

Long-Term Changes in Inhalant Allergy in Asthmatic Children

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In a representative cohort of 55 asthmatic schoolchildren the progress of the allergy *per se* was followed up prospectively for 8 years. Judged by clinical data, skin prick tests and RAST, a large majority of the children retained their allergies to pollen and animal danders. These allergens were predominant, whereas allergy to mites and moulds was less frequent. Serum IgE levels showed a strong tendency to remain high. Positive RAST and skin prick tests were also found in a substantial number of children with normal serum IgE concentrations.

Key words: asthma; children; progress of allergy.

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CLINICAL ASPECTS

Schoolchildren with asthma and allergy to danders or pollen should be advised, when planning their future studies, work and social life, to take their allergies into consideration. Asthmatic schoolchildren should be assessed for possible allergies even if they have normal serum IgE.

There is a widespread belief that allergies in children with asthma are long-lasting, but there have been few studies of the long-term progress of the allergy *per se* in asthmatic children.

In a prospective study, McNicol & Williams (8) followed up asthmatic schoolchildren from 7 to 14 years of age by means of skin scratch tests against six airborne allergens, including one against animal danders (cat), and found a tendency to increasing positivity with increasing age. Their cohort of children was reevaluated at 21 years of age by Martin *et al.* (7), who found an increasing frequency of reactivity between 7 and 21 years of age and that the change at 14 to 21 years of age appeared to be independent of the progress of asthma. Foucard (1) has recently published a 12-year follow-up of 80 infants and toddlers in Sweden with wheezy bronchitis, of whom all but 22 had outgrown their asthma. The total number of positive skin prick tests or

RAST had increased to 68: 31 against animal danders, 30 against pollen and seven against mite or mould.

In the present prospective study we report the progress of clinical allergies, skin prick tests, serum immunoglobulin E (S-IgE), and IgE antibodies against some inhalant allergens in a representative cohort of 55 Swedish schoolchildren followed up for 8 years.

MATERIAL AND METHODS

Material

The main indication for a referral to the Allergy Unit is at least three episodes of bronchial obstruction in children over 3 years of age. The capacity of the unit is good and the indications are well known to the paediatricians in the province (4). An attendance at the unit includes a history taken with the aid of a standardized

questionnaire, a physical examination and skin prick testing (SPT).

The *primary* material consisted of all asthmatic children admitted to the unit during 1974/1975 who will be ≥ 7 years of age at the first follow-up examination, scheduled for 1977/1978. From this material a representative cohort of 58 children (half boys and half girls) was selected at random to be followed into adulthood. One boy and one girl were omitted at the first follow-up visit because of failure to satisfy the criteria and failure to obtain consent, respectively. During the follow-up, one girl died from her asthma. The remaining children reported for the three follow-up examinations during the 8 years. Thus the *final* series consisted of 28 boys and 27 girls (Table 1). The clinical manifestations of asthma ranged from occasional mild wheezing to frequent severe attacks. Only one of the children was treated with hyposensitization (using pollen extracts) during the period. Clinical allergy to animal danders was defined as obvious reactions from the respiratory tract and/or eyes within 1 h of contact with the animal and on at least two occasions. Clinical allergy to pollen was defined as obvious, non-infection reactions from the respiratory tract and/or eyes during at least two pollen seasons.

Procedure

The first visit to the unit is designated as I, the first follow-up visit as II, and so on. Table 1 shows the children's ages at the four examinations, during which they were clinically assessed by SPT. The same two paediatricians conducted the examinations and the same personnel performed the SPT procedures throughout the period. At visits II-IV venous serum samples were drawn for determinations of S-IgE and IgE antibodies against inhalant allergens. Due to a technical fault these serum tests were not performed in the first 14 children at II. At each examination the assessment was made with the child in optimal condition and entirely free from infection. SPTs were performed as single tests on the volar aspect of the forearm using three animal danders (dog, cat, horse), two pollens (a mixture of 4 grasses and birch), one mite (*Dermatophagoides farinae*) and four moulds (*Alternaria*, *Aspergillus*, *Penicillium*, *Cladosporium*).

