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IgE antibody responses in young children with atopic dermatitis

Wahn U, Warner J, Simons FER, de Benedictis FM, Diepgen Th, Naspitz Ch, de Longueville M, Bauchau V, on behalf of the EPAAC Study Group. IgE antibody responses in young children with atopic dermatitis.
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In 2184 young children aged 13–24 months with atopic dermatitis (SCORAD 5–59) serum IgE antibodies to a standard panel of food and inhalant allergens were assayed. The frequency of positive IgE responses (>0.35 kU/l) increased with greater severity of skin disease. A significant minority of infants had levels of IgE antibody to foods to suggest they were at risk of acute reaction to those foods (7% to hen's egg, 3% to cow's milk, 4% to peanut). Our findings indicate that the frequency of positive IgE responses is related to disease severity and suggest that differences in the time course of the development of IgE responses to food, which are at maximum prevalence within the first year of life, while inhalant allergies, are still developing between 1 and 2 yr and beyond.

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IgE antibody responses to food and inhalant allergens represent characteristic immunological markers in individuals with atopic dermatitis. Data obtained from longitudinal observational birth cohort studies indicate that in children with atopic dermatitis elevated serum concentrations of IgE antibodies to inhalant allergens can be considered not only as early markers for atopy, but also as potential predictors for both subsequent allergic airway disease and the long-term persistence of atopic dermatitis (1–4).

The Early Prevention of Asthma in the Atopic Child (EPAAC) study was designed to test the effect of a pharmacologic intervention with levocetirizine in young children with atopic dermatitis aged 1–2 yr aiming at the prevention of the onset of asthma. For this study, a large population of young children with atopic dermatitis was screened, providing a unique opportunity to analyze the relative importance of several potential genetic and environmental determinants.

The aim of our study was to describe the development of IgE-responses to food and inhalant allergens during the second year of life and evaluate their relationship to the severity of atopic dermatitis.

Methods

Study population

The group selected for this cross-sectional study consisted of children with mild, moderate and

severe atopic dermatitis, based on the severity score for atopic dermatitis at the time of initial screening (SCORAD ≥5) and a positive family history for atopy and/or asthma. Overall, 2184 children from 12 different countries with moderate or severe atopic dermatitis and a mean age of 17.6 months were included (57.1% male, 42.9% female). 92% were Caucasians. The group included 30 children from 15 pairs with both twins recruited and 36 children unpaired. Children were born between April 2000 and March 2003, the investigations were performed between March 2002 and March 2004. Informed consent has obtained from all parents, which included the collection of blood samples for IgE determinations.

SCORAD index

SCORAD is a standard tool for measuring the severity of atopic dermatitis, with scores that may range from 0 to 103. SCORAD ratings below 25 define mild atopic dermatitis scores, between 25 and 50 define moderate atopic dermatitis and higher than 50 define severe atopic dermatitis. Before children were screened for the EPAAC Study, all the investigators were trained to use the SCORAD, in order to ensure homogeneity of the assessments (5). Indeed a validation exercise was performed on the use of this assessment tool by the investigators involved with the predecessor study to the EPAAC Study, namely the ETAC Study (5, 6). This showed that after training, non-expert investigators produced evaluations within the range of experts and that can therefore be used for standardized scoring of atopic dermatitis by non-dermatologist investigators.

Total and specific serum IgE antibodies

Total serum IgE and specific IgE antibodies were measured by the Pharmacia ImmunoCAP technology for the following eight allergens: mixed grass pollen, mixed tree pollen (birch, alder, hazel), house dust mite, cat, egg, peanut, milk, and Alternaria. The lower and upper detection limits were 0.35 and 100 kUA/l for specific IgEs, and 0.35–10,000 kU/l for total IgE.

Unless otherwise stated, a specific IgE test was considered positive if ≥0.35 kU/l. Specific IgE serum concentrations were also expressed in Pharmacia CAP-classes for which definitions are presented in Table 1.

Statistical methods

Descriptive statistics (mean, median, range, quartiles, and standard deviation) are reported in a standard way. The association between sensitization (inhalant or food) and severity of atopic dermatitis (SCORAD) was tested by logistic regression. The correlation between the number of positive IgE tests and total serum IgE was analyzed by Pearson correlation.

