

Sensitization to hen's egg at the age of twelve months is predictive for allergic sensitization to common indoor and outdoor allergens at the age of three years

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Background: Specific predictors for atopic sensitization in early infancy are prerequisites for preventive intervention studies.

Objective: To identify predictors of allergic sensitization to common aeroallergens in infancy, 1314 children in five German cities were followed up from birth (1990) to the age of 3 years.

Methods: Blood samples were taken from cord blood and at follow-up visits at the ages of 1, 2, and 3 years. Total serum IgE and specific IgE antibodies to common food and inhalant allergens were determined.

Results: Among our study population, risk factors for sensitization to indoor and/or outdoor allergens at the age of 3 years were a positive family history, the presence of hen's egg-specific IgE antibodies (≥ 0.35 kU/L), and increased log-[total IgE] levels at the age of 12 months. Elevated cord blood IgE was not associated with sensitization to inhalant allergens at the age of 3 years. Egg-specific IgE greater than 2 kU/L in combination with a positive family history of atopy was a highly specific (specificity, 99%) and predictive (positive predictive value, 78%) marker for sensitization to inhalant allergens at 3 years of age.

Conclusions: Hen's egg-specific IgE at the age of 12 months is a valuable marker for subsequent allergic sensitization to allergens that cause asthma, allergic rhinitis, and atopic dermatitis. (*J Allergy Clin Immunol* 1997;99:613-7.)

Key words: Prediction, risk factors, infancy, atopy, food allergens, inhalant allergens

Allergic sensitization to indoor allergens from house dust mites and cats, as well as to outdoor allergens such as birch and grass pollen, plays a major role in facilitating the development of allergic asthma, rhinitis, and

atopic dermatitis.¹⁻³ Specific sensitization is under strong genetic influence, although environmental factors such as early allergen exposure and viral infections may enhance the development of allergen-specific IgE antibodies.⁴⁻⁷ Many longitudinal studies have focused on the prediction of atopic disease and allergic sensitization in newborns.^{8,9} The identification of sensitive and specific markers for atopic disease and allergic sensitization is essential for secondary allergy prevention measures, as well as for preventive intervention studies. Elevated cord blood IgE, positive family history of atopy, maternal smoking during pregnancy, male gender, and prematurity have all been implicated as neonatal risk factors for the development of atopy.¹⁰⁻¹⁸ Because of insufficient sensitivity and/or specificity and low positive predictive values of these factors, a perinatal screening with the objective of primary prevention of allergic diseases does not seem to be feasible at this time.¹⁸ Therefore the identification of nonperinatal but highly specific predictors for allergic sensitization could serve as a basis for secondary preventive measures. Hattevig et al.¹⁹ and Sigurs et al.²⁰ demonstrated an association between sensitization to food allergens in early infancy and the subsequent development of atopic diseases and/or allergic sensitization to aeroallergens later in life in a small cohort followed up from birth to the age of 15 years. These findings were recently confirmed in another prospective intervention study ($n = 165$) by Zeiger and Heller.¹⁷ The determination of food-specific IgE antibodies is easy to perform (skin prick test, RAST) and is cost-effective. However, the usefulness of the determination of food-specific IgE antibodies in screening tests for subsequent inhalant allergies depends on specificity, sensitivity, and positive predictive values. Our objective was the evaluation of these parameters in a large multicenter, nonintervention follow-up study.

METHODS

Study subjects

Study subjects were selected from the ongoing German Multicenter Allergy Study. The Multicenter Allergy Study was initiated in 1990 to identify genetic and environmental risk factors for allergic disease in early childhood.²¹ A total of 1314 healthy mature newborns (of 7609 infants born in 1990 in five

