

Do Infections in Infancy Affect Sensitization to Airborne Allergens and Development of Atopic Disease?

A Retrospective Study of Seven-Year-Old Children

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We studied 145 children aged 7 years, who had been at day-care centers for at least 3 months during the 2 first years of their lives. The group was compared with a matched population of 145 children cared for at home. Of the 290 children, 212 participated in all phases of the study, which included a questionnaire to parents, skin prick tests with seven allergens, and a clinical examination. Day-care-center children had twice as much otitis media in infancy as "home" children ($P < 0.001$), and they also tended to have more other infections. On the other hand, day-care-center children did not have more eczema in infancy, more cumulated atopic disease by the age of seven, or more positive skin tests than home children. When the groups were combined, an increased prevalence of cumulated atopic disease and positive skin tests was found in children with infections in infancy. We conclude that under the conditions of this study infections in infancy did not facilitate the development of hypersensitivity to allergens and atopic disease. The linked tendencies to develop infections and atopy could depend on some third factor.

Key words: atopic dermatitis; atopy; day-care center; eczema; episode of fever; gastrointestinal symptom; infancy; otitis media; skin prick test.

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CLINICAL ASPECTS

The present results suggest that infections in infancy do not facilitate sensitization to allergens and the development of atopic disease. Atopy probably cannot be prevented by protecting small children from infections.

There is probably a sensitive period in early infancy when the child is unusually susceptible to allergens. Avoidance of allergens in infancy – particularly food allergen avoidance – has been found to prevent atopy in small children (9, 12). (We define atopy as clinical disease – asthma, rhinitis, eczema, etc. – due to type I allergy). In the development of respiratory atopy contacts with airborne allergens during the first 6 months of life are of particular importance. Contact with pollens (4, 5, 6, 8), and animals (17, 18) in this period increases the

risk of sensitization more than later contacts do. Overt respiratory symptoms may develop many years later.

Environmental factors, including infections (7, 15), may also affect the development of atopy. In a previous study we found that infections during the first year of life tend to increase the number of positive skin prick test reactions observed in the teenage period (17). In the present study we have investigated the occurrence of atopic allergy and positive skin prick test reactions to airborne allergens in

7-year-old children and the dependence of these on possible risk factors – infections in particular – encountered in infancy.

The working hypothesis was that early infections affect later atopy, and we therefore chose as study group children who had been in day-care centers for a period of at least 3 months during the 2 first years of life. Among small children in day-care centers infection incidences are approximately 150% higher than among children cared for at home (14, 16). We also studied a control group of "home" children.

METHODS

Atopy

We define atopy as clinical disease (asthma, rhinitis, conjunctivitis, eczema, etc.) due to type I allergy. Our atopy prevalences are based on answers to a set of questions in which parents were asked whether a physician had ever diagnosed atopy in the child.

Children in day-care centers (study group). In the autumn of 1980 we tried to reach all children born in 1973 – approximately 7 years old at the time – who had been in day-care centers in Helsinki for at least 3 months in 1973–74, when they were under 2 years of age. Day-care-center children were identified at the first school health examination by Helsinki school nurses and doctors, and their parents received questionnaires. There were 4332 children entering school, 153 children were identified as day-care-center children and answers were received from the parents of 145 children (49% boys). The children were invited to participate in a clinical examination and skin prick testing, and 104 showed up. The identity of the subject (study or control) was not revealed to the examining pediatric allergist (A.B. or K.J.).

Children at home (control group). When a day-care-center child was identified, the next three children seen by the school nurses were chosen as potential members of the control group. The final control group was selected by matching

each day-care-center child for sex, location of home, and length of breast feeding, with a home child. The 145 members of the control group were invited to participate in the clinical examination and skin testing. Of these 109 participated.

Combined group. For several purposes it was found suitable to combine the study and control groups. The combined group numbered 290, and 212 of these were skin tested.

Questionnaire

Parents were given questionnaires in which enquiries were made about symptoms, etc., which indicated past or present atopy in the child, his parents or his siblings. Questions were also made about duration of breast feeding, smoking in the home, family composition, etc. In particular, we sought information concerning environmental factors met and diseases experienced during the first year of life (later called infancy). Four questions proved to be particularly rewarding:

- 1) Eczema. Did the infant suffer from eczema?
- 2) Episode of fever. Did the infant suffer from an episode of fever, which caused the child to be seen by a physician?
- 3) Gastrointestinal symptoms. Did the infant suffer from diarrhea, vomiting or other gastrointestinal symptoms which caused the child to be seen by a physician?
- 4) Otitis media. Did the infant suffer from otitis media (pain in the ear)?

