

Development of Asthma, Allergic Rhinitis and Atopic Dermatitis by the Age of Five Years

A Prospective Study of 543 Newborns

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543 children were followed up from birth to 5 years of age. Children with a positive history of parents' atopy had a 51 % occurrence of respiratory or dermal symptoms of atopy vs. a 19 % occurrence among children with no family history of atopy. There was an association between asthma and allergic rhinitis while atopic dermatitis occurred equally in children with or without respiratory symptoms. The clinical course of atopic symptoms could not be correlated to the family history of atopy. The significance of date of birth, nasal eosinophilia and serum IgE levels seemed to be relatively low in atopic dermatitis while these parameters had a correlation to the development of respiratory atopies.

Key words: atopic diseases; family history of atopy.

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The selection of children for preventive measures of atopic allergy can be based on the allergy history of their probands. To investigate how many potentially allergic children will be selected in this way, children with atopic probands were compared with children from non-atopic families in a 5-year follow-up study. The family histories were obtained from mothers in the delivery unit. No attempt was made to influence the environment of any child.

Despite a strong influence of atopic family history on the cumulative prevalence of atopic diseases, 19% of the children from non-atopic families also developed clinically similar symptoms. This indicated that before preventive atopy recommendations can be made for selected groups of children, or any substantial decrease in the childhood atopic disease prevalence can be anticipated, more accurate selection criteria are required.

There was a growing awareness among paediatricians about childhood allergy in the early 1970's, and preventive measures were felt desirable especially for those children likely to inherit the disease. However, in order to draw meaningful conclusions from such trials a knowledge of the original situation is needed.

Potentially allergic children can be selected and the basis of the family history of atopic diseases as told by the mother. But it is not known how many of all newborn babies will be selected in this way, or how many of those who are not selected will develop atopic diseases. In our previous retrospective study (25) we calcu-

lated that in 24% of the families one of the parents was atopic. However, in consistency with previous literature (5, 34), only 46% of atopic children in this study had an atopic parent. Clearly, these figures indicate that a substantial number of potentially allergic children will not be selected in the aforementioned way. To check these findings we felt it necessary to carry out a follow-up study of childhood atopic diseases. This occurred in 1972–1978 before any preventive dietary recommendations were made in Finland, and solid foods were introduced in early infancy according to instructions given by well-baby centres.

The present paper concerns the development of asthma, allergic rhinitis and atopic dermatitis by the age of 5 years. These diseases are correlated to probands, atopic history, date of birth, and nasal eosinophilia and serum IgE at the age of five.

MATERIAL AND METHODS

While in the delivery unit of the Women's Clinic of the University Central Hospital of Turku the mothers were interviewed by specially trained nurses at intermittent periods in 1971-1973. The interview aimed at disclosing any history of asthma, allergic rhinitis or atopic dermatitis in the parents, grandparents or siblings of the newborn baby.

The mothers who reported a definite history of any of the aforementioned symptoms in

parents or grandparents only were asked to participate in the follow-up study of allergic symptoms in their newborn baby together with those who had no history of allergy in any of their relatives.

In this way 670 families were selected. For various reasons, 127 families refused to continue to take part in the study shortly after leaving hospital. The background data and family history of atopy in this drop-out group were checked and found comparable to that of those who remained in the study. Thus 543 children, 254 boys and 289 girls, formed the follow-up group. 395 of them had atopic probands and 148 had a negative family history of atopy. The distribution of allergic symptoms in probands is presented in Table 1.

The study outline is schematically presented in Table 2. For practical reasons, it was not possible to make regular clinical examinations of all the children. So, in addition to the questionnaires 150 consecutive children attended four clinical examinations during the first year of life. Later on, at the age of five, every second child was asked to attend a final clinical examination. 230 children attended, 61 of these having attended the examinations during the first year of life.

The questionnaire and clinical data of each child were compared and in 85% the data from the questionnaires and the results from clinical examinations were in agreement. Because the

Table 1
Distribution of symptoms in atopic probands

	Asthma %	Allergic rhinitis %	Atopic dermatitis %
Mother	16	25	59
Father	13	36	51
Grandparents	35	16	49

In atopic parents mother was the positive proband in 60%, father 34%, both 6%.

