50; $P = .029$). For cow milk-specific IgE, even the higher cutoff concentrations of 0.70 to 3.50 kU/L were not predictive of asthma (data not shown). Thus, specific IgE to cow milk did not predict later asthma at any level. Sensitization to individual inhalant allergens was rare, and no significant association was seen between asthma and specific IgE to any individual inhalant allergen at any concentration level.

When allergen-specific IgE antibodies were compared with the other markers or characteristics of atopy on entry, significant associations were seen with elevated total serum IgE, elevated serum ECP, blood eosinophilia, and the presence of atopic dermatitis (Table 4). However, all except 1 of the κ values were < 0.40 , indicating only fair agreement. The family history of atopy or asthma had no association with allergen-specific IgE antibodies. It is interesting that only 4 (16%) of the 25 infants with a furry pet at home or at day care had specific IgE to inhalant allergens. Among the 20 RSV-positive children, only 4 (20%) children had specific IgE to food allergens and 1 (5%) child had specific IgE to inhalant allergens. Thus, RSV identification was associated with nondetectable concentrations of specific

TABLE 3. Allergen-Specific IgE Antibodies in Infancy as Predictive Factors for School-Age Asthma

Specific IgE of ≥ 0.35 kU/L to	Asthma at School Age		PV+	P	OR	95% CI
	Present (n = 32)	Not Present (n = 48)				
Food allergens	20	17	54%	.075	2.48	0.91–6.74
Egg white	18	13	58%	.048	2.85	1.01–8.02
Cow milk	12	10	55%	.253	1.85	0.65–5.28
Wheat	9	3	75%	.030	4.93	1.16–20.89
Peanut	8	6	57%	.471	1.61	0.44–5.85
Inhalant allergens	11	3	79%	.006	9.75	1.91–49.71
Cat	5	2	71%	.257	2.94	0.46–18.90
Dog	5	3	63%	.522	1.74	0.32–9.49

P values, ORs, and 95% CIs were determined by logistic regression with adjustment for gender and age at entry. Analyses have been done separately for each factor. Allergens with ≤ 5 positive cases were not included in analyses.

TABLE 4. Specific IgE to Food and to Inhalant Allergens Compared With Other Atopy Markers or Characteristics at Entry

Baseline Data		Specific IgE of ≥ 0.35 kU/L to					
		Food Allergens			Inhalant Allergens		
		<i>n</i> = 37	<i>P</i>	κ	<i>n</i> = 14	<i>P</i>	κ
Atopic dermatitis	(<i>n</i> =23)	15	.031	0.225	9	.001	0.344
Blood eosinophils of $\geq 0.45 \times 10^9$ cells/L	(<i>n</i> =26)	16/35*	.036	0.230	10/13*	.001	0.374
Total serum IgE of ≥ 60 kU/L	(<i>n</i> =17)	14/36†	.002	0.326	8†	<.001	0.396
Serum ECP of ≥ 16 μ g/L	(<i>n</i> =15)	12	.004	0.266	8	<.001	0.453
Family history of atopy	(<i>n</i> =45)	21	.932	0.009	6	.226	-0.087

* Data were available for 78 children.

† Data were available for 77 children.

IgE to food (16 of 20 cases; *P* = .007) or to inhalant (19 of 20 cases; *P* = .170) allergens.

Allergic rhinitis was diagnosed in 29 (36%) children and atopic dermatitis in 39 (49%) children at school age. A significant association was found between allergic rhinitis and specific IgE of ≥ 0.35 kU/L to the mixture of inhalant allergens (*P* = .003; OR: 12.40; 95% CI: 2.35–65.42) and specific IgE of ≥ 0.35 kU/L to the mixture of food allergens (*P* < .001; OR: 7.29; 95% CI: 2.34–22.71) in infancy. However, no such association was found with the later occurrence of atopic dermatitis (data not shown). When specific IgE in infancy was compared with SPT reactivity at school age, all 14 children with specific IgE to inhalant allergens (*P* < .001) and 26 (70%) of 37 with specific IgE to food allergens (*P* = .002) had positive SPT results. Conversely, 9 (24%) SPT-positive children had specific IgE neither to food nor to inhalant allergens in infancy.

