

# Screening of atopic allergy in 5-year-old children – a comparison of the diagnostic properties of Phadiatop Paediatric and Phadiatop

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The ability of Phadiatop Paediatric (PP), Phadiatop (P), mixed-food RAST (MF), and the combination of P and MF to identify children with atopic allergy was evaluated among 193 children who had a family history of atopic disease, and who had an average age of 5 years. If atopy is defined as the presence of at least one positive skin prick test ( $\geq 2+$ ) to common food and/or inhalant allergens, P had a sensitivity of 86%, a specificity of 94%, and an efficacy of 92%. These figures were somewhat better than the results with PP. However, when P was combined with MF, the sensitivity increased to 89%, but at the expense of lowered specificity (83%) and efficacy (84%). If the tests were related only to clinical signs/symptoms of atopic disease, the sensitivity and efficacy were, at maximum, 63% and 81%, respectively. There was a discrepancy between the results of P and PP in 9% of the children. One explanation of this discrepancy may be that PP seems to be incapable of detecting children with respiratory allergies induced by pollens from birch and related trees. The results indicate that in 5–6-year-old children P should be preferred to PP and to the combination of P and MF for atopy screening, at least in places where birch pollen is a common allergen.

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Several studies indicate that the prevalence of childhood allergy has increased in recent decades (1, 20). During childhood, allergy is often IgE-mediated and there is a need for reliable *in vitro* tests that can distinguish children with IgE-mediated diseases (atopy) (17) from those with non-IgE-induced hypersensitivity reactions; i.e., symptoms due to mucosal hyperreactivity simulating allergy. Although foods are the principal allergens in the youngest age groups, inhalant allergens, such as pollens, animal danders, and mites, have also been found to play a role (9, 18, 19, 22). Screening tests for atopic allergy should therefore be age-related and include as many of the relevant allergens as possible.

Phadiatop (P) and Phadiatop Paediatric (PP; Pharmacia Diagnostics, Uppsala, Sweden), two *in vitro* tests that can detect IgE-antibodies (IgE-ab), have been introduced to identify childhood atopy. P detects IgE-ab against inhalant allergens and PP against a combination of food and inhalant aller-

gens. Both tests have high sensitivity, specificity, and efficacy in the identification of childhood atopy (2, 3, 7, 16, 22–25) and are recommended as screening tests for atopy when the child is above (P) or below (PP) 7 years of age. In children 5–6 years of age, the two screening tests are considered to overlap.

However, previous studies of the usefulness of P and PP for identifying atopy in preschool ages conflict. Sigurs et al. (19) showed that P was positive in 91% of atopic children, 4 years of age and older, with IgE-ab against food and inhalant allergens. By combining P with a mixed-food RAST (MF), Zimmerman & Forsyth (25) found that the sensitivity increased without any change in the specificity. On the other hand, van Toorenbergen et al. (22) observed that, among 135 children with a positive PP, the combination of P and MF was negative in 15%. Therefore, the present study aimed to determine whether P and PP analyses were comparable in ability to identify atopy in a group of Swedish children,

5–6 years of age, with a family history of atopic disease. MF was included in the test panel to evaluate the food allergy component.

## Material and methods

A total of 193 children, 77 girls and 116 boys, with a family history of atopic disease and a median age of 5 (range 4.7–5.9) years, was followed from birth (12, 13).

### Skin prick tests

Skin prick tests (SPTs) were performed with eight food allergens: hen's egg-white and hazelnut (Soluprick, w/v 1/100, ALK, Copenhagen, Denmark), soy and fish (Soluprick, w/v 1/20), pure cow's milk (3% fat), ovalbumin (OA), ovomucoid (OVO), and beta-lactoglobulin (BLG). The protein concentration of the last three extracts was 10 mg/ml (for details, see Reference 12).

Nine inhalant allergens – cat, dog, horse, timothy, birch, mugwort, *Dermatophagoides pteronyssinus*, *Aspergillus*, and *Cladosporium* (Phazet, Pharmacia Diagnostics, Uppsala, Sweden) – were also tested. The diluent was used as the negative control. Histamine chloride in a concentration of 10 mg/ml was used as the positive control (ALK, Copenhagen, Denmark). An SPT was considered to be positive if the wheal was at least 3 mm in diameter and half the size of the histamine-induced wheal ( $\geq 2+$ ) (4).

Summarized SPT scores were established for each child. Thus, if at least one of the tested food allergens caused a positive skin prick test reaction, the child was given a positive SPT score to food allergens. A corresponding score for the inhalant allergens was also established.

### Atopic classification

In accordance with Pepys' definition (17), only those children who had at least one positive SPT ( $\geq 2+$ ) to any of the selected food or inhalant allergens were considered to belong to the "atopic" group (A group). Children with no positive SPTs were considered to belong to the nonatopic group (NA group).

