

Sensitization to food and airborne allergens in children with atopic dermatitis followed up to 7 years of age

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Previously we investigated the eczema prognosis and the risk of developing allergic asthma and rhinitis in a cohort of 94 children with atopic dermatitis. In this second study on the same cohort we address the development of sensitization to foods and airborne allergens, risk factors and, the question whether children with atopic dermatitis who will not become sensitized can be recognized early. Children with atopic dermatitis were followed up regularly from infancy or early childhood to 7 years of age with clinical examination and blood sampling. After age 3, skin prick tests with inhalation allergens were performed yearly. In most children both clinical allergy and sensitization to egg and milk were transient but those to peanut were persistent. Eighty per cent of the children became sensitized to airborne allergens and 75% of them noticed symptoms when exposed. Heredity for atopy and eczema, sensitization to hen's egg, and early onset of eczema entailed an increased risk of becoming sensitized. Children never sensitized had late onset of eczema and less heredity for atopic disease but did not differ in other respects from the sensitized children.

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Atopic dermatitis in childhood is a marker of an atopic constitution even if no specific allergy causing the eczema can be found. The atopic constitution will in most cases lead to sensitization to food and/or respiratory allergens, and in many of the children it will give rise to manifest allergy (1–6). This immune response seems to be influenced by several factors, such as heredity, the age at onset and the severity of the eczema, the type and amount of allergens to which the child is exposed, and probably adjuvant factors. In a previous paper (6) we reported on the prognosis of the eczema, and the risk of developing asthma and rhinitis in a cohort of children with eczema of early onset. The aim of this study was to investigate, in the same cohort, the development of sensitization and to see whether it was possible to distinguish at an early age those children with eczema who would not become sensitized before 7 years of age.

Materials and methods

Ninety-four of 100 children with atopic eczema resident in two medium-sized Swedish cities (Uppsala and Örebro) were followed up. Six were drop-outs. The children were recruited from our paediatric outpatient clinics but some were also referred from well-baby settings. In short the study design was as follows (for more details, see Ref. 6). The children were regularly examined up to 7 years of age (median 86 months). The mean number of visits was 6.7 per child. The median age at recruitment was 17 months (range 4–35 months), and the inclusion criterion was pruritic eczema on an area at least the size of the child's hand, with duration of at least 3 months. At each visit an allergy history was taken, and a physical examination that included an eczema score was performed. This score, graded from 0 to 8, was based upon the severity and distribution of the

eczema and its treatment (6). In addition, a serum sample was taken, and from the age of 3 years a skin prick test (SPT) was carried out on the forearm with extracts of nine common respiratory allergens. These were from the Allergological Laboratory, Copenhagen (ALK), Denmark, 10 SQ/ml [cat, dog and horse epithelia, birch, timothy and mugwort pollens, house dust mites (*Dermatophagoides pteronyssinus* and *D. farinae*) and the mould *Cladosporium herbarum*]. In addition, extracts of egg, skimmed cow's milk and fish from ALK were used when needed. Sensitization was defined as an SPT weal with a mean diameter of at least 3 mm, and with a negative control. Pharmacia CAP-RAST was used for determination of panel-specific and allergen-specific IgE in patients' sera. A panel of common food allergens (fx5 that included hen's egg, cow's milk, soya bean, cod, wheat and peanut) and a panel of airborne allergens (Phadiatop) were used. Sensitization was defined as a positive panel test and/or a result of at least RAST class 2 for a specific allergen. Clinical allergy and tolerance were defined on the basis of the parents' opinion about symptoms in exposed children.

Statistics

Relative risks (RR) with 95% confidence intervals (CI) were used in all statistical analyses except for comparisons of eczema scores, where the Mann-Whitney *U*-test was applied.

The Ethics Committee of the Medical Faculty of Uppsala University, Sweden approved the study.

Results

Sensitization to foods

During the study, 62% ($n = 58$) of the children had at least one positive fx5 test. Among children with initially severe eczema (score 6–8 at the first visit), 69% had a positive fx5 test on at least one occasion, as against 53% with initially mild eczema (RR 1.30, 95% CI 0.93–1.81). All 58 children sensitized to food were sensitized to either, hen's egg (46), cow's milk (27) and/or peanut (37). All but a few became sensitized before the age of 3 years. No child developed sensitization to hen's egg after the age of 3 years and only one became sensitized to cow's milk after that age. The RAST titres and SPT reactions to hen's egg and cow's milk decreased with time in most patients, but at follow-up, 20 of the 94 children (21%) were still sensitized to egg. At that time 16 children were

still avoiding eating hen's egg, although four of them were RAST/SPT negative. At follow-up, 24 of 27 children sensitized to cow's milk tolerated ingested cow's milk although only nine of them tested negative.