Skin prick testing

Tests were made on the volar side of the arm using seven allergic extracts, a 1 g/l histamine dihydrochloride solution as positive control, and a solution (solvent) which contained 50% glycerol in physiological buffered saline as negative control. The allergens included (Allergologisk Laboratorium, Copenhagen, Denmark) were birch (*Betula verrucosa*), mugwort (*Artemisia vulgaris*) and timothy (*Phleum pratense*) pollen, cat and dog epithelium, mite (*Dermatoph-*

goides pteronyssinus), and house dust. This list covers the most important airborne allergens in Finland. The concentration of the house dust extract was 1:100 and the biological activity of the other extracts was 1 HEP (cf. ref. 1). A skin prick test was considered positive, if a weal larger than half that caused by the histamine control was observed.

Statistical methods

In addition to the usual cross-tabulation method and chi-square tests of association, we used a parametric statistical method to fit a logistic model of risk. In this model the risk (probability to have a positive response) depends on levels of the explaining factors (X_i) and their coefficient (B_i) according to the equation

$$P = \text{antiln}(-B_0 - \sum B_i X_i) \quad (1)$$

In the model above the logarithm of the odds for a positive response depends linearly on the explaining factors in the following manner:

$$\ln \frac{P}{1-P} = B_0 + \sum B_i X_i \quad (2)$$

The explaining factors have only two levels, 0 and 1 (absent and present). The presence of factor i ($X_i = 1$) affects the odds multiplicatively by the factor $\text{antiln}(B_i)$.

Estimation of the parameters was done with the maximum-probability method (2, 11). Tests of significance for individual coefficients were based on asymptotic t -tests. Asymptotically chi-square distributed probability ratio statistics was used to test the significance of the whole model against a simple alternative of constant odds over the whole population.

RESULTS

The prevalence of positive family histories of atopy and of eczema in infancy were nearly the same in the day-care-center children and in the children taken care of at home. Episodes of fever, gastrointestinal symptoms and otitis media suggested that infections had been more

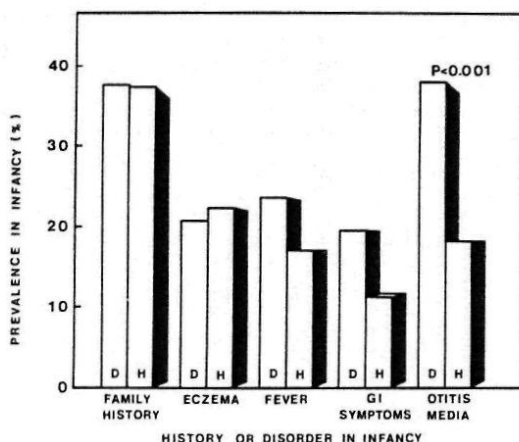


Fig. 1. Prevalence of disorders in infancy, and positive family histories in children who had been in day-care centers for at least 3 months (D) and in children who had been taken care of only at home (H) during the first 2 years of life. GI symptoms = gastrointestinal symptoms.

frequent in day-care-center children in infancy; however, the difference was statistically significant only in the case of otitis media (Fig. 1). At 7 years of age past or present symptoms of atopy and positive skin prick tests were found with roughly equal frequency in day-care-center and home children (Figs. 2 and 3).

The prevalence of past or present symptoms of atopy (Table 1, Fig. 2) and positive skin prick tests (Tables 1 and 2, Fig. 3) was also studied after the children had been grouped on the basis of disorders which they had suffered from during their first year of life. Four early disorders were associated with increased prevalences in a significant manner; these disorders were early eczema, episodes of fever, gastrointestinal symptoms and otitis media.

To capture the *separate* effects of various disorders and environmental influences we proceeded to fit logistic models with several explaining factors. Selected results are shown in Table 3, which gives the odds of past or present atopic disease and positive skin prick tests at the age of seven. It can, for instance, be seen that the odds of developing asthma by the age of seven was 18 times higher in children who had episodes of fever in infancy than in children with no such episodes.

