

Development of atopic disease during childhood and its prediction by Phadiatop Paediatric

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Summary

Background Evaluating *in vivo* and/or *in vitro* tests for 'early' prediction of childhood allergy is of interest in paediatric allergology.

Objective To determine whether the measurement of Phadiatop Paediatric (PP) during early childhood could be used to predict the development of atopic disease during the first 5 years of life among infants with a family history of atopic disease.

Methods Phadiatop Paediatric was evaluated in 134 infants. The analysis was performed at 6 months, at 18 months and at 5 years of age and the numbers of available serum samples were 61, 85 and 134, respectively. The potential capacity of the test to predict the development of atopic disease was studied by relating the result of the test, a positive or a negative score, to the cumulated incidence of atopic diseases from birth to 18 months of age and from birth to 5 years of age.

Results Three of four children with a positive PP at 6 months of age developed clinical signs/symptoms of atopic disease before 18 months and all four before 5 years of age. The predictive value of a positive test at 18 months for symptoms before 5 years of age was 80% (12/15). If the diagnostic criterion, instead of clinical signs/symptoms of atopic disease, was at least one positive skin-prick test to major food or inhalant allergens, the predictive value of a positive PP-test at 18 months decreased to 53% (8/15).

Conclusion Although the presence of circulating IgE antibodies, as detected by Phadiatop Paediatric, can predict the development of atopic diseases during childhood, the usefulness of the test is limited by its low sensitivity (22–47%).

Keywords: atopy, Phadiatop Paediatric, prediction

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Introduction

A number of studies indicate that the prevalence of childhood allergy has increased during the last few decades [1,2]. Several paediatric allergologists have therefore become interested in determining whether it is possible to predict and even prevent the development of the disease [3]. Attempts have been made to find *in vivo* and/or *in vitro* tests that can be used as early predictors of allergy [3–16], but there is no agreement about the usefulness of cord-blood IgE [4–8,11,13,14], skin-prick tests (SPTs) [12,13], T-lymphocyte subsets

[9,13], food-allergen specific IgG antibodies (ab) [13,16], CD23 [17] and metachromatic cells [18] for this purpose. However, there seems to be an agreement that the presence of IgE-antibodies (IgE-ab) in serum to hen's egg during the first year of life precedes the development of atopic disease during childhood [13,15], but the practical usefulness of predicting atopic disease by such a procedure seems to be limited by the low sensitivity of the test.

During childhood, hypersensitivity reactions are mainly IgE-mediated allergies and, even in very young infants, inhalant allergens in addition to food allergens may play an important role [19]. Phadiatop Paediatric (PP), an *in vitro* test for atopy which detects circulating

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IgE-ab against both food and inhalant allergens, has been introduced for the diagnosis of childhood atopy. This test has a high sensitivity, specificity and efficacy to identify childhood atopy [20,21] and it has been recommended for screening of children below 7 years of age. The aim of the present study was to determine whether the measurement of PP during early childhood also could be used to predict the development of atopic disease during the first 5 years of life among infants with a family history of atopic disease.

Subjects and methods

One hundred and thirty-four children, 48 girls and 86 boys were followed prospectively from birth to 5 years of age [22, 23]. All mothers had a history of respiratory allergy towards pollens (tree- and/or grass pollen) and/or animal danders (cat and/or dog). Thirty-eight per cent of the children had a double parental heredity for atopic disease and in 30% a sibling was atopic. Infant feeding during the first year of life was standardized as described in a previous publication [23].

Immunoglobulin determinations

Blood samples were collected at 6 and 18 months and 5 years of age and were stored as serum at -20°C , pending analysis. The numbers of serum samples available at each age were 61, 85 and 134, respectively. Phadiatop Paediatric (Pharmacia Diagnostics, Uppsala, Sweden), was performed on single samples, according to the instructions of the manufacturer. The result of the test was positive or negative.

Total IgE (kU/L) was analysed in duplicate by PRIST (Pharmacia Diagnostics, Uppsala, Sweden), according to the instructions of the manufacturer. A modified PRIST method with higher sensitivity (i.e. 0.125 kU/L) was used to determine low IgE levels [22]. The cut-off limit of an increased serum IgE level on the three sampling occasions was defined as the geometric mean plus 1 standard deviation (sd) in serum samples collected from a group of age-matched non-atopic children [24].

