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Effect of allergen avoidance in infancy on allergic manifestations at age two years

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Background: One hundred twenty children, identified before birth as being at high risk for atopy, were prenatally assigned to prophylactic or control groups.

Methods: The infants in the prophylactic group either received breast milk from mothers on an exclusion diet or an extensively hydrolyzed formula. Their bedrooms and living rooms were treated repeatedly with an acaricide, and they used polyvinyl-covered mattresses with vented head areas. The infants in the control group were fed conventionally, and no environmental control was recommended.

Results: A significant advantage, first demonstrated at 1 year of age, persists for children in the prophylactic group. They have less of any allergy or eczema, but the reduced prevalence of asthma is no longer significant. Only three children in the prophylactic group had positive skin prick test results compared with 16 in the control group, suggesting a significant reduction in sensitization.

Conclusion: A dual approach to allergen avoidance, focusing on foods and aeroallergens, appears to be beneficial in selected high-risk infants. Avoidance of potent allergens in early life increases the threshold for sensitization in these high-risk infants. Whether sensitization has been avoided or merely deferred has yet to be proved. (*J ALLERGY CLIN IMMUNOL* 1994;93:842-6.)

Key words: Allergy, prevention, asthma, eczema, food intolerance, skin prick tests

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Abbreviations used

HDM: House dust mite
SPT: Skin prick test

A number of studies have shown that certain manifestations of IgE-mediated food allergy may be lessened by carefully controlling the diet of the newborn infant. This may be done by offering the infant a formula modified to provide minimal

TABLE I. Effect of allergen avoidance in infancy on allergic manifestations at age 2 years

Allergic disorder	Prophylactic group (n = 58)		Control group (n = 62)	
	No.	%	No.	%
Asthma	9	15.5	17	27.4
Eczema	8	13.8	15	24.2
Rhinitis	2	3.4	7	11.3*
Food intolerance	7	12.1	11	17.7
Positive SPT result	3	5.2	16	25.8†
Any allergy	17	29.3	36	58.1†

* $p < 0.1$ (chi square test with Yates' correction).

† $p < 0.005$.

‡ $p < 0.05$.

antigenic stimulus or by strictly controlling the diet of the lactating mother in an attempt to minimize the passage of small amounts of protein through breast milk. Generally, the benefit of such restriction of food antigen has diminished the prevalence of food-related allergy in the first months and years of life, but such benefit has diminished or disappeared entirely during long-term follow-up, and there has been no protection against asthma and allergic rhinitis.¹

Recently, the importance of sensitization to aeroallergens in the neonatal period has been emphasized, particularly in relation to pollens, animal danders, and the house dust mite (HDM).² In the United Kingdom asthma in mite-sensitive 11-year-old children has been related to exposure to mite antigen (*Der p* I) in infancy.³ In the present study measures were taken to protect a group of infants at high risk for atopy against sensitization by food and HDM antigen in the first year of life. The results after 1 year of follow-up have been reported and showed significantly more allergy in the control group than in the prophylactic group.⁴ The prevalence of both asthma and eczema was greater in the control group. Parental smoking was also recognized as a significant risk factor for total allergy and asthma at 12 months of age. All of the children have now been seen at age 2 years.

METHODS

The study was prospective, prenatally randomized, and controlled. The inclusion criteria were dual heredity (allergic disease in both parents, one parent and a sibling, or two siblings) or single heredity (allergic disease in one first-degree relative) plus a cord IgE level of more than 0.5 kU/L.

At 1 year 58 infants were reported in the prophylactic group and 62 in the control group, and all were reviewed at age 2.

Lactating mothers in the prophylactic group excluded dairy products, eggs, fish, and nuts from their diet. Up to age 9 months breast milk was supplemented if necessary with a soy-based protein hydrolysate (Aptamil HA; Milupa Ltd., Oxbridge, UK). Formula-fed infants received Aptamil HA from birth. Dairy products, eggs, wheat, unhydrolyzed soya, oranges, fish, and nuts were excluded from the infants' diets until 9 months of age. Lactating mothers were given calcium and vitamin supplements, and a research dietitian kept a close eye on progress.

Attempts were made to reduce contact with HDM antigen for the prophylactic group by ensuring that all infants slept on covered mattresses and by treating the carpet in bedrooms, main living rooms, and upholstered furniture with an acaricidal (benzyl benzoate) foam and powder (Acarosan; Crawford Chemicals, Milton Keynes, UK). This treatment was repeated at 3 monthly intervals until 9 months after birth, for a total of four treatments. Dust samples were collected before treatment and at regular intervals through the year. Dust samples were analyzed by a sandwich-type ELISA with monoclonal antibody-labeled discs (ALK, Copenhagen, Denmark) for the main antigen of *Dermatophagoides pteronyssinus* (*Der p* I).

The infants in the control group received either breast milk from mothers on a normal diet or a regular formula feed. Dust samples were assayed at birth and at 9 months for *Der p* I, but no specific antimite measures were taken.