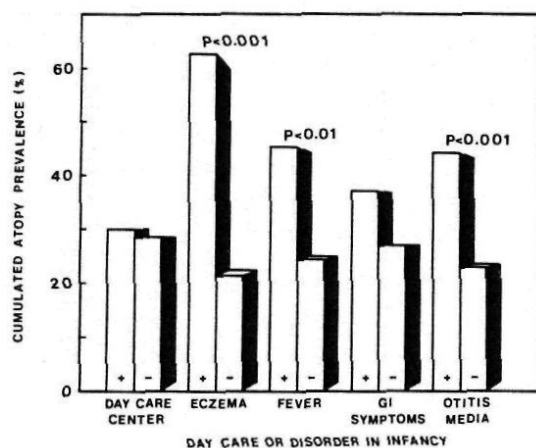


Fig. 2. Cumulated prevalence of atopic disease in 7-year-old children grouped by type of care or disorder encountered in infancy. Presence of factor in infancy is indicated by +, its absence by -.

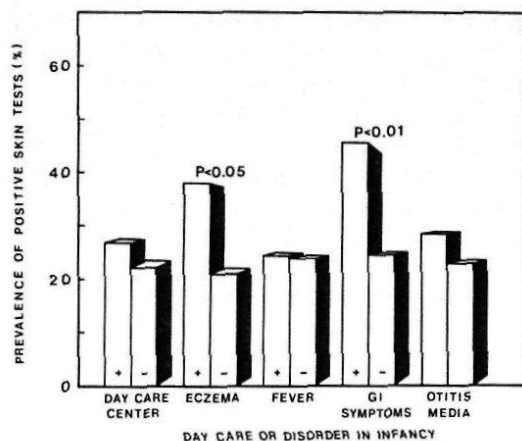


Fig. 3. Prevalence of positive skin prick tests (at least one positive) in 7-year-old children grouped by type of care or disorder encountered in infancy. Presence of factor in infancy is indicated by +, its absence by -.

Table 1

Cumulated prevalence of atopy and of positive skin tests in 7-year-old children grouped by type of care or disorder encountered in infancy

Cumulated atopy or positive skin test at 7 years of age	Type of care or disorder in infancy									
	Type of care		Eczema		Episode of fever ¹		Gastrointestinal symptoms ¹		Otitis media	
	Day-care center	Home only	Present	Absent	Present	Absent	Present	Absent	Present	Absent
Prevalence (%) of cumulated atopy or positive skin tests at 7 years of age ²										
Asthma ³	1.4	3.5	5.9	1.7	9.6	0.4	2.3	2.1	6.2*	1.0
Conjunctivitis ³	11.8	5.6	17.6**	6.4	7.7	8.3	11.9	7.5	17.3**	4.9
Eczema ³	18.8	20.3	54.9***	11.6	28.3	17.0	25.6	18.0	26.6	16.6
Rhinitis ³	11.8	9.1	21.6	7.7	17.0	8.7	18.6	8.8	17.6	7.3
Any atopy ³	29.9	28.5	62.7***	21.5	45.3**	24.5	37.2	26.8	44.3***	22.9
Pos. skin test	26.9	22.2	37.8*	21.1	24.4	24.0	45.7**	19.7	28.4	22.9

¹ According to history, child had been seen by physician.

² Probability of difference between adjacent groups: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

³ According to history, atopy had been diagnosed by physician.

DISCUSSION

Contacts with airborne allergens during the first 6 months of life cause sensitization more readily than later contacts (5, 6, 17). Apparently, an allergen-specific IgE response is initiated,

this response is boostable, and can lead to atopy many years later. Likewise, early food contacts frequently cause atopy, but symptoms become manifest much more rapidly than the respiratory symptoms caused by airborne allergens (3, 12).

Table 2

Prevalence of positive skin prick tests in 7-year-old children grouped by type of disorder encountered in infancy

Allergen	Eczema		Gastrointestinal symptoms ¹	
	Present n = 45	Absent n = 166	Present n = 35	Absent n = 173
Prevalence (%) of positive skin-tests ²				
Birch pollen	22.2*	7.8	22.9*	8.1
Cat epithelium	17.8	7.2	25.7***	5.2
Dog epithelium	6.7	6.0	17.1**	3.5
House dust	22.2	12.0	25.7*	11.0
Mite	2.2	3.0	5.7	2.3
Mugwort pollen	17.8	9.6	28.6***	7.5
Timothy pollen	13.3	4.2	11.4	4.6
Any allergen	37.8*	21.1	45.7**	19.7

¹ According to history, child had been seen by physician.² Probability of difference between adjacent groups: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Table 3

Dependence of odds of atopy and of positive skin tests in 7-year-old children on disorders in infancy

