

Appearance of atopic disease in relation to serum IgE antibodies in children followed up from birth for 4 to 15 years

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Background: Few studies have addressed the relationship between sensitization and the development of atopic disease over many years.

Objective: To study the temporal relationship between the appearance of IgE antibodies in serum and atopic disease, we studied 324 children from three different groups, who were followed up prospectively from birth for 4, 12, and 15 years, respectively.

Methods: Serum samples were obtained at various ages and analyzed for IgE antibodies against egg white, cow's milk, wheat, animal dander, house dust mite, birch and timothy with Phadebas RAST (Kabi Pharmacia Diagnostics AB, Uppsala, Sweden) or Pharmacia CAP system. In addition, a screening test for atopy, the Phadiatop Paediatric test (Kabi Pharmacia Diagnostics AB) was performed. Presence of atopic disease was assessed by means of clinical examination, interviews, and questionnaires.

Results: In 135 children IgE antibodies were detected at least once to at least one allergen. Antibodies to egg white appeared in 46 children before or at 2 years of age: in 57% of them IgE antibodies to inhalants developed within the next 2 years, and in 19 of 25 (76%) IgE antibodies to inhalants developed before or at 12 to 15 years. Antibodies to inhalant allergens appeared in 55 children during the first 4 years of life and in 64 before 12 to 15 years. Among the former 48% and among the latter 32% had previously detectable egg white antibodies. Atopic disease appeared before or at age 4 years in 80% of the 40 children with IgE antibodies against egg white up to 9 months of age and in 69% of the 58 children who had a positive Phadiatop Paediatric test result in infancy.

Conclusions: IgE antibodies in children are usually associated with current or later atopic disease. Sensitization to foods in infants is usually associated with appearance of IgE antibodies to inhalants later in life. (*J ALLERGY CLIN IMMUNOL* 1994;94:757-63.)

Key words: Atopic disease, IgE antibodies to foods and inhalants, atopy prediction

Most previous studies on the occurrence of IgE antibodies in children have been cross-sectional, rather than longitudinal.¹⁻⁵ Only a few studies have addressed the relationship between sensitization and the appearance of atopic disease over many years.⁶⁻⁹ We have performed several pro-

spective studies of the development of atopic disease^{8, 10-16} in children with and without heredity for atopic disease. We report the appearance of atopic disease in three groups of children in whom IgE antibodies against common food and inhalant allergens developed at any time between birth and 4 to 15 years of age.

METHODS

Patient groups

Three groups of children were studied prospectively for 4 to 15 years with repeated clinical examinations, interviews with their parents, questionnaires, and serum sampling (Fig. 1).

The parents of all participating children gave their informed consent. The studies were approved by the Human Research Ethics Committees of the Medical Faculties of the Universities of Linköping and Göteborg.

Group I comprised 125 children born in Linköping,

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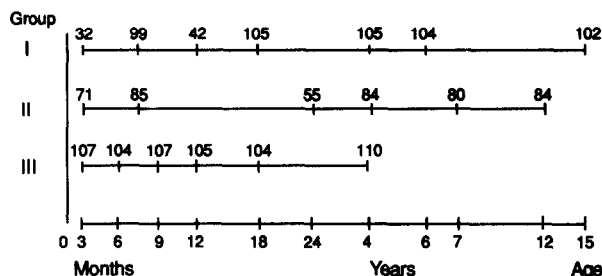


FIG. 1. Number of serum samples at different ages from three groups of children followed up from birth to 15 years of age (group I, $n = 125$), 12 years of age (group II, $n = 84$), and 4 years of age (group III, $n = 115$).

Sweden, between August 1972 and March 1974 and followed up for 15 years. In 52 cases two members of the immediate family (i.e., parents or siblings) had a history of atopy or allergy, in 38 cases one family member was atopic, and in 35 cases no history of atopy was found in the immediate family. The study group has participated in several other studies on atopic diseases.¹¹⁻¹⁶

Group II included 84 girls born to Rh-negative mothers from August 1977 to August 1978 at the central hospital of Skövde, Sweden, and followed up for 12 years. This group was originally recruited for a study of Rh immunization¹⁷ but has also been subject to studies of dextran-reactive antibodies and atopy development.^{8, 18-20}

Group III consisted of 115 children, followed up for 4 years, all recruited prenatally to study the possible effect of maternal diet restrictions on the development of sensitization and atopic symptoms.^{10, 21, 22} They were born at the central hospitals of Skövde and Borås, Sweden, from September 1984 to March 1986. In 103 cases a history of atopy or allergy in two members of the immediate family was seen. Twelve children had a history of atopy in one family member and a cord blood IgE level of 0.9 kU/L or greater.

