

An explorative study of low levels of allergen-specific IgE and clinical allergy symptoms during early childhood

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Abstract

Background: Early identification of children at risk for later development of allergic disease is essential for early intervention and initiation of proper treatment and management.

Objective: To investigate the relationship between low levels (0.1–0.7 kU_A/l) of IgE sensitization to food and inhalant allergens and symptoms of eczema, rhinitis, and asthma from birth to 5 years of age.

Methods: Children (268) were followed prospectively from birth to 5 years of age with physical examinations and measurements of s-IgE at 6, 12, 24, and 60 months of age.

Results: Seventy-four percent of the children with low levels of s-IgE to egg and/or milk at the age of 6 months were still sensitized to one or more allergens at age 2 years. Eighty-four percent of the children with low levels of s-IgE to any of the studied allergens at 12 months of age were still sensitized at age 5. The low levels of egg and milk s-IgE also significantly increased the risk for eczema at the same age and also increased the risk for eczema at 2 years of age.

Conclusion: Low levels of s-IgE can be detected from the age of 6 months and are related to further IgE sensitization. The low levels seem to be of importance for both the association to present symptoms and for prediction of future allergic symptoms, especially eczema during early infancy. A detectable s-IgE level, albeit low, could be a clear signal that the immune system is alerted and should be followed.

The importance of early identification of children at risk for later development of allergic disease has been defined by the European Academy of Allergy and Clinical Immunology (1). Evidence-based recommendations on allergy testing have been established to enable initiation of proper allergy treatment, such as specific allergen avoidance, relevant pharmacotherapy, and specific allergen vaccination (1).

The production of allergen-specific IgE antibodies (s-IgE) is a prerequisite for the development of atopic disease. Precisely when the IgE sensitization starts, before or after birth, is still not fully established (2). Early sensitization and its contribution to the development of allergic disease is sometimes referred to as the atopic March, starting with eczema in the very young child and evolving subsequently into rhini-

tis and asthma for children of school age (3). Several studies have shown a quantitative relationship between s-IgE and allergy symptoms for preschool children (4–7). Also, there are indications that from 6 months stable signals can be measured and are also, in some cases, predictive of future sensitization (2). Furthermore, the levels of s-IgE at 3 years of age have been shown to be predictive of persistent wheeze at 5 years of age (6).

The time delay between sensitization and the expression of symptoms will vary between individuals, owing to different confounders such as genetic influence, infections, type of allergen, degree of exposure, individual clinical reactivity and to the level of IgE antibodies to one or several allergens. Because of the immature immune system in very young children, levels of s-IgE are likely to be very low. Less emphasis has been placed on evaluating whether low levels of s-IgE are related to symptoms and whether they also are predictive of future allergic disease. One reason for this may be previous

Abbreviations

CI, confidence interval; OR, odds ratio; s-IgE, allergen-specific IgE antibodies.

shortcomings of existing tests to precisely and reproducibly measure low levels of s-IgE. In a previously published Swedish study, children were followed from birth up to 4 years of age. By using modifications of the existing method for increased sensitivity, the authors found that low levels of s-IgE to milk and egg frequently appeared during infancy in both atopic and nonatopic children. However, s-IgE levels increased to higher levels exclusively in infants with present or future atopy (8, 9). Using a modified method for detection, Sasai et al. found that low levels of s-IgE against house dust mite were highly predictive of allergic disease at 5 years of age (10), findings recently confirmed by Holt (11).

The aim of the present study was to investigate the relationship between IgE sensitization to food and inhalant allergens, with special emphasis on low levels of s-IgE, and the development of allergic diseases (symptoms of eczema, rhinitis, and asthma) during childhood. With improved test technology for the determination of circulating s-IgE levels, it is now possible to measure down to 0.1 kU_A/l with good precision.

Material and methods

Study design and subjects

This exploratory study includes 268 children born between 1997 and 2000 who are part of a prospective study cohort ($n = 281$). Families who were expecting a child were asked by the midwife at the maternity ward if they were interested in participating in the study. Only parents for whom skin prick tests confirmed their case history were included in the cohort. One-third of the children had two parents with allergy, another third had mothers with allergy, and the remaining third had no allergic parents. All infants were healthy and born full term at hospitals in Stockholm. A detailed description of the cohort has been published elsewhere (12).

The children were followed prospectively from birth to 5 years of age and were clinically evaluated at 6, 12, 18, 24 months, and at 5 years of age by the same pediatric allergologist. The study was approved by the Human Ethics Committee at Huddinge University Hospital, Stockholm, and the parents provided informed consent.