When evaluated as an asthma-predicting marker, specific IgE of ≥ 0.35 kU/L to the mixture of food allergens had a moderate sensitivity (63%) and specificity (65%), whereas specific IgE of ≥ 0.35 kU/L to the mixture of inhalant allergens was less sensitive (34%) but very specific (94%). The PV+ were 54% and 79% (Table 3), and the LR+ were 1.76 and 5.50, respectively. Among individual allergens, specific IgE of ≥ 0.35 kU/L to wheat had the highest specificity (94%) and PV+ (75%), with an LR+ of 4.50. The cutoff concentrations >0.35 kU/L for specific IgE

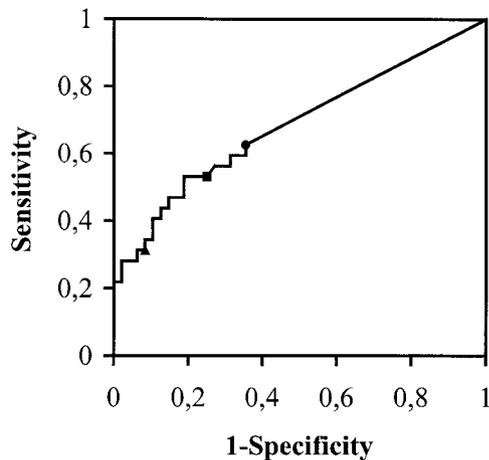


Fig 1. Food-specific IgE concentrations in relation to later childhood asthma displayed as a ROC curve. The concentrations—expressed by a black point, a square, and a triangle—are 0.35 kU/L, 0.70 kU/L, and 3.50 kU/L, respectively.

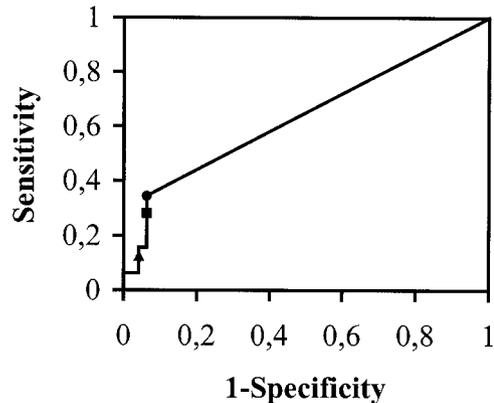


Fig 2. Inhalant allergen-specific IgE concentrations in relation to later childhood asthma displayed as a ROC curve. The concentrations—expressed by a black point, a square, and a triangle—are 0.35 kU/L, 0.70 kU/L, and 3.50 kU/L, respectively.

were evaluated in relation to school-age asthma by applying ROC curves (Figs 1 and 2). There were no substantially better cutoff concentrations for the mixture of inhalant allergens or for any individual inhalant or food allergens (data not shown) than the detection concentration. However, for the mixture of food allergens, the optimal cutoff concentration of specific IgE was higher, close to 0.70 kU/L (*P* = .031; OR: 2.97; 95% CI: 1.10–7.97).

Finally, we evaluated whether specific IgE combined with other atopic manifestations improves the applicability of specific IgE as an asthma-predictive marker. In the present cohort, atopic dermatitis was the only clinically evident atopic manifestation on admission in infancy. We found that the combination of atopic dermatitis and food-specific IgE of ≥ 0.35 kU/L gave the best result (*P* = .0038; OR: 8.13; 95% CI: 1.97–33.54; Table 5). Because specific IgE to the mixture of inhalant allergens was rarely detectable in infancy and, whenever present, highly predictive for asthma at the detection level, any combinations with atopic dermatitis or use of other than detection concentrations in analyses gave no additional advantages (data not shown).