Diagnostic criteria for atopic disease

Atopic dermatitis was defined as a pruritic, chronic, or chronically relapsing dermatitis with typical features and distribution, as suggested by Hanifin and Rajka.²³ Bronchial asthma was defined as three or more episodes of bronchial obstruction diagnosed by a physician. Allergic rhinoconjunctivitis was defined as rhinitis and conjunctivitis appearing at least twice after exposure to a particular antigen and not related to infection. Perennial rhinitis was not included in the diagnoses. Urticaria was defined as allergic if it appeared at least twice within 1 hour after exposure to a particular allergen.

Gastrointestinal allergy was defined as the appearance of diarrhea, colicky pain, and/or vomiting after intake of a specific food on at least two occasions.

Allergy to a defined allergen was defined as the appearance of obvious symptoms within 1 hour at least twice after contact with the allergen.

The clinical observations were made at three different hospitals by three of the authors over a long period. For this study three of the investigators jointly (but not blinded) scrutinized the diagnoses on the basis of descriptions of case histories of patients selected at random from all groups. This retrospective control of the diagnoses agreed well with the initial classification.

Laboratory methods

Sera had been frozen at -20°C at the Pediatric Research Laboratory, University of Linköping. The same laboratory technician performed all the analyses. The number of available serum samples is shown in Fig. 1.

All available serum samples were tested with Phadi-atop Paediatric (Kabi Pharmacia Diagnostics AB, Uppsala, Sweden), a screening test for IgE antibodies containing a secret mixture of food and inhalant allergens.^{24, 25} The test is qualitative, and the result is "positive" or "negative."

Two different techniques were used for detection of IgE antibodies against the various allergens, the Pharmacia CAP System and the Phadebas RAST (Kabi Pharmacia Diagnostics AB). These methods use different technologies but the same allergen source and correlate well with each other.^{26, 27}

Serum samples in group I were analyzed with the Pharmacia CAP system, and values of 0.35 kU/L or greater (allergen specific), corresponding to CAP RAST class 1 or greater were considered positive.

Serum samples in groups II and III were analyzed with a modification of RAST, allowing identification of lower values than 0.35 Phadebas RAST units (PRU)/ml.^{8, 20, 21} In this study only values equal to or greater than 0.35 PRU/ml, corresponding to RAST class 1 or greater, are considered positive to allow comparisons among the three groups of children.

Serum samples from children aged 18 months and older were analyzed for IgE antibodies (in order of priority) against animal dander, birch pollen, mite (*Dermatophagoides pteronyssinus*), and wheat. Antibodies against timothy grass were investigated from age 4. For the detection of IgE antibodies to animal dander group I serum samples were analyzed with cat, dog, and horse allergens; and group II and group III serum samples were analyzed with an animal mix (containing allergens from cat, dog, and horse [Pharmacia Diagnostics AB]).

In children younger than 18 months, antibodies to egg white and cow's milk were analyzed before antibodies to inhalant allergens and wheat. Antibodies against egg white and cow's milk were analyzed in all serum samples from children up to 2 years of age. Serum samples obtained thereafter were analyzed only if the child had IgE antibodies against egg white or cow's milk equal to or greater than 0.35 kU/L or PRU/ml in the previous sample because it has been previously reported, in children followed up prospec-

tively from birth, that IgE antibodies to these antigens rarely appear after the first year of life.^{8, 20}

Some of the serum samples in groups II and III had been analyzed previously with the same sensitive RAST technique as described above.^{8, 20, 21} In this study we included the results of IgE antibody analyses with egg white and cow's milk at the ages of 3 and 8 months in group II, performed in 1983,²⁰ and at the ages of 3, 6, 9, 12, and 18 months in group III, performed in 1987.²¹

Statistical methods

For comparison of proportions and for comparisons between the capacity for IgE antibodies to egg white the Phadiatop Paediatric test (Kabi Pharmacia Diagnostics AB) to identify and predict atopic disease, the two-tailed Fisher's exact test, and binomial distribution were used.