Table 2
Study outline

Birth	First year	2-4 years	5 years
Consecutively selected	393 mothers recorded weekly the diet and health status of their children	543 mothers filled in allergy questionnaire registering diagnosed asthma, allergic rhinitis, onset age and possible observed allergens	a questionnaire was sent, and every second child invited to a clinical study
from atopic families (n = 395)	150 children had additional clinical examinations at 1, 3, 6, and 12 months old		313 mothers filled in the allergy questionnaire
from non-atopic families (n = 148)			230 children received questionnaire clinical plus examination: 169 for the first time; 61 had had it before during the first year of life
total (n = 543)			

data compared so favourably, it was not felt necessary to calculate them separately.

A child was classified atopic if he or she had 1) signs of the disease present at the time of clinical examination, or 2) a convincing history of an atopic disease diagnosed by a paediatrician. Otherwise a child was regarded as non-atopic. For the definition of atopic dermatitis criteria consistent with those presented by Hanifin & Lobitz (15) were used. Atopic dermatitis with generalized distribution and signs of acute inflammation was classified as severe.

Blood samples were separated within an hour of the puncture and stored at -20°C . Serum IgE concentrations were measured in duplicate by the Phadebas® PRIST, a test kit provided by Pharmacia Diagnostics, Uppsala, Sweden. Nasal smears were air-dried and stained according to May-Grünwald-Giemsa, and many scattered eosinophils (++) in all fields were regarded as significant. The slides were studied blind so that the examiner did not know that the sample was being used in a study.

The χ^2 test was used for statistical analysis, with a variant of the binomial distribution

method to compare frequency. The test quotient is, however, approximately χ^2 distributed (14). This test was used for simultaneous comparison of the three family history groups, dates of birth, and prevalence of atopic disease.

RESULTS

Heredity

The cumulative prevalence of atopic diseases by the age of 5 years is summarized in Table 3. Due to the low number of observations, precision of presentation is used instead of calculation accuracy. The differences between three family history groups reached statistical significance only when the prevalence of atopic dermatitis or all allergies were compared. The relative risk of having a particular atopic disease was increased 2–3-fold with a positive family history. There were no significant differences when boys and girls were compared.

Regarding specific symptoms the following observations could be made: 8% of the children of asthmatic parents had asthma as op-

Table 3
Cumulative prevalence of atopic diseases by the age of 5 years

	<i>n</i>	Asthma (%)			Allergic rhinitis, (%)			Atopic dermatitis (%)			All allergies (%)		
		Boys	Girls	All	Boys	Girls	All	Boys	Girls	All	Boys	Girls	All
Negative family history of atopy (parents, siblings and grandparents)	148 M 68 F 80	1	1	1	4	8	6	16	18	17 ^a	18	20	19 ^a
										***			***
Atopic parent(s)	329 M 154 F 175	6	2	4	8	13	11	44	38	40	53	49	51
													*
Atopic grand-parent(s) (non-atopic parents)	66 M 32 F 34	3	0	2	6	12	9	22	32	27	28	44	36
<i>n</i>		254	289	543									
<i>n</i> (diseased)		12	5	17	17	33	50	85	91	176	102	117	219

Statistical significance between boys and girls is analysed in each row and between different family history groups in each column. *** = $P < 0.001$; * = $P < 0.05$.

^a Simultaneous comparison of three family history groups $P < 0.001$.

Table 4
Occurrence of multiple atopic symptoms at the age of 5 years

	Percentage of children with:		
	Atopic dermatitis	Allergic rhinitis	Asthma
Asthma	29.4	35.3	—
No asthma	31.3	7.6**	—
Allergic rhinitis	34.9	—	14.0
No allergic rhinitis	30.9	—	2.2**
Atopic dermatitis	—	8.9	3.0
No atopic dermatitis	—	7.5	3.2

** $P < 0.01$.

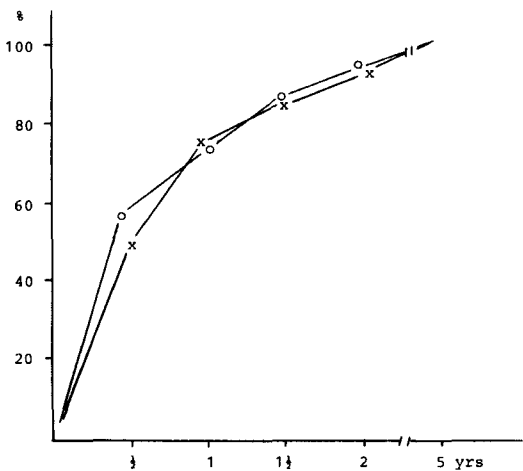


Fig. 1. Onset age of all cases of atopic dermatitis related to family history of atopy (accumulated percentages).
○—○: negative family history of atopy
×—×: positive family history of atopy.

posed to 1% of the children of non-asthmatic parents; similarly, 18% of the children of parents with allergic rhinitis had rhinitis and 56% of the children of parents with atopic dermatitis had dermatitis. Because of the relatively small population it was not possible to make a statistical evaluation of the heredity of one particular symptom. If both parents were atopic there was 80% prevalence of atopy amongst the children.