Outcomes

At each visit (6, 12, 18, 24, and 60 months of age), the presence of allergy-related diseases was recorded for each child. The definitions used were as follows: *Eczema* as defined according to Hanifin and Rajka (13). *Wheezing/asthma* was defined at the clinical evaluations by a pediatric allergologist according to the Swedish Pediatric Allergy Society guidelines. Up to 2 years of age, the children were labeled with the symptom *wheezing* and after 2 years of age with *asthma*. *Wheezing* was defined as three or more episodes of wheezing or hyper-reactivity, or any episode of wheezing or hyper-reactivity if combined with a family history of allergic disease or other allergic symptoms in the child or respiratory symptoms

treated with inhaled glucocorticosteroids. After 2 years of age, any episode of wheezing or signs of hyper-reactivity reaction or wheezing after exposure to an allergen or respiratory symptoms treated with inhaled glucocorticosteroids was defined as *asthma*. *Rhino-conjunctivitis* was defined as symptoms of rhinitis and/or conjunctivitis appearing at least twice after exposure to a particular allergen and unrelated to infection.

Allergen-specific IgE antibodies

Circulating s-IgE against hen's egg white (egg), cow's milk (milk), codfish, peanut, soybean, cat, dog, *Dermatophagoides farinae*, and birch and timothy pollens was determined using ImmunoCAP® System (Phadia AB, Uppsala, Sweden) in plasma collected at 6, 12, 24 months, and 5 years of age. The measuring range of the test was 0.1–100 kU_A/l.

Low levels of allergen-specific IgE antibodies

Low levels were defined as s-IgE concentrations between 0.1 and 0.7 kU_A/l. The levels were dichotomized into levels below 0.1 kU_A/l and low levels between 0.1 and 0.7 kU_A/l. All results above 0.7 kU_A/l were omitted in the risk analysis.

Statistical methods

Primary outcome variables were the three symptoms eczema, rhinitis, and wheeze/asthma at 6, 12, 24, and 60 months of age. All evaluable cases were used for each part of the analysis. An exact binomial test was used for testing differences in numbers between children with low levels of s-IgE, <0.7 kU_A/l, vs children with higher levels of s-IgE, >0.7 kU_A/l. The levels of s-IgE were subject to logarithmic transformation before analysis and presented average levels are the geometric means. The relationship between sensitization status and clinical outcome status was analyzed using logistic regression. The clinical outcome was defined as the presence or absence of investigated symptom and is always presented as current prevalence. Odds ratios (ORs) were estimated using the regression models and confidence intervals (CIs) were generated according to Wald, using a P -level of 0.05 as significant. Being an exploratory study, no adjustments for multiple testing have been made. The results should be interpreted descriptively and as a base for further confirmatory studies.

Results

In total, 268 children were examined and gave blood for testing. The follow-up rate for the visits at 6, 12, 24, and 60 months of age were 99%, 100%, 99%, and 90%, and blood was received from 173, 165, 251, and 230 children, respectively. The distribution of gender was equal with 134 boys and 134 girls. Even if the pattern of symptoms changed over the years, eczema was the most frequent symptom for all ages, followed by wheezing and asthma, while rhinitis was mainly diagnosed at 5 years of age, Fig. 1. There was no

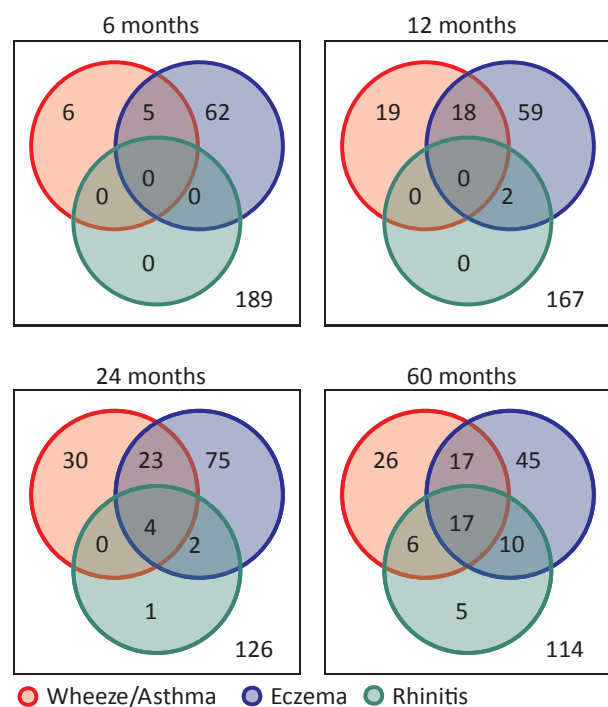


Figure 1 Wenn diagram for Wheezing/Asthma, Rhinitis, and Eczema for the four ages groups.

statistically significant difference between genders in relation to symptoms.