RESULTS

In all, 135 of the 324 children had a positive Phadiatop Paediatric test result and/or IgE antibodies equal to or greater than 0.35 PRU/ml or kU/L at least once to at least one antigen. These 135 children comprise the group described in the following paragraphs. Both a positive Phadiatop Paediatric test result and at least one positive test response to an individual allergen were observed in 86 of these children. In 32 children only a positive Phadiatop Paediatric test result was recorded, and in 17 only IgE antibodies to individual allergens were found. The results of development of IgE antibodies and atopic disease from birth to age 4 are presented together because the outcome was comparable in the three groups of children.

Food antibodies were detected in 66 children. In 46 of them IgE antibodies to egg white were found; in 17 of these 46 children also cow's milk antibodies and in 14 wheat antibodies were seen before or at 18 months of age. Another 10 children with food antibodies had antibodies to cow's milk only, and three had antibodies to wheat only, before or at 18 months of age. In 11 children wheat antibodies appeared after 18 months; three of them had egg white antibodies and one had cow's milk antibodies in infancy.

Of the children with IgE antibodies to egg white up to 2 years of age, 26 of 46 (57%) had inhalant antibodies by age 4, and 19 of 25 (76%) before 12 to 15 years. Of the children with antibodies to cow's milk, but not to egg white, 5 of 10 (50%) had IgE antibodies to inhalant allergens by age 4, and 3 of 3 before 15 years of age.

Antibodies to inhalant allergens developed in 85 children. Of the 55 children who had IgE

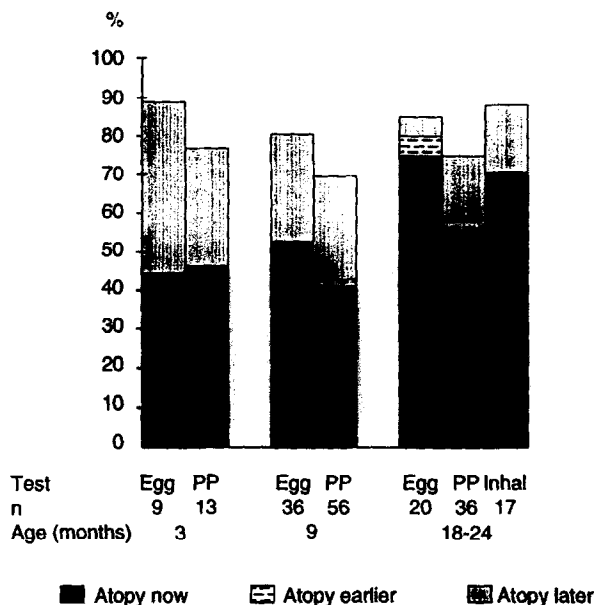


FIG. 2. Proportion of children with earlier, current, or later atopic disease up to age 4 years among those with IgE antibodies to egg white (Egg) and a positive Phadiatop Paediatric test result (PP) at 3, 9, and 18 to 24 months of age. For antibodies to inhalants (Inhal) only data from children aged 18 to 24 months are given.

antibodies to inhalant allergens up to 4 years of age, 26 of 54 (48%) had previously had IgE antibodies to egg white. The corresponding figures among the children who were followed up for 12 to 15 years were 19 of 59 (32%).

The hypothesis that antibodies to timothy grass at any time and wheat antibodies at the age of 18 months or younger were connected was also investigated in group I. Of 34 children with IgE antibodies to timothy grass, 30 had been tested for antibodies to foods at the age of 18 months or younger. Only six of them had antibodies to wheat, whereas 12 had antibodies to egg white. Of eight children with wheat antibodies 18 months of age or younger, six later had antibodies to both timothy grass and birch pollen. Thus antibodies to wheat in infancy did not seem to have any specific relationship to later sensitization to timothy grass.