DISCUSSION

There are 3 main results in the present study on allergen-specific IgE antibodies as predictors of asthma in wheezing infants who are treated in the hospital. First, sensitization to food allergens was common: 35% to 65%, depending on age. Specific IgE to the mixture of food allergens, however, was not

TABLE 5. Specific IgE to Food Allergens, Combined With the Presence of Atopic Dermatitis in Infancy, as a Predictor of Asthma at School Age

Combination	Asthma at School Age		PV+	P	OR	95% CI
	Present (n = 32)	Not Present (n = 48)				
Specific IgE of ≥ 0.35 kU/L to food allergens						
And atopic dermatitis	12	3	80%	.0038	8.13	1.97–33.54
Or atopic dermatitis	23	22	51%	.0696	2.53	0.93–6.87
Specific IgE of ≥ 0.70 kU/L to food allergens						
And atopic dermatitis	10	3	77%	.0136	6.15	1.45–26.03
Or atopic dermatitis	23	18	56%	.0086	3.79	1.40–10.24

associated with school-age asthma at the detection level of 0.35 kU/L, whereas concentrations of ≥ 0.70 kU/L were predictive. However, among individual food allergens, specific IgE to egg white and to wheat predicted later asthma even at the detection level, but specific IgE to cow milk did not, at any level. Second, sensitization to inhalant allergens was less common and only exceptionally present before the age of 12 months. When present, specific IgE antibodies to inhalant allergens were highly predictive of later childhood asthma. Third, there was a significant association between specific IgE to food and inhalant allergens and other markers of atopy in infancy. However, the κ statistics showed that different markers, including allergen-specific IgE antibodies, “found” partly different children at risk for later atopy and asthma.

An automated in vitro screening method, UniCAP fluoroenzyme-immunometric assay, which allows detection of allergen-specific serum IgE antibodies quantitatively, was applied in the present study. The accuracy of the UniCAP assay has been good compared with earlier, nonautomated laboratory methods, such as the CAP System RAST.³ The storage of serum samples as frozen for several years, as was done in the present study, has not significantly interfered with the results.³ The detection concentration for specific IgE, 0.35 kU/L, has been used by Sigurs et al.¹⁶ Other investigators have preferred higher cutoff concentrations, such as 0.70 kU/L, for “positive” results.^{17,18} According to the manufacturer, the specific IgE concentrations of 0.35 kU/L to 0.69 kU/L are comparable to RAST class 1, the concentrations of 0.70 kU/L to 3.49 kU/L to RAST class 2, and the concentrations of ≥ 3.50 kU/L to RAST classes 3 to 4. In food allergy, confirmed by elimination-challenge tests, the diagnostic concentrations of specific IgE have varied from 6 kU/L for egg white to 32 kU/L for cow milk.¹⁹ Low to moderate IgE rises to cow milk are found in infancy even without clinical consequences.¹⁷ Thus, the clinically significant concentrations for specific IgE seem to depend on tested allergens, the age of the child, and the clinical questions in consideration.¹⁹

There are only 2 previous follow-up studies on allergen-specific IgE antibodies as asthma-predicting markers in wheezing infants. Delacourt et al²⁰ studied 67 children, aged 1 to 25 months, the majority of whom already had a diagnosis of asthma, and Wever-Hess et al²¹ studied 231 children, <2 years of age, who were referred to the outpatient clinic be-

cause of suspicion of asthma. Delacourt et al found that specific IgE antibodies to inhalant allergens were rare in infants with asthma, whereas Wever-Hess et al²¹ found an association with asthma and specific IgE to both food and inhalant allergens. In both studies, the assays applied to determine specific IgE antibodies gave the results as either positive or negative,^{20,21} not as concentrations, and, thus, the results are not directly comparable with the results of the present study. The follow-up time in both studies was no more than 2 years, Delacourt et al reported only specific IgE to the mixture of inhalant allergens, and neither study reported specific IgE for individual allergens.