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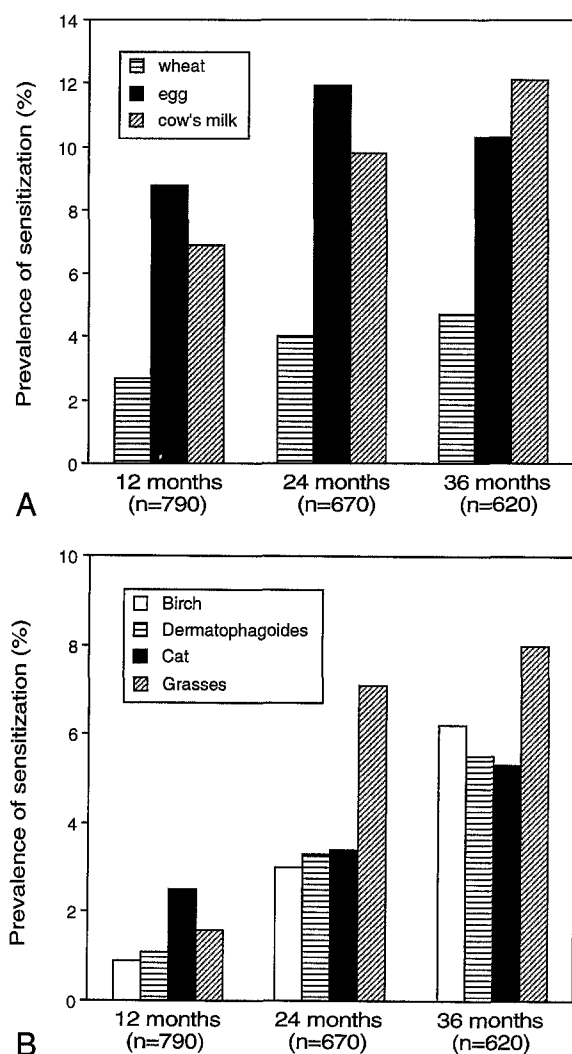


FIG. 1. Prevalence of specific IgE antibodies to common food (A) and inhalant (B) allergens at ages 12, 24, and 36 months. Serum samples were available in 61% ($n = 790$), 51% ($n = 670$), and 48% ($n = 620$) of the total study population.

German cities) were selected for a prospective, nonintervention cohort study. A high-risk group of 499 children (38%) was identified on the basis of having at least two atopic first-degree relatives and/or elevated cord blood IgE levels (>0.9 kU/L). The control group with random risk ($n = 815$, 62%) was chosen from the remaining newborns with one or no atopic family members and cord blood IgE levels of 0.9 kU/L or less. Follow-up visits were conducted at the ages of 1, 3, 6, 12, 18, 24, and 36 months. Each visit comprised a structured interview and a standardized physical examination. Serum samples were collected from cord blood and at the ages of 1, 2, and 3 years for the determination of IgE antibodies. The study participation rate at the third birthday was 80%.

For the assessment of food-specific IgE antibodies as a risk factor for sensitization to inhalant allergens, only children with serum samples obtained at the ages of 1 and 3 years were included in this study. Parents participating in the study gave their informed consent. The study was approved by the local ethics committee.

Determination of total and specific IgE antibodies

Venous blood samples were obtained from cord blood in 96% of the total study population and at the ages of 1, 2, and 3 years in 61%, 51%, and 48%, respectively. Serum samples were frozen at -20°C until they could be analyzed in a central laboratory. Total IgE levels and IgE antibodies to food allergens (cow's milk, egg white, and wheat), indoor allergens (house dust mite and cat dander), and outdoor allergens (mixed grass and birch pollen) were determined by CAP-RAST FEIA (Pharmacia, Freiburg, Germany). The detection limit of this method was 0.35 kU/L. Elevated cord blood IgE was defined as a concentration of 0.35 kU/L or greater. Log[total IgE] at the age of 12 months was used as a continuous trait. Skin prick tests were not performed during the first 3 years of life.

Definition of allergic sensitization and atopic disease

Atopy of first-degree family members was assigned according to questionnaires that included requests for information on diagnoses, relevant symptoms of atopic diseases, and parental smoking history.²² A positive family history of atopy required at least one atopic first-degree family member (parent or sibling). The definition of evident or possible atopic dermatitis was described in detail recently.¹⁸ Allergic sensitization to food allergens or indoor or outdoor allergens was diagnosed when specific IgE antibodies to the tested allergen were equal to or greater than 0.35 kU/L.

Statistical methods

The statistical analysis was performed by using the software program BMDP (Statistical Software Inc.). Logistic regression was used to assess the effects of log[total IgE] and sensitization to food allergens at the age of 12 months, positive family history of atopy, month of birth, and sex on the risk of sensitization to inhalant allergens simultaneously. Odds ratios and approximate Cornfield's 95% confidence intervals were analyzed with Epi-Info 6 (USD Inc.). Pearson's chi square tests with the SPSS program (SPSS Inc.) were applied for the assessment of associations in two-dimensional contingency tables.²³ Total IgE measurements at the age of 12 months were log-transformed to approximate a better Gaussian distribution. Specific IgE antibodies to food and inhalant allergens and cord blood IgE were categorized according to the detection limit of 0.35 kU/L. Statistical significance was defined by a two-sided alpha level of 0.05.