Information was collected on smoking habits and presence of pets in the house, but no specific advice was given on these matters. All infants were followed up closely by the research team and were seen by the research fellow every 3 months in the first year of life. At the ages of 10 to 12 months and approximately 24 months they were all seen by a pediatric allergist who was unaware of whether the child was in the prophylactic or control group. At all of these visits the presence of symptoms or signs of allergic disease, according to defined criteria, was recorded, and skin prick tests were done. Information on exposure to passive smoke and pets was updated. As at 12 months, there were

TABLE II. Effect of risk factors on development of total allergy and positive SPT reaction (logistic regression analysis)

Risk factor	Total allergy			Positive SPT reaction		
	OR	CI	p Value	OR	CI	p Value
Control group	9.70	2.7-34.6	0.0005	10.26	1.6-66.7	0.01
Male sex	1.85	0.7-5.3	NS	2.21	0.6-8.6	NS
Maternal allergy	7.97	1.9-34.4	0.005	1.19	0.1-10.8	NS
Paternal allergy	2.03	0.5-7.6	NS	0.89	0.27-2.91	NS
Sibling allergy	3.36	0.9-12.8	0.08	0.44	0.13-1.5	NS

Maternal and paternal smoking, presence of pets, and high cord IgE level (>0.5 kU/L) included in regression model but nonsignificant for all allergic disorders.

OR, Odds ratio; CI, confidence interval; NS, not significant.

TABLE III. Effect of risk factors on development of asthma and eczema (logistic regression analysis)

Risk factor	Asthma			Eczema		
	OR	CI	p Value	OR	CI	p Value
Control group	2.18	0.81-5.87	NS	9.52	1.8-50.1	0.008
Male sex	1.07	0.42-2.71	NS	1.89	0.5-7.1	NS
Maternal allergy	1.73	0.55-5.42	NS	14.9	1.4-155.0	0.02
Paternal allergy	1.25	0.46-3.42	NS	1.08	0.3-4.7	NS
Sibling allergy	1.58	0.55-4.56	NS	4.11	0.8-20.9	0.09

OR, Odds ratio; CI, confidence interval; NS, not significant.

TABLE IV. Effect of risk factors on development of rhinitis and food intolerance (logistic regression analysis)

Risk factor	Rhinitis			Food intolerance		
	OR	CI	p Value	OR	CI	p Value
Control group	2.60	0.3-23.2	NS	1.25	0.3-5.8	NS
Male sex	0.76	0.1-4.9	NS	5.26	1.1-25.3	0.04
Maternal allergy	1.78	0.1-26.1	NS	12.94	1.4-119.9	0.02
Paternal allergy	0.62	0.1-5.7	NS	8.07	1.4-45.1	0.02
Sibling allergy	1.75	0.1-21.6	NS	7.11	1.2-41.2	0.03

OR, Odds ratio; CI, confidence interval; NS, not significant.

fewer smoking mothers in the prophylactic group (10 of 58 vs 26 of 62), but paternal smoking habits were not significantly different in the two groups. Thirty-five (60%) households had pets in the prophylactic group compared with 44 (70%) in the control group. Corresponding figures for cats were 18 (31%) and 23 (37%).

Statistical analysis was done with SPSS/PC+ V4 (SPSS, Chicago, Ill.). The chi square test with Yates' correction was used to detect differences in proportions. Logistic regression analysis was used to assess the independent contribution of factors to the risk of allergic disorders.

RESULTS

The mean concentrations of *Der p* I fell from 25.9 µg/gm dust at birth to 6.0 µg/gm dust at 9

months in the prophylactic group. Levels of *Der p* I remained similar in the control group.

At 12 months one or more allergic conditions had developed in 25 (40%) children in the control group and 8 (14%) children in the prophylactic group. By their second birthday, the figure had increased to 29 (48%) and 15 (26%), respectively. If children with positive skin prick test (SPT) results (latent atopy) are included, the control group contains 36 (58%) and the prophylactic group 17 (29%) (Table I).

Asthma had been diagnosed in nine children in the prophylactic group (four at the age of 1 year) and eczema in eight (also four at the age of 1 year). In the control group, the number of chil-

TABLE V. Effect of allergen avoidance in infancy on positive SPT reaction at 2 years

Positive SPT reaction	Prophylactic group		Control group	
	No.	%	No.	%
Patients positive	3	5.17	16	25.81*
Single allergen	2	3.45	10	16.13†
> Two allergens	1	1.72	6	9.68‡
Allergens tested				
HDM	1	1.72	6	9.68‡
Cat dander	1	1.72	7	11.29†
Dog dander	2	3.45	1	1.61
Molds	0		2	3.23
Cow's milk	0		3	4.84
Egg	2	3.45	3	4.84
Wheat	0		2	3.23

* $p < 0.005$ (chi square test with Yates' correction).

† $p < 0.05$.

‡ $p < 0.1$.