At the first examination aqueous extracts (concentrations: 1/10 - w/v) from Vitrum, Stockholm, were used in all tests except for mite, which was from Dome/Hollister-Stier, England (concentration: 5000 protein nitrogen units/ml). At visits II and III all extracts were

Table 1

55 asthmatic children underwent interviews, clinical examinations and skin prick tests on four occasions (I-IV) during a period of 8 years

Children and clinical data	Examinations							
	I		II		III		IV	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
No. children	28	27	28	27	28	27	28	27
Age (years)								
mean	9	10	11	12	13	14	17	17
range	6-14	5-14	8-17	7-17	10-19	9-19	14-22	13-22
Time interval (years)	0	0	2	3	4	5	8	8
No. specimens								
for RAST	0	0	16	25	28	27	28	27
for IgE	0	0	16	25	28	27	28	27
Clin allergy								
to pollen	14	11	15	12	18	14	15	16
to danders	19	17	18	15	20	18	19	19

from Dome/Hollister-Stier, England. At visit IV the pollen extracts were from Pharmacia, Uppsala (concentration: 10,000 biological units/ml). The dander mite mould extracts were from Allergologisk Laboratorium A/S, Denmark (Soluprick - SQ, concentration: 1 HEP). At all examinations the same concentration of histamine (1 mg/ml) was used as a reference. Skin test wheals with a diameter equalling that obtained with the histamine reference were rated 3+ and a wheal size between 3+ and half of that obtained with the histamine reference was rated 2+. As different extracts were used during the 8 years, only $\geq 3+$ reactions are rated as positive in this study.

S-IgE was determined by Phadebas IgE PRIST® (Pharmacia Diagnostics, Uppsala) according to the recommendations of the manufacturer.

IgE antibodies against inhalants were determined by Phadebas RAST® (Pharmacia Diagnostics, Uppsala) using the following antigens: dog, cat, horse, timothy, English rye-grass, birch, mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*) and moulds (*Penicillium*, *Cladosporium* and *Aspergillus*). The RAST-class ratings of 0-4 were used as recommended by the manufacturer. Positive RAST, i.e. RAST-class ≥ 1 was defined as ≥ 0.35 Phadebas RAST units/ml.

RESULTS

Clinical allergy

At the first examination 11 children (20%) denied any allergies, 25 children (45%) had an allergy to pollen and 36 (65%) to animal danders. At the last examination only five children (9%) denied any allergy, 30 children (55%) reported an allergy to pollen and 38 (69%) to animal danders. During the follow-up period eight children developed an allergy to pollen and four lost their allergy. Five children developed an allergy to animal danders and three lost their allergy.

Thus, 22 of the initial 25 children allergic to pollen (88%) and 33 of the initial 36 children with clinical allergy to danders (92%) retained their allergies.

Fourteen of the 25 children with a history of pollen allergy had adverse reactions to fruits, berries or nuts, whereas only four of the other children had such reactions.

Skin prick test

At the first examination 44 children (88%) had a positive SPT and the number was the same at the last examination. The distribution of the positive tests for the different allergens is shown in Table 2.

Table 2

Positive skin prick tests (SPT) and RAST (%) in 55 children with asthma. The tests were done on four occasions (I-IV) during a period of 8 years

Allergen	I		II		III		IV		Pos SPT I and IV ¹	Pos RAST II and IV ²
	SPT	RAST	SPT	RAST	SPT	RAST	SPT	RAST		
Grass or birch	60	-	65	68	64	73	69	76	94	82
Grass and birch	29	-	35	29	18	40	20	33	44	83
Dog, horse or cat	62	-	64	56	53	78	60	67	74	96
Dog, horse, and cat	22	-	11	22	9	45	25	31	42	78
Mites	7	-	11	12	7	27	7	9	0	60
Moulds	7	-	13	10	2	45	4	15	0	75

¹ In percentages of children with positive SPT at I.

² In percentages of children with positive RAST at II.

The predominance of positive reactions to pollen and animal danders is evident. Most of the children with a positive SPT at I were still positive at IV: 94% of the children initially positive to pollen and 74% of those initially positive to danders were positive at IV.

At the first examination nine children had a positive SPT for pollen but no clinical allergy. Four of them developed this allergy during the follow-up period and four children with negative reactions also developed clinical allergies. One of three children with positive reactions to danders but no clinical allergy, compared with four with negative reactions, developed such an allergy.

IgE antibodies against inhalants

At visit II (when serum samples were first taken) 80% of the children were RAST-positive and at IV, 87%. Most positive specimens were in RAST class 2 or higher: 84% at II and 90% at IV. The results for the different allergens are shown in Table 2. Most children with a positive RAST at II remained positive: 82% of the children with a positive RAST for pollen and 96% with a positive RAST for danders were still positive at the last examination.

At visit II six children had a positive RAST for pollen but no clinical allergy. Two of them, and six with initially negative RAST, developed pollen allergies during the follow-up period.

Two of four children with positive RAST to danders but without clinical allergy, compared with three with initially negative RAST, developed an allergy to danders.

Six children were consistently RAST-negative to all allergens. They were also SPT-negative and neither had nor developed clinical allergies. Five of them had S-IgE values under +1 SD for non-atopic Swedish children and one had between +1 SD and +2 SD throughout.