### Clinical classification

The type of atopic disease was determined in each child. The diagnosis of atopic disease (14, 15) was based on information obtained from a questionnaire and a physical examination of each child. This clinical evaluation was performed "blindly" – i.e., without information on the results of the *in vivo* and *in vitro* analyses performed at 5 years of age. Children with obvious and probable clinical signs/symptoms

of atopic disease were combined in the "clinical" atopic group (CA group) (15). The remaining children formed the group with no clinical signs/symptoms of atopic disease (NCA group).

### Immunoglobulin determinations

Serum samples were collected from all children and were stored at  $-20^{\circ}\text{C}$ , pending analysis.

Phadiatop (P) and Phadiatop Paediatric (PP; Pharmacia Diagnostics, Uppsala, Sweden) were performed on single samples, according to the manufacturer's instructions. The result of each test was expressed as positive or negative.

The presence of food-specific IgE-ab was analyzed in single samples by mixed-food RAST (MF; fx5), which detects IgE-ab against hen's egg, cow's milk, soy, peanut, fish, and wheat (Pharmacia Diagnostics, Uppsala, Sweden). The test was performed according to the manufacturer's instructions, and the result was defined as either positive or negative.

For improvement of the capacity of P to identify atopic allergy and make it more comparable with PP, the result of P was combined with that of MF. Thus, a new parameter (PMF) was established which was considered to be positive when at least one of the two tests was positive.

Total IgE (kU/l) was analyzed in duplicate by PRIST (Pharmacia Diagnostics, Uppsala, Sweden) (11). An increased serum IgE level was defined as a value above the geometric mean plus 1 SD ( $> 24.3$  kU/l) in serum samples collected from a group of age-matched nonatopic children (10).

### Ethics

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

### Statistics

The capacity (sensitivity, specificity, and efficacy) of PP, P, MF, PMF, and total IgE to identify atopy was related to the prevalence of children with clinical atopy (CA group) or atopy (A group).

## Results

### Skin prick tests

There were 20 (10%) children with at least one positive SPT ( $\geq 2+$ ) to the selected food allergens (Table 1). Ninety-four percent (45/48) of the positive SPTs to the food allergens were found among children with clinical signs/symptoms of atopy (CA

Table 1. Number (n) of positive skin prick tests to food allergens and inhalant allergens among 193 children in relation to clinical definition (CA; NCA) and number of positive *in vitro* tests (PP=Phadiatop Paediatric, P=Phadiatop, MF=mixed-food RAST)

| Food allergens                                                | n  | CA | NCA | PP | P  | MF |
|---------------------------------------------------------------|----|----|-----|----|----|----|
| Children with at least one positive SPT to food allergen      | 20 | 17 | 3   | 15 | 18 | 15 |
| Cow's milk                                                    | 2  | 2  | 0   | 2  | 2  | 2  |
| BLG                                                           | 1  | 1  | 0   | 1  | 1  | 1  |
| Hen's egg                                                     | 9  | 8  | 1   | 8  | 8  | 8  |
| OA                                                            | 9  | 8  | 1   | 8  | 8  | 9  |
| OVO                                                           | 7  | 7  | 0   | 7  | 7  | 7  |
| Fish                                                          | 5  | 5  | 0   | 5  | 5  | 5  |
| Soy                                                           | 5  | 5  | 0   | 5  | 5  | 5  |
| Hazelnut                                                      | 10 | 9  | 1   | 7  | 10 | 6  |
| Inhalant allergens                                            |    |    |     |    |    |    |
| Children with at least one positive SPT to inhalant allergens | 32 | 29 | 3   | 24 | 29 | 16 |
| Cat                                                           | 14 | 14 | 0   | 12 | 12 | 7  |
| Dog                                                           | 5  | 5  | 0   | 5  | 5  | 3  |
| Horse                                                         | 4  | 4  | 0   | 4  | 4  | 1  |
| Birch                                                         | 15 | 14 | 1   | 11 | 15 | 8  |
| Timothy                                                       | 9  | 9  | 0   | 9  | 9  | 6  |
| Mugwort                                                       | 1  | 0  | 1   | 0  | 1  | 0  |
| Dpt                                                           | 2  | 2  | 0   | 1  | 2  | 1  |
| Cladosporium                                                  | 1  | 1  | 0   | 1  | 1  | 1  |
| Aspergillus                                                   | 1  | 0  | 1   | 0  | 0  | 0  |

BLG=beta-lactoglobulin; OA=ovalbumin; OVO=ovomucoid.

Dpt=Dermatophagoides pteronyssinus; CA=children with clinical signs/symptoms of atopic disease; NCA=children with no clinical signs/symptoms of atopic disease.

group). Furthermore, 80% (16/20) of the children with positive SPTs to food allergens also had positive SPTs to the selected inhalant allergens.

Thirty-two (17%) of the children had positive SPTs to at least one of the inhalant allergens. Of these, 50% (16/32) had positive SPTs to food allergens at the same time. Of the 52 positive SPTs to the individual inhalant allergens, all but three occurred in children in the CA group (Table 1).