Results

Atopic dermatitis severity was distributed over a wide range (SCORAD 5–59). The mean SCORAD total index for the study population was 33.3 (median: 31.0; n = 2.152; standard deviation = 14.7; range = 0.6–93.8). By definition 68.8% of the children belonged to the moderate to severe (SCORAD >25) subgroup (Fig. 1).

Total serum IgE

As expected for total IgE, levels below detection limits (0.35 kU/l) were found in only three children. Regarding the upper detection limit, five children had IgE concentrations above 10,000 kU/l (maximum 13,800 kU/l), the mean serum concentration of total IgE in the study population was 191.0 (standard deviation 813.4, median 34.9). The full distribution is illustrated in Fig. 2.

Specific serum-IgE antibodies

For 2.096 children all specific IgE results were available. 933 of the children (44.5%) were not

Table 1. Percentage of atopic dermatitis children sensitized to food and environmental allergens as expressed in Pharmacia CAP classes

Allergen (kU/l)	I (0.35–0.69)	II (0.70–3.49)	III (3.50–17.49)	IV (17.50–49.99)	V (50.00–99.99)	VI (≥100)	Percentage of sensitized children
Egg white	8.2	15.8	11.5	4.3	1.4	0.8	42.0
Cow's milk	6.9	11.8	5.0	2.2	0.8	0.6	27.3
Peanut	4.9	9.3	6.2	2.7	0.8	0.7	24.6
Grass pollen	2.2	4.0	1.6	0.3	0.0	0.0	8.1
Tree pollen	3.1	3.7	1.1	0.3	0.1	0.1	8.4
Alternaria	1.5	1.6	0.4	0.1	0.0	0.0	3.6
House dust mites	2.1	5.1	6.7	4.0	1.0	1.6	20.5
Cat dander	2.3	5.0	3.5	1.7	0.2	0.2	12.9

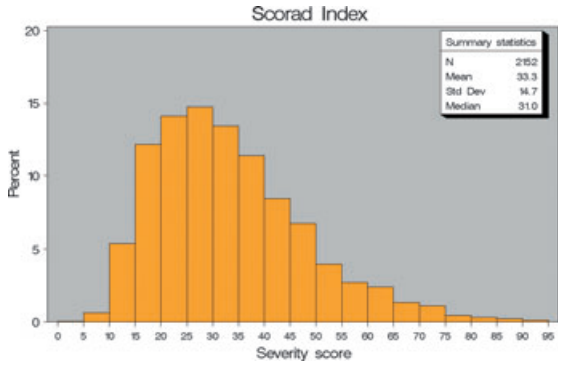

Fig. 1. Severity of atopic dermatitis in 2184 young children as assessed by using the SCORAD index.

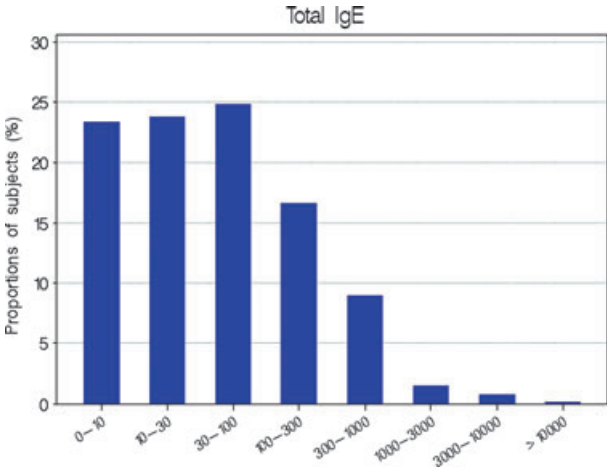

Fig. 2. Distribution of total serum IgE concentrations (kU/l) in 2096 young children with atopic dermatitis.

sensitized to any of the allergens tested, 391 (18.7%) were sensitized to one allergen, and 772 (36.8%) were polysensitized, showing elevated serum IgE antibody levels to a variety of food and/or inhalant allergens.

When the children were grouped into four quartiles by increasing atopic dermatitis severity, the proportion of children sensitized to both food ($p < 0.0001$)and inhalant allergens ($p < 0.0001$) increased (Table 2). The results were very similar when adjusted for age, sex, and country.

The tendency to develop specific IgE responses by the second year of life was significantly related to the total IgE serum concentrations. The group of children with the highest total IgE had the highest number of specific IgE responses (Pearson correlation coefficient $r = 0.72$, $p < 0.0001$; Fig. 3).