In our study, a large panel of specific IgE antibodies to several common allergens, including 6 individual food and 8 inhalant allergens, was investigated as a predictor of asthma in infants that had been hospitalized for the first time for wheezing. Among analyzed allergens, specific IgE to egg white was both common in infancy and predictive of school-age asthma, being thus an applicable marker. However, IgE responses to food allergens, such as responses to egg white and wheat in the present study, may rather reflect the atopic reactivity in general than specific contribution to the development of atopic symptoms or later asthma. In addition to large panel size, the other strengths in our study were a prospective follow-up of a 6-year duration and a good participation of >80% of the original cohort of 100 infants in the long-term follow-up. In addition, the diagnosis of asthma, being based on the presence of symptoms, the need for maintenance medication, and the changes in lung function tests, was done at the age when symptomatic children have real asthma, not any more transient wheezing.^{1,2}

Other studies on specific IgE in infants have been either cross-sectional studies in wheezing infants with^{22,23} or without²⁴ controls or follow-ups of non-selected¹⁷ or selected^{16,18,25} birth cohorts or of children selected by other criteria²⁶ not particularly aiming at the outcome of wheezing infants. In addition, such large panels of allergens, such as Phadiatop Combi, or automated quantitative methods for determining specific IgE antibodies, such as UniCAP, have been rarely available.

In a German birth-cohort study, specific IgE antibodies to food allergens were found in 10% of all children in infancy¹⁷ and in a Dutch follow-up study in 20% of infants with asthma.²¹ In the present study, the occurrence of specific IgE to food allergens was

much more common, up to 50%, in children selected by hospitalization for wheezing in infancy, suggesting a connection between atopy and wheezing in infancy.² In fact, the figure was close to that of 60% in infants with clinical atopy²⁶ and clearly higher than that of 10% to 20% in nonsymptomatic infants at risk for atopy.²⁵ Consistent with the recent findings of Yunginger et al,²⁷ specific IgE antibodies to an individual food allergen, egg white, were common, approximately 40%, being predictive for later asthma and atopy. In our study, another asthma-predictive individual food allergen was wheat, and we could find no earlier report emphasizing the association between wheat-specific IgE in infants and asthma in later childhood. Specific IgE to cow milk was common, next to egg-specific IgE. However, it was not associated with later asthma at any cutoff concentration level.

In the Dutch birth-cohort study, specific IgE antibodies to inhalant allergens were present in 8% of children with asthma younger than 2 years.²¹ In the present study, specific IgE antibodies to inhalant allergens were more common, 18%, in wheezing children who were treated in the hospital at the same age. Although sensitization to any certain inhalant allergen alone, probably as a result of small numbers of positive cases, was not significant in predicting asthma, sensitization to inhalant allergens as a mixture was highly predictive, which is consistent with the Dutch findings.²¹ Opposite to the observations of a North American group²² and in line with a Scandinavian pediatric study,¹⁶ specific IgE to house dust mites was rare, as is typical in the northern climate, and it was not able to predict later asthma.

In the present study, specific IgE antibodies to both food and inhalant allergens in infancy significantly predicted allergic rhinitis and SPT reactivity. Thus, allergen-specific IgE antibodies, when found at young age, can be used to predict later atopy²⁵ and, in the case of wheezing infants, also later atopic asthma.²¹ Allergen-specific IgE antibodies are especially useful in discovering subclinical atopy in children. Sensitivities and specificities of all tests are highly dependent on the cutoff concentration levels used. In the present ROC analyses, raising the cutoff level over the detection concentration of ≥ 0.35 kU/L led to diminished sensitivity, with no substantial improvement in specificity, concerning most allergen-specific IgE antibodies. In recent studies, algorithms based on atopic findings and family histories of atopy have been developed to predict later asthma in young children.^{2,28} These algorithms have thus far included blood eosinophilia ($>4\%$ – 5%) as the only laboratory marker of atopy.^{2,28} Our results suggest that elevated specific IgE, especially to egg white and wheat, even in children with no clinical atopy or family history of atopy, may be used to predict asthma after infantile wheezing.