TABLE VI. Allergen exposure related to skin test reactivity at 2 years

Children with positive SPT reactions	Allergen exposure		OR	95% CI	p Value
	Prophylactic (n = 58)	Control (n = 62)			
Any	3	16	6.4	1.8-23.3	0.004
HDM	1	6	6.1	0.7-52.4	0.06
Other*	2	10	5.4	1.1-25.7	0.04
	Without cat (n = 79)	With cat (n = 41)			
Any	6	13	5.9	2.0-17.2	0.001
Cat	1	7	16.1	1.9-135.6	0.0002
Other†	6	12	5.0	1.7-14.7	0.003

OR, Odds ratio; CI, confidence interval.

*Allergens other than HDM.

†Allergens other than cat.

dren with asthma had increased from 12 to 17 and eczema from 12 to 15. The number of children with food intolerance had increased from 2 to 7 in the prophylactic group and from 7 to 11 in the control group. By the age of 2 years two children in the prophylactic group and seven children in the control group had been diagnosed as having allergic rhinitis.

Multivariate logistic regression analysis was carried out to control for the possible effects of genetic and environmental factors and to determine other risk factors. At 12 months the control group had been found to be at significantly greater risk for all allergies and for eczema and asthma. Parental smoking, maternal allergy, sibling allergy, and male sex were other risk factors. At 2 years, infants in the control group remained considerably more likely to manifest any allergy

than those in the prophylactic group (Tables II, III, and IV). The infants in the control group also had significant risk of eczema, but the enhanced risk of asthma shown at 1 year could no longer be demonstrated.

Maternal allergy was a significant risk factor for any allergy, eczema, and food intolerance. Paternal allergy and male sex also predisposed subjects to food intolerance. Factors tested but found not significant included maternal and paternal smoking and high cord IgE levels (>0.5 kU/L).

All children underwent skin prick testing to a battery of common food allergens and aeroallergens. A highly significant difference was found in the number of positive SPT results between prophylactic and control groups (Table V). Only one child had a positive SPT reaction to HDM in the prophylactic group compared with six children in

the control group. Preventive measures applied in the prophylactic group had some effect on sensitization to other allergens (Table VI). Conversely, children exposed to cat exhibited significantly more positive SPT reactions not only to cat dander but also to other common allergens.

In the prophylactic group only one of 18 (5.6%) children exposed to cat had positive SPT reactions to cat dander compared with six of 23 (26%) in the control group. The difference just failed to reach statistical significance ($p = 0.08$).

Thirty-eight percent of the children whose mothers smoked had asthma at 1 year, compared with 7% of children with nonsmoking mothers, which is a highly significant difference. This has narrowed to 31% and 18%, respectively, at 2 years. The effect of paternal smoking was similar.

DISCUSSION

Results continue to show a benefit from an intervention program that attempts to protect infants who are at high risk for atopy from early sensitization. Overall, there remains substantially less atopic disease in the prophylactic group. The prevalence of asthma and eczema remains lower in the prophylactic group, but the difference in asthma rates is no longer statistically significant. Possibly in some children in the control group bronchial hyperreactivity was a temporary phenomenon in response to exposure to a high level of HDM allergen. Convergence of prevalence rates has been demonstrated by Zeiger et al.¹ in their study of food allergen avoidance in children of atopic parents up to the age of 4 years. That study showed a similar prevalence of respiratory allergy and positive inhalant skin test results during the period of surveillance. Although our follow-up period is only 2 years to date, there is a trend toward less respiratory allergy and significantly fewer positive SPT reactions to aeroallergens in the prophylactic group. We are cautiously optimistic that the stringent measures to reduce exposure to HDM antigen are proving beneficial and that a regimen such as the one we have used does reduce manifestations of food-related allergy and asthma in the first year of life and continues to reduce allergy in the second year. Follow-up is continuing with the intention to review the children at the ages of 4 and 7 years.

Sensitization to both food allergens and aeroallergens, as revealed by skin prick testing, is

significantly less in the prophylactic group despite the fact that no active allergen avoidance was advocated during the second year. It is hypothesized that the threshold for sensitization increased in the children in the prophylactic group after allergen avoidance during infancy. Children in either group who were not exposed to cat were sensitized less often to common allergens than children with a cat or cats in their homes.

The difference in HDM sensitization at 2 years may be explained by lower levels of *Der p* 1 during the second year in the prophylactic group after earlier treatment with Acarosan (last treatment was done at the age of 9 months). Alternatively, anti-dust mite treatment may have also reduced levels of cat antigen in the house dust, explaining the fewer positive reactions to cat dander in children in the prophylactic group. Both of these possibilities are being explored by measuring *Der p* 1 and *Fel d* 1 levels in the house dust collected at 2 years.

The profound effect of parental smoking on prevalence of asthma at 1 year could not be demonstrated at 2 years. It seems that in a subgroup of infants, bronchial hyperreactivity secondary to passive smoking subsided as they grew older.

Conclusion

At the age of 2 years, a group of children considered to be at high risk for atopy, who had been protected against major food antigens and HDM in infancy, continue to manifest less allergy than a control group not similarly protected.

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