S-IgE

A total of 151 specimens were available for IgE determinations and the results, fitted into the nomogram for non-atopic Swedish children, show that 50% were over +2 SD, 29% between +1 SD and +2 SD, and 21% under +1 SD. The IgE values tended to persist within the same range during the 6-year follow-up period: 52% remained within these ranges throughout the period and 97% of the children with an initial IgE over M+1 SD remained at that level. Only one child showed a pronounced change. She started with an IgE under +1 SD and ended with a value over +2 SD. She had no clinical allergy initially and was a nonreactor in the tests, but developed an allergy and RAST positivity to grass. The relation between positive RAST and SPT reactions and the S-IgE levels is shown in Table 3.

DISCUSSION

The present cohort consists of schoolchildren with established asthma that still produced symptoms in the year prior to their first visit to the Allergy Unit. Thus they differ from the Swedish group followed up by Foucard (1).

Table 3

55 asthmatic children examined on three occasions (II-IV) during a period of 6 years. Distribution of positive RAST and skin prick test (SPT) within the ranges of S-IgE. The IgE range classification refers to the nomogram for healthy Swedish children. The percentages of positive tests within each S-IgE range are given

IgE range	II (n = 41)		III (n = 55)		IV (n = 55)		All specimens (n = 151)	
	RAST-pos %	SPT-pos %	RAST-pos %	SPT-pos %	RAST-pos %	SPT-pos %	RAST-pos %	SPT-pos %
< M + 1 SD	36	36	50	25	44	33	43	32
1 SD-2 SD	75	75	94	76	80	80	84	75
> 2 SD	95	95	100	81	100	81	99	84

Our aim is to follow the children's clinical, social, physiological and immunological progress for a longer period of years. This communication is an interim report on the progress of the allergy *per se*.

The incidence of clinical allergy to inhalant allergens is high, and allergies to pollen and animal danders dominate. This overrepresentation could be false since it is much easier to find a clinical cause-effect relationship for these allergens than for mites and moulds. Nevertheless, the same pattern is seen in the SPT and RAST results, which agree with those found in other Swedish studies but differ from some reports from other parts of Europe (1, 9, 10).

The 65% clinical allergy to animal danders found at visit I agrees with the 57% clinical allergy to danders found in a previous questionnaire survey of asthmatic schoolchildren in this Swedish province (5, 6). Further, the 62% positive SPT responses to animal danders closely agrees with the 60% positive responses noted in a previous evaluation of the test results at our Allergy Unit (3). These similarities support our belief that the present cohort is representative of asthmatic children in our province. Allergy to both pollen and danders and to more than one pollen or animal was frequent, which also agrees with our previous studies (3).

In general, the children showed no tendency to outgrow their allergy to danders and pollen, judged clinically and by tests, when they passed puberty into young adulthood. It would therefore seem wise to advise schoolchildren with asthma to plan their future studies, work and social life on the assumption that they will retain their allergies.

We are aware that the change in extracts for SPT during the follow-up period decreases the accuracy of comparison between SPT results. The reason that we changed was because we preferred to use the more highly purified and standardized extracts when they became available.

As expected, this cohort of children had higher S-IgE levels than healthy children, and these levels remained high during the follow-up period. Only one child showed a pronounced change in S-IgE level during the follow-up. Most positive RAST and SPT reactions were

found in the children with high IgE levels, but there was still a 30–40% risk of finding a positive RAST or SPT in children with S-IgE under +1 SD for healthy children. This decreases the value of S-IgE as an indicator for further assessment of the allergy in an asthmatic child and supports the opinion that schoolchildren with asthma should have their allergy assessed regardless of the results of a S-IgE determination. Only six children (11%) were consistently negative at SPT and RAST determinations and had S-IgE levels under +2 SD from those of healthy children. In a recently published Danish study Östergaard (10) found that 12% of asthmatic children had such a "non-IgE asthma".

In some children a positive RAST or SPT preceded the development of clinical allergy, and positive allergy tests seemed predictive, a finding which agrees with that of Hattevig et al. (2). However, most children developing a clinical allergy were initially test-negative and some children with initially positive tests and no clinical allergy did not develop an allergy. The predictive value of SPT and RAST seemed thus unclear.

In conclusion, the present study shows that allergies to pollen and animal danders in schoolchildren with asthma persist into young adulthood. Furthermore, high S-IgE concentrations remain high in a large majority of the children. There are more positive RAST and SPT responses in children with high IgE concentrations, but positive tests are also noted in a considerable number with normal S-IgE levels.

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