Pattern and levels of allergen-specific IgE antibodies

The presence of IgE antibodies to the allergens studied varied at different ages. The most common IgE sensitizations at all ages were to egg and milk. At 6 months of age, some children also showed sensitization to peanut, cat, and dog, and at 12 months of age, sensitizations against soy, birch, and timothy were observed. From the age of 24 months and over, sensitization against all allergens studied could be detected, Fig. 2A. No differences between genders could be found.

The majority of the children were sensitized to one or two allergens. Sensitization to several allergens was mainly found in children of 24 months and 5 years of age, Fig. 2B.

The development of s-IgE levels with respect to age varied for different allergens. For egg and milk, the average s-IgE concentration (geometric mean) decreased with increasing age, whereas for the other studied allergens, the average s-IgE levels increased with increasing age. Except for birch, cat, and peanut at age 5, the average s-IgE concentrations were low, Table 1. There were no differences in s-IgE concentrations between genders.

Low levels of allergen-specific IgE antibodies

Low levels (0.1–0.7 kU_A/l) of s-IgE were significantly more frequent than levels above 0.7 kU_A/l for most of the

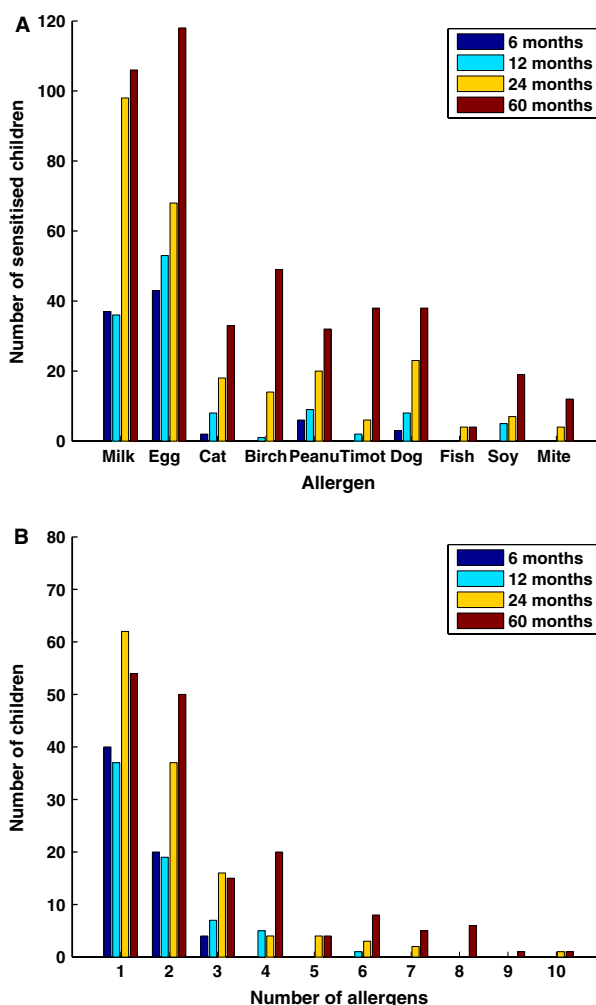


Figure 2 (A) Number of children sensitized for each allergen. (B) Number of poly-sensitizations.

selected allergens at all ages studied. Only for birch-sensitized children at 5 years of age, there were significantly more children with levels above than below 0.7 kU_A/l of s-IgE, Table 2.

Of the children with low levels of any studied s-IgE at 6 months of age, 77% were still sensitized to one or more allergens at the age of 2 years and 81% at the age of 5 years. The corresponding prevalence of sensitization at 2 and 5 years in children sensitized with low levels at 12 months of age was 85% and 84%, respectively. Having low levels of s-IgE at 6 and 12 months of age increased the risk for IgE sensitization above 0.7 kU_A/l to any of the analyzed allergens at 5 years of age, OR = 3.08 (95% CI: 1.05–9.03) and OR = 5.20 (95% CI: 2.00–13.5), respectively.