RESULTS

In our study population, the prevalences of IgE antibodies to at least one of the tested allergens were 16.4%, 26.1%, and 26.7% at the ages of 1, 2, and 3 years, respectively. IgE antibodies to food allergens were the most common IgE antibodies detected during the first 3 years of life. Sensitization to at least one of the tested food allergens was observed in 14.1%, 17.9%, and 18.1% at the ages of 1, 2, and 3 years, respectively. The prevalence for IgE antibodies against cow's milk and wheat increased steadily throughout the age of 3 years. Also, the prevalence of IgE antibodies to hen's egg, the most common food allergen in our study population, increased from 1 to 2 years of age and decreased at the age of 3 years (Fig. 1, A).

The prevalence of IgE antibodies to indoor and outdoor allergens increased markedly at successive time points. Sensitization to mixed grass was the most com-

mon aeroallergen sensitivity in our study population at the ages of 2 and 3 years (Fig. 1, *B*). At 3 years of age, sensitization to outdoor allergens was found in 10.3% and sensitization to indoor allergens was observed in 8.6% of the children.

According to multiple logistic regression analysis, the following risk factors for allergic sensitization to indoor and/or outdoor allergens were identified (odds ratios and significance levels are summarized in Table I):

1. Children with a positive family history of atopy had a significantly greater risk of allergic sensitization to aeroallergens at the age of 3 years compared with children with a negative family history of atopy.
2. Sensitization to hen's egg was determined to be a significant risk factor for subsequent sensitization to aeroallergens. The highest risk for developing sensitization to inhalant allergens was observed in children with hen's egg-specific IgE antibodies greater than 2 kU/L (Fig. 2).
3. Log[total IgE] at the age of 12 months was positively correlated with sensitization to indoor and outdoor allergens at the age of 3 years.

Sensitivity, specificity, and positive predictive values for the above-mentioned risk factors are presented in Table II. Regardless of a positive or negative family history of atopy, hen's egg-specific IgE antibodies at the age of 12 months appear to be highly specific in regard to subsequent sensitization to inhalant allergens. However, the highest positive predictive value (78%) for this trait in our study population was obtained with the combination of two relevant risk factors: a positive family history of atopy and hen's egg-specific IgE antibodies greater than 2 kU/L at the age of 12 months.

Male gender, parental smoking, elevated cord blood IgE, and sensitization to food allergens other than hen's egg were not significantly associated with allergic sensitization to aeroallergens at the age of 3 years.

Atopic dermatitis was a common finding in children sensitized to hen's egg at the age of 1 year (data not shown). The 12 months' lifetime prevalence of evident atopic dermatitis was significantly higher in children with egg-specific sIgE antibodies (39.7%, $n = 27$) compared with children without egg-specific IgE antibodies (10.8%, $n = 78$) and was highest in children with specific sIgE antibodies to hen's egg greater than 2.0 kU/L (53.3%, $n = 8$, $p < 0.0001$). However, according to multiple logistic regression analysis (taking into account evident atopic dermatitis, sensitization to food allergens, cord blood IgE levels, log[IgE] at 12 months of age, and family history of atopy simultaneously), atopic dermatitis through the first year of life could not be evaluated as an additional risk factor for sensitization to inhalant allergens at the age of 3 years.

DISCUSSION

Our data demonstrate that a marked IgE response to hen's egg at the age of 12 months is predictive of subsequent sensitization to inhalant allergens. Screening of