The presence of food-specific IgE-ab towards ovomucoid (OVO) was analysed in duplicate by RAST (Pharmacia Diagnostics, Uppsala, Sweden), as described in detail elsewhere [22]. A RAST value ≥ 0.35 PRU/mL (RAST class 1) was considered to be positive.

Skin-prick tests

Skin-prick tests (SPTs) were performed at 6 and 18 months and at 5 years of age with ovalbumin (OA), ovomucoid (OVO), beta-lactoglobulin (BLG) (10 mg/mL)

and pure cow's milk (3% fat) [23]. At 5 years of age the SPT panel was extended to include four additional food allergens: hazelnut and hen's eggwhite (Soluprick w/v 1/100, ALK, Copenhagen, Denmark), fish and soy (Soluprick w/v 1/20) — and nine inhalant allergens — cat, dog, horse, timothy, birch, mugwort, *Dermatophagoides pteronyssinus*, *Aspergillus* and *Cladosporium* (Phazet, Pharmacia Diagnostics, Uppsala, Sweden). The diluent was used as the negative control. Histamine chloride in concentrations of 1 mg/mL (at 6 and 18 months) was used as the positive control. During the study, the Swedish Association for Paediatric Allergology changed the recommendation for the positive reference in SPT. Thus, a histamine solution of 10 mg/mL was used as the positive control at 5 years of age [25]. In accordance with Nordic guidelines [26], a SPT at 6 and 18 months was considered positive if the weal was as large as or larger than the positive control ($\geq 3+$). At 5 years of age a SPT was positive if the weal was at least 3 mm in diameter and half the size of the histamine (10 mg/mL)-induced weal ($\geq 2+$ [25]).

A 'combined' SPT score was established for each child on each testing occasion. Thus, if at least one of the tested food allergens induced a positive skin-prick test reaction, the child was assigned a positive SPT score to food allergens at that age. Similarly, at 5 years of age the child was considered to have a positive SPT score to inhalant allergens, if at least one of the nine inhalant allergens was positive.

Clinical classification

At 18 months and at 5 years of age the presence and type of atopic disease was defined in each child.

Atopic dermatitis was defined according to Hanifin and Rajka [27] as a pruritic, chronic or chronically relapsing non-infectious dermatitis with typical morphology and distribution in atopic persons.

Bronchial asthma was defined as a bronchial obstruction after exposure to a particular allergen and/or three or more episodes of wheezing in association with respiratory infections.

Allergic rhino-conjunctivitis was defined as a rhinitis and/or conjunctivitis appearing at least twice after exposure to a particular allergen and unrelated to infection.

Food allergy was defined as repeatedly, at least on two occasions, acute onset of symptoms, skin reactions, wheezing, vomiting, diarrhoea — after ingestion of the offending food.

The diagnosis was based on information collected in a questionnaire and on a physical examination. The clinical evaluation at 18 months of age was performed 'blindly', i.e. without information about the result of

the *in vitro* and *in vivo* investigations [23]. At 5 years of age the clinical evaluation was undertaken in the same manner and was performed by one paediatric allergologist (GL) who, however, was aware of the results of the analyses performed at 18 months of age. Children with obvious or probable clinical signs/symptoms of atopic diseases were combined to form the 'clinically atopic' group (CA-group) [10,13]. Children with no clinical signs/symptoms of atopic disease were grouped together as the 'non-clinical atopic' group (NCA-group).

Atopic classification

At 5 years of age a further classification was performed. According to Pepys, atopy is defined as the presence of positive SPTs towards common environmental allergens but not necessarily associated with clinical symptoms of atopy [28]. Thus, infants with positive ($\geq 2+$) SPTs towards any of the selected food and inhalant allergens were considered as the 'atopic group' (A-group). Children with negative SPTs were classified as the 'non-atopic group' (NA-group).

Ethics

The study was approved by the Human Research Ethics Committee at the Karolinska Institute and at the Söder Hospital, Stockholm, Sweden. Informed consent was given by all the parents before their children were included in the study.

Statistics

The IgE-levels were log-transformed to satisfy normality criteria. This also allowed the use of Student's *t*-test for unpaired samples when comparing IgE results. Chi-square analysis was used for the comparison of distributions. A *P*-value (two-tailed) <0.05 was considered significant.