Of the 118 children with a positive Phadiatop Paediatric test result at any age, 73 (62%) had positive results during the first 2 years of life. Antibodies to individual allergens were seen before or at the same time as the first positive Phadiatop Paediatric test result in 31 (42%) of them. The corresponding figure among the 45 children in whom a positive Phadiatop Paediatric

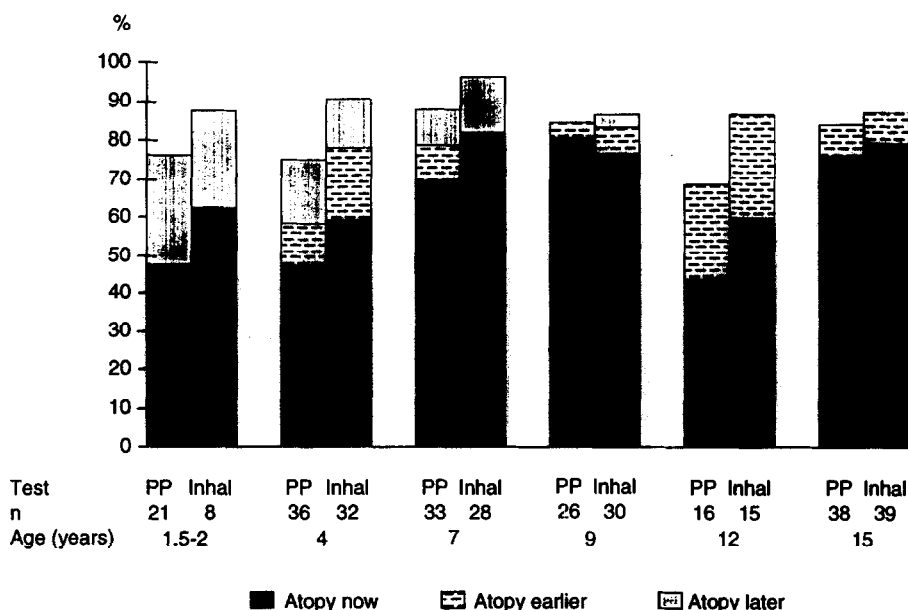


FIG. 3. Proportion of children followed up for 12 to 15 years with earlier, current, or later atopic disease among those with IgE antibodies to inhalants (*Inhal*) and/or a positive Phadiatop Paediatric test result (*PP*) at 18 to 24 months, 4, 7, 9, and 12 or 15 years of age.

TABLE I. Positive tests up to 9 months of age and their relation to time of diagnosis of atopic disease up to age 4 years

Test	n	Atopic disease		
		At positive test	After test	Total
EW*	40	22 (55%) NS	10 (25%) NS	32 (80%) NS
PP†	58	25 (43%)	15 (26%)	40 (69%)

NS, Not significant.

*Egg white antibodies.

†Positive Phadiatop Paediatric test result.

test result was demonstrated for the first time after age 2 was 30 (67%).

In all, 96 of the 135 children with detectable IgE antibodies at any time had atopic disease (71%). Asthma was diagnosed in 21, allergic rhinoconjunctivitis in 52, and atopic dermatitis in 69 of them. Among the children who were followed up for 12 to 15 years, 28 of 34 with food antibodies (82%) and 53 of 64 with inhalant antibodies (83%) eventually had atopic disease. Among 32 children with Phadiatop Paediatric as the only positive test result during the whole study period, 20 had positive results before or at 2 years. In total 15 of 32 (47%) had atopic symptoms, among them 7 of 17 (41%) who were followed up for 12 to 15 years.

Appearance of IgE antibodies early in life was usually associated with an early development of disease, often already at the time of the first positive test (Figs. 2 and 3, Table I). Among the children with egg white antibodies in infancy, 18 of 22 (82%) eventually experienced atopic symptoms before 12 to 15 years, as compared with 25 of 35 (71%) of those with a positive Phadiatop Paediatric test result (not significant). Among 66 children with atopic disease and detectable IgE antibodies up to 4 years of age, 32 were identified with both IgE antibodies to egg white and a positive Phadiatop Paediatric test result in infancy, eight with Phadiatop Paediatric as the only positive test result, and none with only egg white antibodies ($p < 0.01$).

The relationship between IgE antibodies at different ages and atopic disease at the time of the test or earlier or later is shown in Figs. 2 and 3. As expected, the proportion of children with previous or present atopic symptoms at the time of the test increased with age. The proportion of children with later atopic disease among children with egg white antibodies and/or a positive Phadi-atopic Paediatric test result at 9 months were similar.