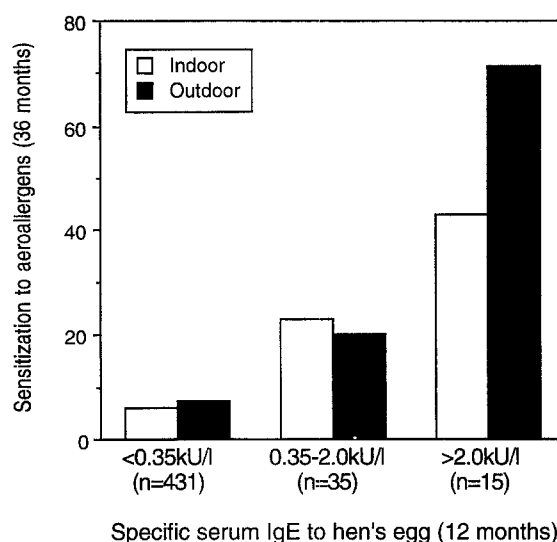


FIG. 2. Prevalence of sIgE antibodies to at least one of the tested indoor and/or outdoor allergens at age 36 months according to different concentrations of hen's egg-specific IgE antibodies at age 12 months.

children with a positive family history of atopy for hen's egg-specific IgE antibodies as a risk marker is a simple, inexpensive procedure. The high specificity and positive predictive value of a positive test result (hen's egg-specific IgE > 2 kU/L) offers us a profound basis for advising parents to undertake measures to reduce indoor and outdoor allergen exposure. Furthermore, the identification of children who are most likely to become sensitized to aeroallergens is a prerequisite for preventive intervention studies. Hen's egg-specific IgE during the first year of life may therefore become a crucial inclusion criterion for studying prevention of inhalant allergies.

The development of atopic diseases is the result of a complex interaction of genetic and environmental factors. Several follow-up studies have implicated family history of atopy, elevated cord blood IgE or soluble CD23, early peripheral blood eosinophilia, male gender, ethnicity, lymphocyte dysfunction, chromosomal mutations, and immune response genes as factors predisposing an individual to atopy.* Elevated cord blood IgE as a predictor for atopic disease has been recently questioned.^{18, 28, 29} Although linkage of atopy, IgE responsiveness, and bronchial hyper-responsiveness to different regions of the human genome has been described,³⁰⁻³² specific genetic markers for allergic sensitization are unlikely to be available in the near future.

Environmental factors such as early and high allergen exposure, season of birth, frequent viral respiratory tract infections, air pollution, early cow's milk feeding, early tobacco smoke exposure, and perinatal complications appear to facilitate the expression of the atopic phenotype.^{8, 10, 11, 26}

Sensitization to food allergens occurs in the majority of cases during the first years of life and is usually transient.³³⁻³⁵ Most sensitized children remain free of symp-

*References 5, 10, 15, 17, and 24-27.

TABLE I. Odds ratios with 95% confidence interval and level of significance of risk factors for sensitization to at least one of the tested aeroallergens, indoor allergens (cat, mite), and outdoor allergens (grasses, birch) at the age of 36 months

Risk factor	Sensitization to		
	Aeroallergens (<i>n</i> = 63, no. tested = 434)	Indoor allergens (<i>n</i> = 39, no. tested = 450)	Outdoor allergens (<i>n</i> = 47, no. tested = 455)
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Log[total sIgE] at 12 mo	2.3 (1.3-4.2) <i>p</i> = 0.006	2.2 (1.1-4.4) <i>p</i> = 0.022	2.4 (1.2-4.6) <i>p</i> = 0.01
IgE to egg at 12 mo (≥ 0.35 kU/L)	4.2 (1.9-9.2) <i>p</i> = 0.0005	4.1 (1.7-9.8) <i>p</i> = 0.0021	5.2 (2.3-8.1) <i>p</i> = 0.002
IgE to egg at 12 mo (0.35-2 kU/L)	2.9 (1.2-7.0) <i>p</i> = 0.023	3.1 (1.1-8.2) <i>p</i> = 0.027	2.3 (0.8-6.2) <i>p</i> = 0.11
IgE to egg at 12 mo (> 2 kU/L)	15.0 (3.2-71) <i>p</i> = 0.001	4.9 (1.2-20.4) <i>p</i> = 0.025	23.6 (4.6-121) <i>p</i> = 0.0004
IgE to cow's milk at 12 mo (≥ 0.35 kU/L)	0.9 (0.3-2.7) <i>p</i> = 0.8	1.4 (0.4-4.2) <i>p</i> = 0.56	0.4 (0.1-1.5) <i>p</i> = 0.12
IgE to wheat at 12 mo (≥ 0.35 kU/L)	1.0 (0.2-6.7) <i>p</i> = 0.97	1.6 (0.3-8.0) <i>p</i> = 0.53	1.2 (0.2-7.6) <i>p</i> = 0.98
Positive family history of atopy	2.8 (1.4-5.7) <i>p</i> = 0.002	2.8 (1.2-6.7) <i>p</i> = 0.012	2.6 (1.1-5.9) <i>p</i> = 0.017

OR, Odds ratio; CI, confidence interval.