Multiple atopies

There was a correlation between the prevalence of asthma and allergic rhinitis (Table 4).

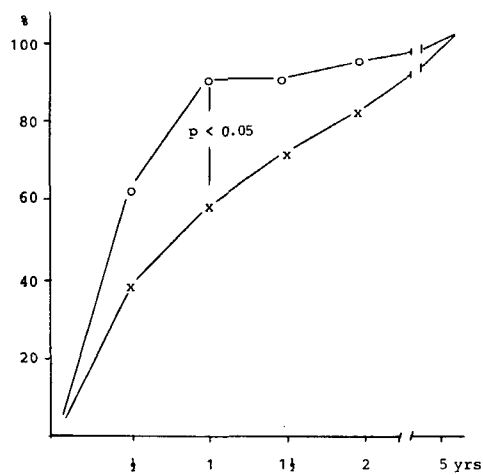


Fig. 2. Onset ages of all cases of atopic dermatitis related to severity of disease at the age of 5 years (accumulated percentages).
○—○: severe or moderate atopic dermatitis
×—×: mild atopic dermatitis.

Table 5
Significant eosinophilia (%) in nasal smears at the age of 5 years

Clinically healthy	21
Atopic eczema	20
Allergic rhinitis	46
Asthma	100

Asthma and allergic rhinitis occurred equally in children with or without atopic dermatitis, and had no relation to family history.

Onset of symptoms

The onset of atopy occurred during the first year of life in 75% of atopic children (Fig. 1), presenting mainly as atopic dermatitis. The age of onset of atopy could not be correlated to family history but was related to the severity of the disease (Fig. 2). In the final clinical examination 23% of the parents of children with atopic dermatitis reported that their children had outgrown their symptoms. However, it became obvious that the parents regarded dermatitis as healed if there had been a marked improvement of the disease.

Table 6

Mean IgE values (IU/ml) in healthy and atopic subjects at the age of 5 years

	n	Mean	Mean + 1 SD	Mean + 2 SD
No atopy and no family history of atopy	43	24	100	4×10^2
Atopic dermatitis	45	26	120	6×10^2
Asthma and/or allergic rhinitis	25	53	560	6×10^3
allergic rhinitis	13	35	500	7×10^3
asthma	3	451	8×10^3	13×10^4
Atopic dermatitis and asthma or allergic rhinitis	13	54	220	9×10^2

Severity of symptoms

The 17 asthmatic children had been treated at a paediatric hospital and 55% of the atopic subjects had been prescribed medical treatment by a paediatrician. The children from atopic families did not have a more severe atopic dermatitis, nor was the frequency of medical treatments based on the severity of symptoms. At the final clinical examination the atopic dermatitis was classified severe or moderate in one third of the atopic children aged 5 years.

Birth weight and season of birth

Children with low birth weight tended to suffer from atopic dermatitis more often than mature infants, but the difference was not significant. The prevalence of respiratory allergies was similar in all birth weight groups.

The children were divided into groups according to date of birth: 1) Dec.–Feb., 2) March–May, 3) June–Aug., 4) Sept.–Nov., and the percentage prevalence of atopic diseases was calculated within each group.

The prevalence of atopic dermatitis could not be correlated to this grouping, but in group 3 the risk of developing asthma or allergic rhinitis was less among boys than among girls (< 0.05 ; (14)).

Nasal eosinophilia

Eosinophils in nasal secretion were more common among children with respiratory allergy

than among those with dermatitis or those who were non-allergic (Table 5). However, one fifth of the non-allergic children had eosinophils in their nasal smears.

Serum IgE at the age of 5 years

The mean serum IgE level for healthy children in non-atopic families was 24.5 IU/ml (range 1–470 IU/ml) (Table 6). 73% of the children with a serum IgE level above 100 IU/ml had atopy (41% respiratory or combined, 32% atopic dermatitis). However, of those children with serum IgE levels below 24 IU/ml, 31% had atopic dermatitis and 23% respiratory atopy. The IgE could not be correlated to nasal eosinophilia.