Although the study was cross-sectional, a clear relationship between age and some of the specific IgE antibody levels could be demonstrated: While the prevalence of children with sensitization to food proteins such as hen's egg, cow's milk and peanut was not higher with increased age during the second year of life [there was even a slight, but significant decrease in sensitization to egg ($p < 0.05$) and peanut ($p < 0.0001$)], a comparison between the age group up to 17 months and the group 18 months and older shows for all the indoor and outdoor inhalant allergens tested (house dust mite, tree and grass pollen) a highly significant ($p < 0.001$) increased proportion of sensitized children with age (Fig. 4).

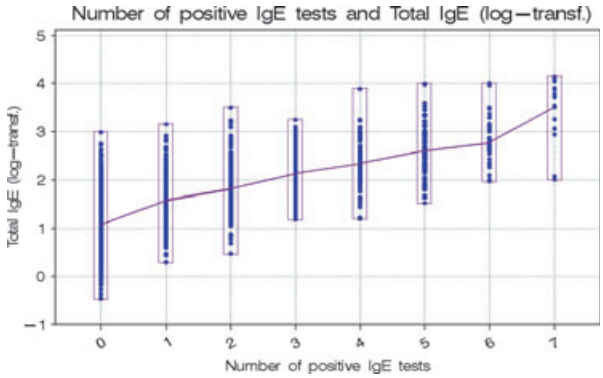

Fig. 3. Association between total serum IgE concentration and a number of specific sensitizations to food and inhalant allergens.

Table 2. Elevated specific serum IgE antibodies in relation to severity of atopic dermatitis in young children

Quartile (SCORAD index)	I (0–22)	II (22–31)	III (31–41)	IV (>41)
Proportion sensitized to any inhalant allergen ($p < 0.0001$) (%)	20.5	25.7	33.9	45.4
Proportion sensitized to any food allergen ($p < 0.0001$) (%)	40.7	43.0	49.0	61.4

Discussion

To our knowledge the present study represents the largest ever group of young children with atopic dermatitis in whom immunologic parameters have been investigated. Compared with other atopic conditions, atopic dermatitis is known to be the clinical phenotype with the highest total serum IgE concentrations. The likelihood of specific IgE antibody responses to both food and inhalant allergens increases with the total serum IgE concentration.

Genetic studies utilizing positional cloning in large groups of families with affected siblings suggest that atopic dermatitis and specific IgE responses in infancy as two different atopic

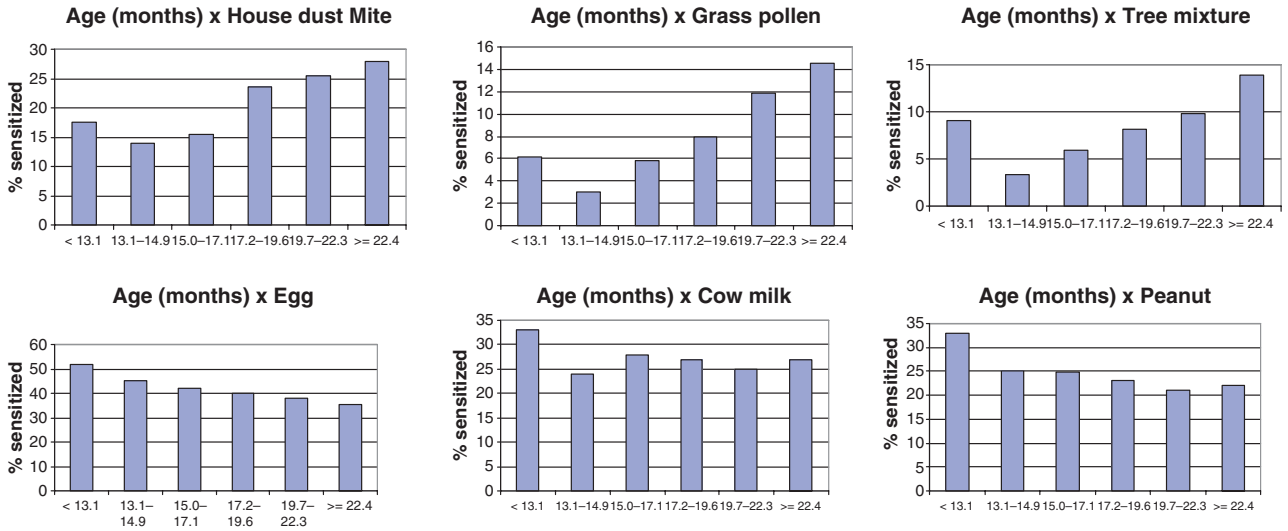

Fig. 4. Sensitization (serum IgE >0.35 kU/l) to food (egg, cow's milk, and peanut) and inhalant (house dust mite, grass pollen, tree mixture) allergens in the study population in relation to age (months).

phenotypes might be regulated by one common gene (7).