Atopy (cumulated) or positive skin test at 7 years of age	Disorder in infancy				Constant odds ¹	Signifi- cance of the model ²
	Eczema	Episode of fever ³	Gastrointestinal symptoms ³	Otitis media		
	Effect on the odds ^{2,4}					
Asthma ⁵	2.87	18.43**	0.51	8.42*	0.001	***
Conjunctivitis ⁵	3.10**	0.58	1.47	4.39***	0.04	**
Eczema ⁵	10.10***	1.97*	1.03	1.52	0.09	***
Rhinitis ⁵	2.74*	1.56	1.42	2.62*	0.05	**
Any atopy ⁵	6.35***	2.41**	1.04	2.65***	0.16	***
Pos. skin test	1.81	0.87	3.27***	1.43	0.20	**

¹ antiln B_0 (cf. equation 2).² Significance: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.³ According to history, child had been seen by physician.⁴ In the absence of an effect the figure is 1.00.⁵ According to history, atopy had been diagnosed by physician.

Although early contacts are of particular importance, it is obvious that persons with an inherited disposition to atopy become sensitized to various allergens at variable times. This suggests that the conditions required for the development of hypersensitivity occur infrequently. If sensitization usually is a one-time or one-period occurrence, the epidemiology of sensitization is important because of the potential for

finding preventable environmental factors among those that set the stage for the development of atopy (13).

It has frequently been suggested that infections (7, 15), immunizations, early weaning and possibly other events, which perturb the immune system or mucous membranes, could be "adjuvant" factors required for an IgE response. In this study we tried to find adjuvant

factors effective in infancy, when sensitization is initiated most easily. Like other retrospective studies, our study is affected by certain difficulties, and results should be interpreted with caution. It might, for instance, be suggested that some of the infections in infancy may in fact have been early manifestations of atopic disease, possibly hyper-reactivity of affected organs during episodes of acute viral disease.

Day-care-center children are known to suffer from an increased number of infections (14, 16). Our results tended to confirm this; in infancy the day-care-center children had had otitis media twice as often as home children (Fig. 1). However, we did not find a significant difference in the prevalence of atopic allergy in the two groups (Figs. 2, 3).

We combined the groups and analyzed the dependence of past or present allergy at 7 years of age on disorders experienced in infancy. Of the six children with asthma, five had had an episode of fever treated by a physician in infancy, and four had had otitis media in infancy. These conditions could have been identical. The odds of asthma were increased 18-fold and 8-fold in children with fever and otitis, respectively. These numerical values should be regarded with caution due to the small number of children. However, the relative odds are significantly larger than 1 ($P < 0.01$ and $P < 0.05$ respectively) (Table 3).

The interrelated diseases, allergic rhinitis and conjunctivitis, also depended on early otitis media, which caused a 3- and 4-fold increase in odds. Early eczema increased odds to a 3-fold level (Table 3).

Predictably, past and present eczema diagnosed by a physician was explained best by early eczema observed by parents. In this case the increase in odds was 10-fold (Table 3).

Much more unexpectedly, positive skin prick tests at 7 years of age depended on early gastrointestinal symptoms (Table 2), which caused a 3-fold increase in odds. Early eczema also affected the risk (Table 3 and Fig. 3). In children with gastrointestinal symptoms, parents had been aware of a food allergy in infancy in only 27% of cases. Thus food allergy appears to explain the symptoms only in part. Rota virus

and toxigenic *Escherichia coli* are frequently the cause of diarrhea in children in Finland (10, 19), and they might have caused infections in our group of children.

At first look our results seem to suggest that clinical atopy in 7-year-old children depends on early respiratory infections (Fig. 2), while skin reactivity depends on early gastrointestinal symptoms, which may have been due to infections (Fig. 3). However, we are not convinced that responses to various infections truly differ, as the number of children studied was small, and chance events could have affected the result. The number of children with past or present clinical atopy was 84.

Two of our risk factors, episodes of fever and otitis media, were in part identical; they performed better when the other was excluded from models. We also tried models which included sex, a positive family history, length of breast feeding and early food allergy as explaining factors, but results were negative. Here again the relatively small numbers of children causes uncertainties.

The main observations of this study can be summarized as follows:

- 1) In agreement with previous investigators (14, 16) we find that small children in day-care centers have more infections than children at home.

- 2) Also in agreement with previous results (7, 15, 17) we observe that children with many or relatively serious infections in infancy tend to develop atopy by the age of seven.

- 3) Although children in day-care centers had many infections in infancy they did not develop atopy more often than children at home.

These observations must be interpreted as showing that under the conditions of our study infections did not act as "adjuvant" factors, i.e. did not affect the development of atopy. The linked tendencies to develop infections and atopy could depend on some third factor, which for instance could be genetic in nature.

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