The parameters for the prediction of atopic diseases were defined as follows:

$$\begin{aligned}\text{Sensitivity} &= \text{true positive} / \\ &\quad (\text{true positive} + \text{false negative}) \\ \text{Specificity} &= \text{true negative} / \\ &\quad (\text{true negative} + \text{false positive}) \\ \text{Positive predictive value} &= \text{true positive} / \\ &\quad (\text{true positive} \\ &\quad + \text{false positive}).\end{aligned}$$

The allergy-predictive capacity of the Phadiatop Paediatric test was related to the cumulated incidence of any clinical signs/symptoms of atopic disease in children (CA-group). The cumulated incidence was calculated as

children with past or present clinical signs/symptoms of atopic disease from birth to 18 months of age and those with signs/symptoms from birth to 5 years of age. The allergy-predictive capacity of the test was also related to children in the A-group, i.e. children with positive SPTs to at least one of the selected food and inhalant allergens at 5 years of age.

Results

Clinical evaluation of atopic allergy

The cumulated incidence of one or more clinically defined signs/symptoms of atopic disease ('clinical atopy'; CA) from birth to 18 months of age was 19% ($n = 26$; Table 1). The corresponding value from birth to 5 years of age was 40% ($n = 53$). This increase in CA was highly significant (chi-square analysis; $P < 0.001$).

The prevalences of different atopic diseases at 18 months and 5 years of age are also presented in Table 1. At 18 months of age, atopic dermatitis and food allergy (cow's milk, hen's egg and fish) predominated as isolated atopic manifestations. During the first 18 months of age none of the children who had shown clinical symptoms of atopy did recover. However, between the ages of 18 months and 5 years, cow's milk allergy (Type I allergy) disappeared in three children. On the other hand, during this period, another child developed an allergy to fish and four children reacted with allergic urticaria, angioedema of the lips and itching in the mouth when eating hazelnuts.

From 18 months to 5 years of age there was a significant increase in the prevalence of children with bronchial asthma ($P < 0.001$) and allergic rhinoconjunctivitis ($P < 0.001$; Table 1). At 5 years of age 27% (36/134) of the children had respiratory allergy, of these 81% (29/36) had bronchial asthma and 56% (20/36) had allergic rhinoconjunctivitis. All 20 children with clinical signs/symptoms of allergic rhinoconjunctivitis at 5 years of age reported an allergy either to animal danders (12/20; 60%) and/or to pollens (12/20; 60%).

Among the 29 children with bronchial asthma, 28 (97%) had asthmatic symptoms in connection with upper respiratory infections, while only 14 (48%) reported similar symptoms when exposed to inhalant allergens, such as animal danders and pollens.

Atopic diseases in the A-group

There were 25 children in the A-group, 19% (25/134) of all children in the study. This figure corresponded to 51% (25/49) of the children with ongoing signs/

Table 1. Atopic classification and atopic disease according to the clinical evaluation among 134 children with atopic heredity. The results are given as the prevalence at 18 months and 5 years of age and as the cumulated incidence of past or present atopic diseases during 0–18 months and during 0–5 years of age

	Prevalence				Cumulative incidence			
	18 months		5 years		0–18 months		0–5 years	
	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)
CA	26	19	49	37	26	19	53	40
Atopic dermatitis	23	17	40	30	23	17	42	31
Food allergy	6	4.5	8	6	6	4.5	11	8
Food allergen								
Cow's milk	4	3	1	1	4	3	4	3
Hen's egg	4	3	4	3	4	3	4	3
Fish	1	1	2	1.5	1	1	2	1.5
Nuts	–	–	4	3	–	–	4	3
Respiratory allergy	2	1.5	36	27	2	1.5	36	27
Bronchial asthma	2	1.5	29	22	2	1.5	29	22
Rhinoconjunctivitis	–	–	20	15	–	–	20	15
Inhalant allergen								
Pollen	–	–	13	10	–	–	13	10
Animal dander	2	1.5	14	10	2	1.5	14	10

CA = clinical atopy.

symptoms of atopic allergy at 5 years of age. Sixty per cent (15/25) of the children in the A-group had atopic dermatitis and 72% (18/25) had respiratory allergy. In the latter group 83% (15/18) and 67% (11/18) had allergic rhinoconjunctivitis and bronchial asthma, respectively.