In our study cohort, which represents children with atopic dermatitis of varying clinical severity, IgE antibody responses to hen's egg proteins (42%) were found to be most prevalent, while sensitization to cow's milk and peanut was detected in 24–27% of the children. Similar results have been reported previously from other birth cohort studies, suggesting that early IgE antibody responses to hen's egg represent the most important infantile marker for atopy (8–10). Whether or not these infantile responses are related to nutritional hen's egg exposure via mother's milk, or to any other environmental exposure is still not completely understood. However, the relationship between the level of exposure and sensitization is not necessarily linear, as very low doses may sensitize while high doses may induce tolerance (11).

Although the study design was cross-sectional, the number of children who were sensitized to the most common food allergens (egg, cow's milk, and peanut) did not increase during the second year of life, thus suggesting that the process of sensitization was completed by the first birthday. Similar results were reported from the ETAC trial (4) and the German birth cohort study MAS (9).

In contrast, aero-allergens from the indoor (house dust mite) or outdoor (grass pollen, tree pollen) environment were found to increasingly induce sensitization with age during the time window, which was investigated. It can be concluded that the process of sensitization, which in many cases may later be associated with clinically manifest allergic reactions of the upper and lower airways takes more time and in many cases is preceded by infantile sensitization to food proteins. A variety of longitudinal studies in which sequential blood samples were obtained from atopic children during the first years of life have demonstrated that a switch from infantile IgE responses to hen's egg, to indoor or outdoor aero-allergens is associated with a high risk of developing asthma (10). The data, however, could also be interpreted as showing a specific association between egg allergy and inhalant allergy being regulated by a subgroup of as yet unknown genes.

Clearly, early IgE antibody responses to foods as well as inhalant allergens are related to the severity of atopic dermatitis (3). Comparing the proportion of sensitized children in four quartiles for atopic dermatitis severity, it is obvious that children with the most severe atopic dermatitis are twice as frequently sensitized to inhalant allergens, and compared to children with mild atopic dermatitis, they show 50% more sensitization to food allergens.

Several studies have suggested that the serum concentration of specific IgE antibodies to food proteins can be related to their clinical significance. Cutoff or decision points for specific IgE antibodies to hen's egg, cow's milk and peanut have been reported, above which the clinical relevance of IgE antibodies in terms of clinically observed adverse reactions can be predicted with a 95% or 99% likelihood (12, 13). Taking these decision points for children under age 2 yr (egg, 2

kU/l; milk, 5 kU/l,), or over 2 yr of age (egg, 7 kU/l; milk 15 kU/l), it is obvious that a small percentage (>7% to hen's egg, >3% to cow's milk, >4% to peanut) of our young children with atopic dermatitis have a 95% risk of developing clinically relevant allergic reactions and possibly even anaphylaxis. Therefore, according to the current evidence, the caregivers of this group of children with atopic dermatitis should be instructed to avoid giving these foods, until repeat assessment has established that they are safe to be re-introduced onto the diet (2, 12).

In the majority of young children with atopic dermatitis, the long-term outcome of the disease is a remission that may be complete or incomplete. At the same time, a high percentage of this study group is likely to develop persistent asthma, which may be triggered by inhalant allergens. It has been shown that the severity of infantile atopic dermatitis together with high IgE antibody concentrations in the first years of life are not only suggestive of clinically relevant allergies, but also have to be considered as predictors of persistence of atopic dermatitis and the development of allergic asthma (1, 6, 10). Indeed, in ETAC, sensitization to house dust mite, cat, grass pollen, or egg (but not milk) amongst 1- to 2-yr-old infants with atopic dermatitis was associated with a significantly higher probability of developing asthma over the subsequent 3 yr (14).

In conclusion the present cross-sectional study of a large group of children with atopic dermatitis demonstrates a relationship between early disease severity and specific IgE responses and provides evidence for differences in the time course of the development of IgE responses to food allergens compared to inhalant allergens.

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