Of the 46 children with IgE antibodies to egg white 18 (39%) had experienced allergic symptoms when exposed to the food. Twelve of them were tested before the appearance of clinical symptoms, and they were sensitized. Of the 48 children with IgE antibodies to birch pollen 25 (52%) experienced symptoms of allergy to birch pollen during the observation period. In 15 (63%) of 24 children who had been tested at the nearest time preceding the diagnosis of birch pollen allergy, IgE antibodies appeared before symptoms. Of 38 children with IgE antibodies to animal danders, only 19 (50%) were aware of any allergy to furred animals. Of these 19 children, 16 were tested at the nearest time preceding diagnosis, and 10 (63%) were sensitized.

The IgE antibody levels were usually higher in children with atopic disease than in healthy children. Of 170 positive CAP test results in the children with atopic disease, 65 were equal to or greater than 3.5 kU/L (CAP class 3 or greater). The corresponding number was 2 of 14 positive test results in healthy children (not significant, $p = 0.055$). The results were similar for the RAST, 45 of 109 test results were equal to or greater than 3.5 PRU/ml in the atopic group compared with 2 of 15 in the healthy group ($p = 0.047$).

DISCUSSION

The study population consisted of three groups of children with similar clinical criteria for atopy or allergy who were followed up with repeated serum sampling for IgE antibody determination, and it thus allows an analysis of the appearance of atopic disease versus the appearance of IgE antibodies. Because various principles of selection of the groups have been used, the population does not allow an epidemiologic approach in terms of frequencies of atopy or allergy or of different IgE antibodies.

The appearance of IgE antibodies followed the previously described pattern, with food antibodies (especially to egg white) being the most common

in infancy and antibodies to inhalant allergens beginning to be more important from 18 months of age.^{1, 3, 4, 7, 8} IgE antibodies to food allergens in infancy predisposed children to have antibodies to inhalant allergens later, but only 32% of the children who eventually had inhalant antibodies could be identified in this way.

Most of the children with IgE antibodies to individual allergens could be identified with the Phadiatop Paediatric test, as has been previously reported.^{22, 24, 25} During the first years of life, a positive Phadiatop Paediatric test result without evidence of IgE antibodies to individual allergens before or at the same time was more common than later in life. The test uses a mixture of food and inhalant allergens, and it is possible that the children were sensitized to antigens included in the mixture but not used in the individual IgE tests. Furthermore, because transient low levels of IgE antibodies to food allergens are a normal part of the early immune response,^{20, 28} young children may show positive results in a screening test, which measures the sum of IgE antibodies against several different allergens. A similar development of low levels of IgE antibodies to inhalant allergens might also be possible, as indicated by studies in rats and human beings.^{29, 30}

Most children with IgE antibodies had atopic symptoms, and the presence of antibodies often preceded the disease similar to the findings in other studies.^{1, 2, 8, 28} Furthermore, in older children IgE antibodies could also imply earlier atopic disease. IgE antibodies to the individual food and inhalant allergens often developed before the appearance of allergic symptoms to these allergens, as observed previously.^{2, 8, 20, 28} The demonstration of the presence of IgE antibodies does not necessarily imply atopic disease, however,^{6, 28, 31} and this was confirmed in this study with a long follow-up time. The IgE antibody levels were mostly higher among the children with atopic disease than among sensitized children who remained healthy.

Many different tests for early prediction of atopic disease have been tried (e.g., determination of serum IgE levels in cord blood, different food antibodies in serum of the IgE or IgG classes, and skin prick tests).^{8, 20, 32, 33} In particular, IgE antibodies to egg white in infancy have a high predictive value.^{8, 20} This was also confirmed in the present extended study, in which 82% of children with egg white antibodies in infancy had atopic symptoms before 12 to 15 years of age. However, in many IgE antibodies to egg white in

infancy indicated current atopic disease. In comparison with egg white antibodies, IgE antibodies to cow's milk and wheat were considerably less important, as has been previously shown with cow's milk antibodies.^{8, 20} In addition to IgE antibodies to egg white, a positive Phadiatop Paediatric test result in infancy was a good predictor of atopic disease. Thus 71% of children with a positive test result had atopic disease before or at 12 to 15 years of age.

In conclusion, IgE antibodies in children are usually associated with current, future, or previous atopic disease. Sensitization to foods in infants is usually associated with the appearance of IgE antibodies in response to inhalants later in life. IgE antibodies to egg white and a positive Phadiatop Paediatric test result in infancy are both good indicators of atopy and predict the development of disease later in life.

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