TABLE II. Sensitivity, specificity, positive predictive values, and *p* value of rate ratios for sensitization to inhalant allergens at the age of 36 months with the combination of two relevant risk factors

Sensitization to inhalant allergens (36 mo)	Sensitivity (%)	Specificity (%)	PPV (%)	<i>p</i> Value (RR)
IgE (egg 12 m) not detectable and famh+ (<i>n</i> = 213)	86	46	21	<0.001
IgE (egg 12 m) 0.35-2 kU/L and famh- (<i>n</i> = 10)	32	94	46	0.38
IgE (egg 12 m) 0.35-2 kU/L and famh+ (<i>n</i> = 20)	29	96	55	<0.001
IgE (egg 12 m) > 2 kU/L and famh- (<i>n</i> = 4)	16	99	77	<0.01
IgE (egg 12 m) > 2 kU/L and famh+ (<i>n</i> = 9)	11	99	78	<0.001

The prevalence of sensitization to at least one of the tested aeroallergens at age 36 months was 0.15. Similar prognostic indices were observed when sensitization to indoor allergens and outdoor allergens at 36 months were analyzed separately.

PPV, Positive predictive value; RR, rate ratios; IgE (egg 12 m), serum IgE antibodies to hen's egg at age 12 months; famh+, positive family history of atopy; famh-, negative family history of atopy.

toms.³⁵ Immediate hypersensitivity to food allergens is a very common finding in children with atopic dermatitis.^{36, 37} Wheezing in early infancy does not appear to be related to allergic sensitization to food allergens.³⁸

The mechanism that predisposes children with food allergy to atopic disease later in childhood remains poorly understood.^{17, 19, 20} Studies of various dietary regimens during the first months or first years of life³⁹ have demonstrated a decreased incidence of food allergies and atopic dermatitis in children who followed a prescribed dietary regimen. Unfortunately, long-term follow-up studies have shown that once an allergenic food (e.g., egg, milk, or peanut) is subsequently introduced, the prevalence of food allergies and atopic dermatitis reverts to the normal level. Furthermore, food allergen avoidance does not seem to protect predisposed children from inhalant allergies later in childhood.³⁹ However, the long-term effect of dietary regimens during the first months or years of life on the development of asthma, atopic dermatitis, and allergic rhinitis remains controversial. In conclusion, food allergen avoidance appears to prevent sensitization or allergic dis-

ease caused by the particular food allergens in question, but it is probably not effective in the prevention of sensitization to inhalant allergens.

The overall objective in pediatric allergy is primary prevention, specifically, the inhibition of an IgE response. Secondary prevention focuses on the deterrence of disease expression after asymptomatic allergic sensitization.¹⁷ Screening at the age of 12 months can be interpreted as secondary rather than primary prevention. The quality of a screening test depends on sensitivity, specificity, and predictive values. In our study population, more than 50% of the children who were sensitized to inhalant allergens at the age of 3 years had no sensitization to hen's egg at the age of 1 year. Consequently, the sensitivity of this risk marker is clearly unsatisfactory. However, none of the risk factors that have been identified during the last 2 decades are highly sensitive and specific.^{8, 9, 18} We found that use of egg-specific IgE greater than 2 kU/L in combination with a positive family history of atopy was a highly specific (99%) and predictive (positive predictive value, 78%) marker for sensitization to inhalant allergens at 3 years of age. The

identification of very specific risk factors for early sensitization to aeroallergens will be of considerable value in allergy research.

The first 12 months are a vulnerable period for the development of a specific IgE response to aeroallergens.^{4,6} Longitudinal studies may determine whether environmental and/or therapeutic interventions can prevent sensitization to aeroallergens and the development of allergic asthma or allergic rhinitis after the identification of children at risk during the first year of life. Because sensitization to aeroallergens usually precedes symptomatic inhalant allergies by several years, the further follow-up of our cohort will show the predictive value of hen's egg-specific IgE antibodies for allergic asthma and rhinitis.

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