CONCLUSION

Specific IgE antibodies to food allergens are common and to inhalant allergens are uncommon in infants who are hospitalized for wheezing. Specific IgE antibodies to the mixture of inhalant allergens, as

well as to the individual allergens egg white and wheat, are predictive for later asthma. Detection of specific IgE antibodies in wheezing infants thus may facilitate the early diagnosis of asthma, especially in cases with no clinically evident atopic manifestations.

ACKNOWLEDGMENTS

This study was financially supported by the Ida Montin Foundation, the Kerttu and Kalle Viik Fund, and an EVO grant (code 440054) from Kuopio University Hospital.

REFERENCES

- Morgan WJ, Martinez FD. Risk factors for developing wheezing and asthma in childhood. *Pediatr Clin North Am.* 1992;39:1185–1203
- Martinez FD. Recognizing early asthma. *Allergy.* 1999;54(suppl 49):24–28
- Paganelli R, Ansotegui IJ, Sastre J, et al. Specific IgE antibodies in the diagnosis of atopic disease. Clinical evaluation of a new in vitro test system, UniCAP, in six European allergy clinics. *Allergy.* 1998;53:763–768
- Koller DY, Wojnarowski C, Herkner KR, et al. High levels of eosinophil cationic protein in wheezing infants predict the development of asthma. *J Allergy Clin Immunol.* 1997;99:752–756
- Reijonen TM, Kotaniemi-Syrjänen A, Korhonen K, Korppi M. Predictors of asthma three years after hospital admission for wheezing in infancy. *Pediatrics.* 2000;106:1406–1411
- Reijonen T, Korppi M, Kuikka L, Remes K. Anti-inflammatory therapy reduces wheezing after bronchiolitis. *Arch Pediatr Adolesc Med.* 1996;150:512–517
- Saarinen UM, Juntunen K, Kajosaari M, Björkstén F. Serum immunoglobulin E in atopic and non-atopic children aged 6 months to 5 years. *Acta Paediatr Scand.* 1982;71:489–494
- Peterson CGB, Enander I, Nystrand J, Anderson AS, Nilsson L, Venge P. Radioimmunoassay of human eosinophil cationic protein (ECP) by an improved method. Establishment of normal levels in serum and turnover in vivo. *Clin Exp Allergy.* 1991;21:561–567
- Eisen A. Eosinophilia. In: Bierman CW, Pearlman DS, eds. *Allergic Diseases in Infancy, Childhood and Adolescence.* 1st ed. Philadelphia, PA: WB Saunders; 1980:761–762
- Reijonen TM. *Early Childhood Wheezing. A Study on Therapy and Risk Factors for Recurrent Bronchial Obstructions.* Kuopio, Finland: Kuopio University Printing Office; 1997
- Carlsen KH. Exercise-induced asthma in children and adolescents and its relationship to sports. In: Naspitz CK, Szeffler SJ, Tinkelman DG, Warner JO, eds. *Textbook of Pediatric Asthma: An International Perspective.* London, England: Martin Dunitz; 2001:211–222
- Remes S, Korppi M, Remes K, Pekkanen J. Prevalence of asthma at school age: a clinical population-based study in eastern Finland. *Acta Paediatr.* 1996;85:59–63
- The European Academy of Allergology and Clinical Immunology. Position paper: allergen standardization and skin test. *Allergy.* 1993;48(suppl 14):48–82
- Petrie A, Sabin C. *Medical Statistics at a Glance.* Oxford, England: Blackwell Science; 2000
- Sackett DL, Richardson WS, Rosenberg W, Haynes RB. *Evidence Based Medicine: How to Practice and Teach EBM.* London, England: Churchill Livingstone; 1997
- Sigurs N, Hattévig G, Kjellman B, Kjellmann NIM, Nilsson L, Björkstén B. Appearance of atopic disease in relation to serum IgE antibodies in children followed up from birth for 4 to 15 years. *J Allergy Clin Immunol.* 1994;94:757–763
- Kulig M, Bergmann R, Klettke U, Wahn V, Tacke U, Wahn U. Natural course of sensitization to food and inhalant allergens during the first 6 years of life. *J Allergy Clin Immunol.* 1999;103:1173–1179
- Lau S, Illi S, Sommerfeld C, et al. Early exposure to house-dust mite and cat allergens and development of childhood asthma: a cohort study. *Lancet.* 2000;356:1392–1397
- Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol.* 1997;100:444–451
- Delacourt C, Labbé D, Vassault A, Brunet-Langot D, de Blic J, Scheinmann P. Sensitization to inhalant allergens in wheezing infants is pre-