Of the 28 children sensitized to peanut before the age of 3 years, four became RAST negative during follow-up. All had low RAST values (class 2 or 3). Nine children became sensitized to peanut after 3 years of age, all in RAST classes 2 or 3. All but five (14%) of the peanut-sensitized children were also sensitized to hen's egg.

Adverse food reactions, of any kind, were reported to have occurred in 81% of the children under study. Such reactions were reported after intake of hen's egg, milk, fish, peanut or soya bean in 64% of those with a positive fx5 vs. in 25% of those with a negative fx5 (RR 2.55, 95% CI 1.40–4.64). Children with a low degree of sensitization were more often tolerant to the food than those with more pronounced sensitization.

Sensitization to airborne allergens

During the follow-up period 80% ($n = 75$) of the 94 children became sensitized to inhalant allergens (Table 1). Table 2 shows that heredity for atopy and eczema, age at onset of eczema and sensitization to hen's egg, significantly increased the risk. Exposure to furry animals and tobacco smoke early in life, the severity of the eczema, and breast-feeding did not influence the risk. All but three children sensitized to food became sensitized to airborne allergens.

The allergens were divided into four groups:

1. Pollens (birch, timothy and mugwort).
2. Animals (cat, dog and horse).
3. Mites (*D. farinae* and *D. pteronyssinus*).
4. Mould (*Cladosporium herbarum*).

Table 1. Number of children who became sensitized to inhalant allergens (SPT ≥ 3 mm/RAST ≥ 2) up to 79 months of age (median). (One child lacks data on specific sensitization and is omitted)

	$n = 93$	%
Birch	57	61
Timothy	45	48
Mugwort	15	16
Cat	45	48
Dog	41	44
Horse	39	42
<i>Dermatophagoides pteronyssinus</i>	14	15
<i>D. farinae</i>	5	5
<i>Cladosporium herbarum</i>	22	24
Total sensitized	80	75

Table 2. The impact of different factors on sensitization to airborne allergens

	Sensitization to inhalants		Significant risk ratios, 95% CI
	Yes (%)	No (%)	
Heredity for atopy	88	65	1.40, 1.03–1.89
Heredity for eczema	89	67	1.33, 1.05–1.70
Sensitization to hen's egg	98	60	1.57, 1.25–1.96
Exposure to dog/cat before 3 years of age	73	81	n.s.
Exposure to environmental tobacco smoke before 3 years of age	81	79	n.s.
Breast-feeding ended before 6 months of age	80	80	n.s.
Age at onset of eczema			
Before 4 months of age	90		1.29, 1.04–1.60
After 4 months of age	70		
Initial severity of eczema			
Severe eczema (score 6–8)	84		n.s.
Mild eczema (score 1–5)	76		

n.s., Not significant.

Nineteen children were sensitized only to allergens in one of the above groups, 33 to allergens in two groups and 16 and six to allergens in three and four groups, respectively. Children sensitized to allergens in only one group were mostly sensitized to pollen or animals, but two children were sensitized only to mites and one child only to mould. Sensitization to mould was mainly observed in multi-sensitized children. The age at first sensitization is given in Table 3. In children sensitized to more than one airborne allergen, sensitization to other allergens occurred within a year after the initial sensitization in most cases. Among those who became sensitized to airborne allergens, 75% had noticed clinical symptoms when exposed.

The skin test reactions and/or RAST titres to airborne allergens increased with time or remained unchanged in most of the sensitized children, but there were single exceptions, mainly

Table 3. Age at first sensitization to inhalant allergens in all children ever sensitized

Age (years)	Sensitized	
	n	%
<3	39	52
3–4	19	25
4–5	10	13
5–6	4	5
6–7	3	4
Total sensitized	75	100

in low-grade pollen allergic children. A transient sensitization to animal allergens was also occasionally observed. In addition, such sensitizations were of a low grade.

Children not sensitized to inhalant allergens had in comparison with sensitized children significantly less heredity for atopy and eczema, less often sensitization to hen's egg, and a later onset of their eczema (Table 2). In other respects the groups did not differ.

Discussion

Few prospective studies have dealt with the sensitization of children with atopic eczema, and we have not been able to trace any other study with a similar duration and with such frequent check-ups as in our current one (1, 2, 4, 5, 7–11). This has enabled us to follow variations in IgE antibody concentrations in more detail over time. Our study confirms the previously reported association between atopic dermatitis in infants and young children and sensitization to foods (1, 4, 5, 12). Of children with initially severe eczema, 69% were sensitized to food as reflected by a positive screening test (fx5) for food sensitization. Surprisingly, even 53% of children with mild eczema were sensitized to foods. No controlled food challenges were performed in our study, but many young children with only mild sensitization, as indicated by a low RAST level of food-specific IgE, and/or small SPT weals, displayed no signs of clinical food allergy. This corroborates earlier reports that the presence of low concentrations of food-specific IgE antibodies is an immune phenomenon not necessarily associated with clinical symptoms (13–15).