Phadiatop Paediatric

Number of positive tests in relation to increasing age Serum samples were positive in four infants (7%) at 6 months of age (Table 2), although they had been negative when analysed at 2 months of age (data not

Table 2. The sensitivity, specificity and positive predictive value (Pv +) of Phadiatop Paediatric, RAST-ovomucoid (RAST-OVO) and total IgE at 6 and 18 months of age and SPT score to food allergens*** in relation to the cumulated incidence of clinical signs/symptoms of atopic disease from birth to 18 months and from birth to 5 years of age

	Phadiatop Paediatric			RAST-OVO			Total IgE			SPT score to food allergens***		
Age at analysis (months)	6	6	18	6	6	18	6	6	18	6	6	18
Clinical evaluation (months)	18	60	60	18	60	60	18	60	60	18	60	60
Cut-off limit (kU/L)	–	–	–	–	–	–	6.3	6.3	9.4	–	–	–
Number of positive tests (<i>n</i>)	4	4	15	1	1	4	21*	21*	44*	4	4	12
Number of available tests (<i>n</i>)	61	61	85	61	61	85	61	61	85	61	61	85
CA-groups** (<i>n</i>)	7	18	30	7	18	30	7	18	30	7	18	30
NCA-group** (<i>n</i>)	54	43	55	54	43	55	54	43	55	54	43	55
Sensitivity (%)	43	22	40	14	6	13	71	44	63	43	22	40
Specificity (%)	98	100	95	100	100	100	70	70	55	98	100	100
PV+ (%)	75	100	80	100	100	100	24	38	43	75	100	100

* Number of serum samples above the cut-off limit.

** Number of infants *clinically* classified as atopic (CA-group)/non-atopic (NCA-group) among those with available test-results.

*** Ovalbumin, ovomucoid, betalactoglobulin and cow's milk (3% fat).

shown). The number of positive Phadiatop Paediatric (PP) increased to 15 (18%) and 31 (23%) at 18 months and 5 years of age, respectively.

Prediction and clinical atopy

A positive PP at 6 months has an allergy predictive capacity of 75% (3/4) if the cumulated incidence of CA (any clinically defined sign/symptom of atopic disease) is evaluated at 18 months of age (Table 2). This figure increases to 100% (4/4) by 5 years of age. When the results of the tests performed at 18 months were compared with the cumulated incidence of CA from birth to 5 years, the predictive value of a positive test was 80% (12/15) (Table 2). The specificity of the test was high (94–100%) at both 6 and 18 months of age while the sensitivity was low (22–43%).

The specificity and positive predictive value of PP in predicting CA was higher than that of total IgE at 6 and 18 months of age although the sensitivity for IgE was better (Table 2). A positive RAST to OVO (≥ 0.35 PRU/mL) was highly predictive (100%; Table 2), but it had a very low sensitivity (6–14%). The SPT food score at 18 months of age had an allergy predictive capacity of 100% (12/12) and a sensitivity of 40% (12/30; Table 2).

Prediction of atopy among infants in the 'A-group'

When PP was related to the infants in the 'A-group' the predictive values of a positive test at 6 and 18 months were 75% (3/4) and 53% (8/15), respectively (Table 3). The specificity was high (90–98%), but the sensitivity was still low: 38% at 6 months and 47% at 18 months of age.

Table 3. The sensitivity, specificity and predictive value (Pv +) of a positive Phadiatop Paediatric at 6 and 18 months in relation to classification in the A-group* at 5 years of age

Age at analysis (months)	6	18
Clinical evaluation (months)	60	60
Number of positive tests (n)	4	15
Number of available tests (n)	61	85
Children classified to the		
A-group** (n)	8	17
NA-group** (n)	53	68
Sensitivity (%)	38	47
Specificity (%)	98	90
Pv+ (%)	75	53

* Positive SPT ($\geq 2+$) to any food or inhalant allergen.

** Number of children with available tests as regards atopic evaluation and testing occasion.

The SPT food score at 18 months of age had a capacity to predict atopy in the A-group of 75%. The specificity and sensitivity was 96% and 53%, respectively.

Association with total IgE, RAST and SPT

Children with a positive PP had significantly higher levels of IgE than did those with negative scores at 6 months ($P < 0.05$), 18 months ($P < 0.01$) and 5 years ($P < 0.001$) of age (Student's *t*-test).

A total of six serum samples showed a positive RAST (≥ 0.35 PRU/mL) to OVO during the observation period. All of them had a positive PP and were found among children classified in the 'A-group'.

All four infants with a positive PP at 6 months of age had a positive SPT food score at the same age. No infant had a positive SPT food score to the selected food allergens and a negative PP at 6 months of age.