Relationship to eczema in young children

Children with low levels of egg and/or milk s-IgE at 6 months of age had an increased risk of displaying symptoms of eczema

Table 3 The association between low levels (0.1–0.7 kU_A/l) of s-IgE and eczema at different ages, OR (95% CI)

Allergen	Sensitisation at	Symptoms of eczema at age			
		6 months	12 months	24 months	60 months
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Egg	6	1.39 (0.67–3.74)	0.99 (0.42–2.35)	1.78 (0.79–4.02)	1.03 (0.43–2.44)
	12		1.14 (0.52–2.56)	3.32 (1.54–7.18)	1.17 (0.52–2.61)
	24			2.00 (1.09–3.66)	1.50 (0.80–2.83)
Milk	6	1.85 (0.72–4.74)	1.02 (0.39–2.66)	4.86 (1.84–12.8)	0.70 (0.25–1.93)
	12		2.40 (1.03–5.55)	3.52 (1.48–8.37)	0.85 (0.34–2.14)
	24			1.54 (0.90–2.65)	1.16 (0.66–2.04)
Egg and or Milk	6	2.36 (1.06–5.09)	1.31 (0.60–2.87)	3.07 (1.44–6.55)	1.18 (0.54–2.60)
	12		1.43 (0.67–3.08)	3.33 (1.60–6.96)	0.99 (0.45–2.15)
	24			1.74 (1.01–3.01)	1.20 (0.68–2.12)
Dog	6				
	12		3.05 (1.38–6.77)	9.33 (1.09–79.7)	10.5 (1.23–90.1)
	24			7.89 (2.20–28.4)	3.36 (1.19–9.47)

All the bold figures are statistically significant odds ratios.

at the same age, OR = 2.36. At 12 months of age, low levels of milk s-IgE were related to eczema at the same age, OR = 2.40, Table 3. When the children had reached the age of 24 months, low levels of s-IgE to egg were related to an increase in the risk for eczema at the same age, OR = 2.00, Table 3. On the other hand, at 5 years of age, a relationship between egg and/or milk and eczema could no longer be found. The numbers of children sensitized to the other investigated allergens were too low to allow risk evaluation.

The low s-IgE levels at 6 and 12 months of age were also studied in relation to the development of eczema at higher ages. At 6 months of age, low levels of s-IgE to milk increased the risk for eczema at 2 years of age, OR = 4.86, whereas at 12 months of age, low levels of s-IgE to both egg and milk increased the risk for eczema at 2 years of age (OR = 3.52 and OR = 3.32, respectively), Table 3. There were no statistically significant associations between low levels of s-IgE antibodies to egg and milk at young ages and eczema at 5 years of age. There was, however, an increased risk, OR = 3.36, for eczema at 5 years of age in children

with low levels of s-IgE to dog at 24 months of age, but this association was based on a low number of children, Table 3.

Relationship to wheeze in young children

No valid relationship could be found between low s-IgE levels at 6, 12, or 24 months and wheeze at the same age (data not shown). However, when low s-IgE levels at 12 months of age were related to wheeze at 2 years of age, a slightly increased risk could be noticed for the sum of egg and milk s-IgE levels, OR = 2.65 (95% CI 1.04–6.73).

Relationship to asthma and rhinitis in preschool children

When the children had reached the age of 5 years, all three symptoms were prevalent, however with a rather severe comorbidity between them, Fig. 1. The low levels of s-IgE to egg and milk had no relation to any of the two respiratory allergic symptoms at this age (data not shown). For the other studied allergens, low levels of s-IgE to cat, timothy, and soybean were found to be risk factors for both asthma and rhinitis, birch only for eczema, and finally peanut and dog only for rhinitis, Table 4. However, as the number of affected children was small, the confidence intervals were rather wide.

No valid relationships between low levels of s-IgE at previous ages (6 and 12 months of age) and respiratory symptoms at 5 years of age were found. A weak association between low levels of s-IgE to birch and peanut at 2 years of age and rhinitis at 5 years of age was also found (data not shown).

Discussion

In this exploratory study, we found that the prevalence of IgE sensitization to all examined allergens increased with increasing age and that inhalant s-IgE were mainly present from age 24 months. Most of the children were sensitized to

Table 4 The association between low levels of s-IgE at age 5 years and diagnosed symptoms at 5 years of age

Allergen	Eczema	Asthma	Rhinitis*
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Peanut	1.87 (0.67–5.20)	2.01 (0.69–5.84)	9.39 (3.06–28.8)
Soybean	1.79 (0.56–8.90)	4.46 (1.35–14.7)	5.39 (1.58–18.3)
Birch	3.73 (1.16–11.9)	3.00 (0.98–9.19)	2.56 (0.51–12.9)
Timothy	4.83 (1.89–12.4)	2.98 (1.24–7.14)	9.20 (3.55–23.8)
Cat	3.52 (1.22–10.1)	4.74 (1.67–13.5)	8.80 (2.89–26.8)
Dog	2.10 (0.92–2.10)	2.20 (0.93–5.21)	17.31 (6.58–45.5)

*Low number of children.