As shown by others, sensitization to hen's egg was most prevalent, and this occurred in 49% of all children under study, providing the panel test fx5 detects all children who are sensitized (1, 4, 7, 16). Furthermore, most of the adverse clinical reactions were caused by this food. The prognosis of egg and milk allergy was good. The concentration of specific IgE decreased or became non-detectable with time and at the end of the study most children tolerated these foods.

In contrast, sensitization to peanut was more persistent. This was the second most common food causing sensitization, and this occurred early, 81% of all cases being detected before the age of 3 years. During the follow-up period, four children became RAST-negative to peanut, but they all had a fairly low concentration of peanut-specific IgE (RAST class 2–3 initially). Our

results thus confirm that peanut sensitization may sometimes disappear with time in children with low-degree sensitization (17). It has also been reported that peanut sensitization is more common among children who are sensitized to other foods as well (18). This was verified in our study, as all but 14% of the children sensitized to peanut were also sensitized to hen's egg. As sensitization to peanut may occur even in children who have never been given peanut-containing food, the question has arisen as to whether sensitization can occur *in utero* or by transfer of peanut allergen in breast milk. Supporting the concept of an early sensitization is the finding in a study from South Africa that mothers who consumed peanuts more often than once a week were four times more likely to have a peanut allergic child than mothers who consumed peanuts less often (19). It was also found that early introduction of peanut into the child's diet entailed an increased risk of developing peanut allergy. However, this does not settle the question as to whether sensitization to peanut is caused by allergen transferred via the mother or by ingested or inhaled peanut allergen.

Reported adverse reactions to foods were very common in the studied group, being noted in 81%. This figure is more than twice as high as those found among cohorts of children of corresponding ages without eczema, reflecting a marked atopic constitution in most of the children with eczema (13, 20–21). In our subgroup with a positive fx5 test, a clearly larger proportion of children was reported to have experienced adverse reactions to classical allergens, such as hen's egg, cow's milk, fish, peanut and soya, compared with the subgroup with a negative fx5 test (64% vs. 25%).

As reported by others, children with eczema are at increased risk of becoming sensitized with time to airborne allergens (1–5). Altogether 80% of the children became sensitized during the follow-up period. A family history of atopic disease increased the risk and an early onset of the eczema increased it further. We also confirmed that sensitization to hen's egg during infancy or early childhood is accompanied by an increased risk of becoming sensitized to airborne allergens (22–24), most often to pollens and animals. As the allergens involved were the same as those found in older children with inhalant allergy, the early sensitization in our group of children with eczema probably just reflects a great propensity to become sensitized. In our study, only less heredity for atopic disease and a later onset of eczema characterized the children who did not become sensitized.

Sensitization to food allergens is often transient, even in cases of clinical allergy. Transient sensitization to airborne allergens is less common, at least in a perspective of 5–10 years (25, 26). But there are exceptions. In our study transiently positive SPT and RAST reactions to pollen allergens were observed in a few children who had mild symptoms during the pollen season for some years. Transiently positive SPT reactions were also seen in some children who had no symptoms when in contact with these allergens. The reverse may also occur. A minority of children with atopic dermatitis seem to lack a propensity to produce specific IgE antibodies both to foods and airborne allergens, and they do not have an increased risk of developing allergic asthma or rhinitis. This atopic dermatitis is often referred to as 'intrinsic', and it has recently been shown that phenotyping of epidermal dendritic cells makes it possible to separate this 'intrinsic' type from atopic dermatitis associated with production of specific IgE (3, 27). The relationship between these two types of atopic dermatitis is unclear, and it is possible that a sharp border does not separate them. Novembre et al. (28) found that 64% of children with atopic eczema had at least one positive skin test at the age of 2 years, but at 11 years of age this figure had increased to 84%, indicating that apparently 'intrinsic' forms may develop into 'extrinsic'.

References

1. GUILLET G, GUILLET MH. Natural history of sensitizations in atopic dermatitis. A 3-year follow-up in 250 children: food allergy and high risk of respiratory symptoms. *Arch Dermatol* 1992; 128: 187–92.
2. BERGMANN RL, EDENHARTER G, BERGMANN KE, et al. Atopic dermatitis in early infancy predicts allergic airway disease at 5 years. *Clin Exp Allergy* 1998; 28: 965–70.
3. WÜTRICH B. Clinical aspects, epidemiology and prognosis of atopic dermatitis. *Ann Allergy Asthma Immunol* 1999; 83: 464–70.
4. PATRIZI A, GUERRINI V, RICCI G, NERI I, SPECCHIA F, MASI M. The natural history of sensitizations to food and aeroallergens in atopic dermatitis: a 4-year follow-up. *Pediatr Dermatol* 2000; 17: 261–5.
5. BUSINCO L, ZIRUOLO MG, FERRARA M, BENINCORI N, MURARO A, GIAMPIETRO PG. Natural history of atopic dermatitis in childhood: an updated review and personal experience of a five-year follow-up. *Allergy* 1989; 44(Suppl. 9): 70–8.
6. 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: 240–45.
7. VARJONEN E, VAINIO E, KALIMO K, JUNTUNEN-BACKMAN K, SAVOLAINEN J. Skin-prick test and RAST responses to cereals in children with atopic dermatitis. Characterization of IgE-binding components in wheat