- dictive of the development of infantile asthma. *Allergy*. 1994;49:843–847
21. Wever-Hess J, Kouwenberg JM, Duiverman EJ, Hermans J, Wever AMJ. Prognostic characteristics of asthma in early childhood in clinical practice. *Acta Paediatr*. 1999;88:827–834
 22. Duff AL, Pomeranz ES, Gelber LE, et al. Risk factors for acute wheezing in infants and children: viruses, passive smoke, and IgE antibodies to inhalant allergens. *Pediatrics*. 1993;92:535–540
 23. Price GW, Hogan AD, Farris AH, Burks AW, Platts-Mills TAE, Heymann PW. Sensitization (IgE antibody) to food allergens in wheezing infants and children. *J Allergy Clin Immunol*. 1995;96:266–270
 24. Tridon A, Fauquert JL, Dibet P, Betail G, Labbe A. Atopy parameters in asthmatic infants. *J Investig Allergol Clin Immunol*. 1999;9:222–228
 25. Bruno G, Cantani A, Ragno V, Milita O, Zirulo G, Businco L. Natural history of IgE antibodies in children at risk for atopy. *Ann Allergy Asthma Immunol*. 1995;74:431–436
 26. Gustafsson D, Sjöberg O, Foucard T. Development of allergies and asthma in infants and young children with atopic dermatitis: a prospective follow-up to 7 years of age. *Allergy*. 2000;55:240–245
 27. Yunginger JW, Ahlstedt S, Eggleston PA, et al. Quantitative IgE antibody assays in allergic diseases. *J Allergy Clin Immunol*. 2000;105:1077–1084
 28. Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med*. 2000;162:1403–1406

Allergen-Specific Immunoglobulin E Antibodies in Wheezing Infants: The Risk for Asthma in Later Childhood

Anne Kotaniemi-Syrjänen, Tiina M. Reijonen, Jarkko Romppanen, Kaj Korhonen, Kari Savolainen and Matti Korppi

Pediatrics 2003;111:e255

DOI: 10.1542/peds.111.3.e255

Updated Information & Services

including high resolution figures, can be found at:
<http://pediatrics.aappublications.org/content/111/3/e255>

References

This article cites 23 articles, 2 of which you can access for free at:
<http://pediatrics.aappublications.org/content/111/3/e255#BIBL>

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
<http://www.aappublications.org/site/misc/Permissions.xhtml>

Reprints

Information about ordering reprints can be found online:
<http://www.aappublications.org/site/misc/reprints.xhtml>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®



PEDIATRICS[®]

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Allergen-Specific Immunoglobulin E Antibodies in Wheezing Infants: The Risk for Asthma in Later Childhood

Anne Kotaniemi-Syrjänen, Tiina M. Reijonen, Jarkko Romppanen, Kaj Korhonen, Kari Savolainen and Matti Korppi

Pediatrics 2003;111;e255

DOI: 10.1542/peds.111.3.e255

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/111/3/e255>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 345 Park Avenue, Itasca, Illinois, 60143. Copyright © 2003 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN[®]