DISCUSSION

In our previous questionnaire study on the prevalence of atopy among the general population (44) 24% of the families had a positive history of parents' atopy. In the present study we have estimated the cumulative prevalence of atopy among the children from such families and from non-atopic parents. Thus on the basis of these two studies the prevalence of atopic diseases amongst 5-year-old children in Finland can be roughly calculated: asthma 2%, allergic rhinitis 7% and atopic dermatitis 23%, in total 27%.

The reasons for the apparently high prevalence of atopic allergies in Finland (Table 7)

Table 7
Prevalence of asthma, allergic rhinitis and atopic dermatitis in Finland

	Time of study	Asthma %	Allergic rhinitis %	Atopic dermatitis %	Total %	Notes
Alanko (1)	1968	1.4	5.9	—		S.W. Finland rural population
Luoma (25)	1972–1974	1.2	2	9	11	children mean age 6 years S.W. Finland
Malmberg (26)	1978	3.9	13 28	30	41	schoolchildren and students S.W. Finland
Haahtela (12)	1978	1.8	14	21	32	adolescents S.E. Finland
Haahtela (13)	1978	3.9	20	18	36	18–19 years, males S.E. Finland
Estimation based on present study and ques- tionnaire study (25) by the same authors	1978	2	7	23	27	children aged 5 years S.W. Finland

may be 1) a real increase in atopy, which is difficult to prove, 2) highly developed means for diagnosing allergic diseases, which is undoubtedly true, and 3) general awareness of allergies among the population because of the widespread information available. This third possibility may have influenced the increased prevalences found in the present study since part of the information was obtained from questionnaires only. However, the questionnaires were found to be 85% reliable among children who had a clinical examination. Presuming that they were as reliable among the other children, the increase due to inaccurate questionnaire information is probably insignificant.

The influence of a positive family history on the risk of atopy was comparable to that found by Edfors-Lubs (8). For a newborn baby a positive family history can be an indicator of an eventual atopic disease. However, a negative family history does not exclude these diseases in the infant; on the contrary, the risk is still considerable. In addition, if one third of the adults are estimated atopic (12), then more than half

of the children should have a positive family history, and therefore a majority of the children will be at risk, i.e. the selection of potentially allergic children by using family histories becomes even more purposeless.

An association between asthma and hay fever was found, but these two symptoms were not associated with atopic dermatitis. However, the relationship of respiratory and atopic skin symptoms is established in older populations (24, 26). Thus more respiratory allergies are to be expected in the future among those children who now have only skin symptoms. We found no definitive evidence that a "familial" atopic disease differed from an atopic disease with a negative family history.

In the present population severe or moderate atopic dermatitis had had a slightly earlier onset age than the mild symptoms, thus stressing the importance of the first months of life in the development of atopy.

Date of birth has been seen to influence the incidence of respiratory allergies (3, 4, 28, 37). Our observations may confirm this.

Nasal eosinophilia was frequently found in children who had respiratory allergies. It is a usual diagnostic finding (2, 7, 27, 29) and its significance increases with age (6), but nasal eosinophilia has been reported to occur in 30% of children with infantile asthma (6) as opposed to 52% in infants with atopic dermatitis (7). There are many respiratory allergies which remain undetected, and these may exist among the 20% in this study with a positive nasal smear who were healthy or had dermatitis. Repeated nasal smear samples are needed to evaluate the significance of nasal eosinophilia in subjects suffering from equivocal allergic symptoms.

Mean serum IgE levels in atopic and possible atopic populations are increased (22, 36). A high IgE level may precede subsequent atopic disease (17, 22). However, there is a wide variation within each group (10, 18, 19). Mean serum IgE levels of 20 IU/ml (22), 36 IU/ml (31) and 100 IU/ml (9) are reported normal for children aged 4–5 years. The lowest values are found when the population has been carefully selected with respect to both family history and signs and symptoms of the disease (22).

Among atopic individuals IgE is independent of family history (39) but can be correlated to the mean serum IgE levels of the parents (38). If the symptoms are absent for a time, the IgE tends to return to normal (16, 20).

Serum IgE in atopic dermatitis may correlate with the severity of the disease and with co-existing respiratory atopic symptoms (16, 30, 39), but many authors have failed to demonstrate significant differences between the normal range of serum IgE and the serum IgE in atopic dermatitis (10, 11, 16, 21, 39). Thus, the poor correlation between atopic dermatitis and the total serum IgE in the present population is not surprising.

The mean normal level of serum IgE in the present population is comparable to previous Swedish reports (22, 39), and may be due to common geographical and environmental factors. There remains a possibility that those with atopic dermatitis and high IgE levels will later develop respiratory symptoms.

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