At 18 months of age 75% (9/12) of the infants with a positive SPT food score had a positive PP. Of three infants with positive SPTs food score, but a negative *in vitro* test, all showed clinical signs/symptoms of atopic allergy during the observation period but only two had a positive SPT score at 5 years of age and were therefore classified to the 'A-group'. At 18 months of age six cases with a positive PP had a negative SPT score to food allergens.

At 5 years of age 31% (4/13) of the children with a positive SPT food score had a negative PP. Moreover, there were 22 children with a positive PP, but with a negative SPT food score.

The concordance between a positive SPT score to inhalant allergens and a positive Phadiatop Paediatric was 82% (18/22) at 5 years of age. Interestingly, there were 13 cases with a positive PP but with a negative SPT inhalant score. Only one of these 13 children had positive SPT food score.

Discussion

This study shows that it is possible to predict a later development of atopic diseases at very young ages by using the results of a PP determination. This has also been shown for food-RAST [13,15,29], but both PP and food-RAST are characterized by a low sensitivity; however, higher for PP than food RAST (Table 2). Our results are in agreement with those of Sigurs *et al.* [29] but our results also indicate that PP does not become positive until after 2 months of age. Together with the low sensitivity this limits the usefulness of the test as a 'very early' atopic predictive tool.

It is noteworthy that when we selected infants ($n = 25$) where atopy was defined as proposed by Pepys [28], the predictive value of the 18 month's Phadiatop Paediatric test was only 53% (8/15; Table 3). This observation should be compared with a predictive value of 80% (12/15) when the same tests were related strictly to the cumulated incidence of 'clinical signs/symptoms of atopic diseases' from birth to 5 years of age (Table 2). These data show that the results obtained in the present study, as in other similar studies [4–8,10–14], depend greatly on the criteria used for the atopic classification. Atopic dermatitis is the predominant isolated atopic disease in young children, but our knowledge of the role of IgE in the pathogenesis of this disease is still very limited. Furthermore, of 36 infants with clinical signs/symptoms of respiratory allergy only 50% (18/36) had positive SPTs to pollens and/or animal danders. Thus, like Ruiz *et al.* [8], Wood *et al.* [19] and Sigurs *et al.* [29], we suggest that, when using *in vitro* tests measuring the presence of IgE-ab (like Phadiatop Paediatric) as an atopy-predictive marker, one should distinguish between an infant with only clinical signs/symptoms of atopic disease ('clinical atopy'; CA-group) and an infant with a positive *in vivo* test, such as SPTs ('atopy'; A-group).

Some other observations emerged from this study. Hen's egg is one of the principal food allergens during childhood [12,13,15,29] and a positive RAST (≥ 0.35 PRU/mL) to this food allergen predicts the development of atopic disease [13,15,29]. Our results indicate that the presence of IgE-ab to hen's egg (OVO) in a concentration ≥ 0.35 PRU/mL is likely to be detected by PP. On the other hand, positive PP scores were found more often than positive SPT to the selected food allergens. Positive SPT against the food allergens without concomitant positive blood tests occurred, but rarely. These discrepancies between the *in vitro* and *in vivo* tests against food allergens became more evident as the infants grew older.

The lack of concordance between the SPTs to the selected food allergens and PP may be of interest in relation to allergy prediction. At 18 months of age the predictive capacity of the 'combined' SPT score to food allergens and the occurrence of infants with 'clinical atopy' (CA-group) and infants with 'atopy' (A-group) was 100% (12/12; Table 2) and 75% (9/12), respectively. These figures were higher than the corresponding values for PP (Tables 2 and 3). Moreover, in two cases, belonging to the A-group at 5 years of age, SPTs to the food allergens were positive at 18 months while the PP was negative. This indicates that PP may not detect some case of IgE sensitization to major allergens in hen's egg and cow's milk and that this seems to influence the allergy predictive capacity of the test.

The discrepancy between the SPT reactions to the selected inhalant allergens and PP at 5 years of age was surprising. The inhalant allergens used for SPT in this study are generally supposed to cover 90–95% of the respiratory atopic allergies found among children and adults in Scandinavia (25). In 13 cases the PP was positive but the SPTs were negative to the selected inhalant allergens. One explanation of this observation may be that the changes in IgE-mediated skin reactivity and the presence of clinical atopic symptoms may develop later than the increase in IgE reactivity in serum (15,29). However, in four cases, of whom three belonged to the A-group, SPTs to inhalant allergens were positive while PP was negative. This observation may indicate that the present mixture of inhalant allergens in PP is not optimal, at least for infants living in the Nordic countries [30].

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