- and oats by an immunoblotting method. *Clin Exp Allergy* 1995; 25: 1100–7.
8. KEKKI OM, TURJANMAA K, ISOLAURI E. Differences in skin-prick and patch-test reactivity are related to the heterogeneity of atopic eczema in infants. *Allergy* 1997; 52: 755–9.
9. NIGGEMANN B, REIBEL S, WAHN U. The atopy patch test (APT) – a useful tool for the diagnosis of food allergy in children with atopic dermatitis. *Allergy* 2000; 55: 281–5.
10. EIGENMANN PA, CALZA AM. Diagnosis of IgE-mediated food allergy among Swiss children with atopic dermatitis. *Pediatr Allergy Immunol* 2000; 11: 95–100.
11. BOHME M, SVENSSON A, KULL I, NORDVALL SL, WAHLGREN CF. Clinical features of atopic dermatitis at two years of age: a prospective, population-based case-control study. *Acta Derm Venereol* 2001; 81: 193–7.
12. HILL DJ, SPORIK R, THORBURN J, HOSKING CS. The association of atopic dermatitis in infancy with immunoglobulin E food sensitization. *J Pediatr* 2000; 137: 475–9.
13. HATTEVIG G, KJELLMAN B, BJÖRKSTÉN B. Clinical symptoms and IgE responses to common food proteins and inhalants in the first 7 years of life. *Clin Allergy* 1987; 17: 571–8.
14. BOCK SA, ATKINS FM. Patterns of food hypersensitivity during 16 years of double-blind, placebo-controlled food challenges. *J Pediatr* 1990; 117: 561–7.
15. BRUIJZEEL-KOOMEN C, ORTOLANI C, AAS K, et al. Adverse reaction to food. Position paper. *Allergy* 1995; 50: 623–35.
16. SAMPSON HA, MCCASKILL CC. Food hypersensitivity in atopic dermatitis: evaluation of 113 patients. *J Pediatr* 1985; 107: 699–705.
17. TARIQ SM, STEVENS M, MATTHEWS S, et al. Cohort study of peanut and tree nut sensitisation by age of 4 years. *BMJ* 1996; 313: 514–7.
18. ZIMMERMAN B, FORSYTH S, GOLD M. Highly atopic children: formation of IgE antibody to food protein, especially peanut. *J Allergy Clin Immunol* 1989; 83: 764–70.
19. FRANK L, MARIAN A, VISSER M, WEINBERG E, POTTER PC. Exposure to peanuts in utero and in infancy and the development of sensitization to peanut allergens in young children. *Pediatr Allergy Immunol* 1999; 10: 27–32.
20. BOCK SA. Prospective appraisal of complaints of adverse reactions to foods in children during the first 3 years of life. *Pediatrics* 1987; 79: 683–8.
21. CRONER S, KJELLMAN N-IM. Development of atopic disease in relation to family history and cord blood IgE levels. Eleven-year follow-up in 1654 children. *Pediatr Allergy Immunol* 1990; 1: 14–20.
22. NICKEL R, KULIG M, FORSTER J, et al. 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. *J Allergy Clin Immunol* 1997; 99: 613–7.
23. SIGURS N, HATTEVIG G, KJELLMAN B, KJELLMAN 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: 757–63.
24. TARIQ SM, MATTHEWS SM, HAKIM EA, ARSHAD SH. Egg allergy in infancy predicts respiratory allergy by 4 years of age. *Pediatr Allergy Immunol* 2000; 11: 162–7.
25. 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: 1173–9.
26. HATTEVIG G, KJELLMAN B, BJÖRKSTÉN B. Appearance of IgE antibodies to ingested and inhaled allergens during the first 12 years of life in atopic and non-atopic children. *Pediatr Allergy Immunol* 1993; 4: 182–86.
27. OPPEL T, SCHULLER E, GÜNTHER S, et al. Phenotyping of epidermal dendritic cells allows the differentiation between extrinsic and intrinsic forms of atopic dermatitis. *Br J Dermatol* 2000; 143: 1193–98.
28. NOVEMBRE E, CIANFERONI A, LOMBARDI E, BERNARDINI R, PUCCI N, VIERUCCI A. Natural history of 'intrinsic' atopic dermatitis. *Allergy* 2001; 56: 452–3.