All the bold figures are statistically significant odds ratios.

one or two allergens. We also found that 84% of the children with low levels of s-IgE at the age of 12 months were still sensitized at 5 years of age. Low levels of s-IgE at young ages were associated with an increased risk of increasing s-IgE levels at higher ages and also related to an increased risk for allergic symptoms at each age and to future symptoms. These associations were most pronounced for low s-IgE levels to milk and egg and eczema.

Before the age of two, low level IgE sensitization was mainly because of food allergens, followed by pet allergens. Sensitization to inhalant allergens became more frequent at 2 years of age, still mainly from cat and dog, and more children were also diagnosed with respiratory symptoms at this age. Low s-IgE levels to dog increase the risk for both eczema and asthma at 5 years of age. However, because the majority of children with low s-IgE levels to dog were diagnosed with both eczema and asthma, we could not allocate the risk to either of these two individual symptoms.

In the present study, in agreement with previous observations (2), stable, albeit low, levels of s-IgE to egg and milk already at 6 months were related, not only to eczema but also to further sensitization at the age of 5 years. This pattern was even more pronounced when the children reached the age of 12 months. It should, however, be emphasized that although the presence of low s-IgE levels to milk and egg is associated with eczema, there is not necessarily a causal relationship between allergen exposure and disease. We did not have the resources to perform food challenge to confirm the relationship between eczema and these food allergens.

With improved test technology, it is now possible to accurately measure IgE antibody concentrations down to 0.1 kU_A/l, and there are a few cases where low s-IgE levels have been studied (6, 10). However, most published studies apply the previous technical detection limit of ≥ 0.35 kU_A/l as a threshold also of clinical importance, which is not based on clinical evidence.

The implications of s-IgE concentrations in the low interval for the clinical situation have not been studied thoroughly, although recent studies among patients with allergic reactions to drugs (14) and to insect stings (15) indicate the importance of a low detection limit. For drugs, the authors found an optimal threshold for clinical reaction of 0.13 kU_A/l for rocuronium and of 0.11 kU_A/l for suxamethonium.

To support wasp venom allergy, the authors concluded that a detection limit of 0.10 kU_A/l was useful in patients previously determined as seronegative but with a history of wasp venom allergy.

We decided in the present study to define low s-IgE levels as the interval between 0.1 and 0.7 kU_A/l, where the lower limit is determined by the ability to measure precisely and quantitatively and the upper limit in common practice as values below 0.7 kU_A/l are seldom considered to be associated with clinical allergy.

We found that low levels of s-IgE to the studied allergens were equally or more prevalent than higher (> 0.7 kU_A/l) levels at all ages, except for birch at 5 years of age. However, the importance of the low levels in relation to symptoms was most pronounced at the very young ages, indicating the need for early testing and careful evaluation of low levels of s-IgE. A detectable s-IgE level, albeit low, is a clear signal that the immune system is alerted and needs to be followed.

This study is unique in that we have focused on the effect of these low levels of s-IgE while other publications, such as from the MAAS (Manchester Asthma and Allergy Study) study, focus on the effect of different cut-offs and hence also include high s-IgE levels. The present study is strengthened by the prospective design, including a physical examination by the same pediatric allergologist and s-IgE measurements for 10 allergens when the children were 6, 12, 24, and 60 months of age.

However, the difficulty in drawing blood from all children, at all age groups, made the groups in some cases rather small. This also did not allow for subdivisions of the symptom groups, which may have made interpretations clearer with regard to relationships between groups of allergens and symptoms. Also, predicted ORs must be interpreted with appropriate limitations compared with analyses performed in a large cohort and viewed in the perspective of an exploratory study without adjustments for multiple testing. Furthermore, our results are based on a high-risk group of children and are not population based. However, we do not believe that the study design has any severe impact on the generalization of the study results.

Low levels of s-IgE can be detected from the age of 6 months and can be related both to ongoing symptoms, especially eczema, and to further sensitization and development of clinical symptoms of allergy during childhood.

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