### Atopic classification

Thirty-six (19%) of the children had positive SPTs to at least one of the tested foods and/or inhalant allergens, and they constitute the A group. All except four (89%) of the children had clinical symptoms of atopic diseases. Atopic dermatitis was found in 67% (24/36) and respiratory allergies in 72% (26/36) of the children (Table 2). Of these, 62% (16/26) had bronchial asthma and 85% (22/26) rhinoconjunctivitis.

### Clinical classification

Sixty-eight (35%) children were classified as clinically atopic (CA group – i.e., children with all kinds

Table 2. Atopic disease among 193 children classified at 5 years of age as clinically atopic (CA group; n=68) and atopic (i.e., with positive SPT (≥2+) to common food and inhalant allergens; A group; n=36)

| Clinical atopy                                     | Atopy          |                |    |     |
|----------------------------------------------------|----------------|----------------|----|-----|
|                                                    | n <sub>1</sub> | n <sub>2</sub> | %* | %** |
| Atopic dermatitis                                  | 56             | 24             | 67 | 43  |
| Food allergy                                       | 18             | 16             | 44 | 89  |
| Cow's milk                                         | 2              | 2              | 5  | 100 |
| Hen's egg                                          | 12             | 10             | 27 | 83  |
| Fish                                               | 5              | 5              | 14 | 100 |
| Hazelnut                                           | 4              | 4              | 11 | 100 |
| Respiratory allergy                                | 47             | 26             | 72 | 55  |
| Bronchial asthma                                   | 39             | 16             | 44 | 41  |
| Associated with respiratory infections             | 36             | 13             | 36 | 36  |
| Associated with exposure to pollens/animal danders | 21             | 14             | 39 | 67  |
| Allergic rhinoconjunctivitis                       | 30             | 22             | 61 | 73  |

n<sub>1</sub>=number of children with clinical signs/symptoms of isolated atopic disease.

n<sub>2</sub>=number of children with clinical signs/symptoms of isolated atopic disease and positive (≥2+) SPT to common food and inhalant allergens.

\* In relation to number of children in A group (n=36).

\*\* In relation to number of children with clinical symptoms of isolated atopic disease.

of clinically defined signs/symptoms of atopic disease; Table 2). Atopic dermatitis (n=56; 29%) was the principal atopic disease isolated. Furthermore, there were 18 children with food allergies (23 different food reactions), of which reactions to hen's egg, fish, and hazelnut were the most common.

Respiratory allergies, bronchial asthma, and allergic rhinoconjunctivitis were found in 47 patients, of whom 39 had bronchial asthma and 30 rhinoconjunctivitis (Table 2). All children in the latter group reported reactions to either animal danders or pollens, or to both, while only 21 children with bronchial asthma had reactions to the same inhalant allergens. None of the children with respiratory allergy showed only nocturnal bronchial asthma or nasal stuffiness, symptoms associated with an allergy to mites. However, in 92% (36/39) of the children with bronchial asthma, the disease was associated with respiratory infections and other manifestations of bronchial hyperreactivity.

### Phadiatop, Phadiatop Paediatric, and mixed-food RAST

**Number of positive tests.** There were 41 (21%) children with positive P at 5 years of age, as compared to 44 (23%) and 36 (19%) children with positive PP and MF, respectively. When the results of P were combined with the results of MF, this new parameter (PMF) was positive in 58 (30%) of the cases.

### Capacity of Phadiatop Paediatric, Phadiatop, mixed-food RAST, and IgE to identify atopy

In children with atopy, P showed high values for all three variables, sensitivity (86%), specificity (94%), and efficacy (92%) (Table 3). PP had lower values, ranging from 72% to 89% for the three variables. Sensitivity for PMF was high (89%), but specificity and efficacy were not as high as for P.

In children with clinical symptoms of atopy, The capacity of the tests to identify "clinical atopy" (CA group) showed low sensitivity for P, PP, MF, and PMF (Table 3). However, the specificity was high (88–96%), and the efficacy varied between 73% and 81%. On the other hand, a raised IgE level had a sensitivity of 81% in clinical atopy but a very low specificity (48%) and efficacy (60%).

### Concordance between Phadiatop Paediatric and Phadiatop

PP and P gave similar results in 176 (91%) children (Table 4). However, in 17 (9%) children, the results differed; in 10 children, only PP was positive, and in the remaining seven children, only P was positive. Among 10 children with positive PP but negative P, none were found in the A group; i.e., they had no positive SPTs (Table 4). In contrast, among the seven children with a positive P but a negative PP, five were classified as atopic (A group).

### Concordance between Phadiatop Paediatric and the combination of Phadiatop and mixed-food RAST

Combining P and MF increased the number of positive tests from 41 to 58. The concordance between

Table 4. Concordance between Phadiatop Paediatric (PP) and Phadiatop (P), and between Phadiatop Paediatric and combination of Phadiatop plus mixed-food RAST (PMF) in relation to number of children with "clinical atopy" and "atopy"

|                | PP+ | PP- | PP+ | PP- | PP+  | PP-  | PP+  | PP-  |
|----------------|-----|-----|-----|-----|------|------|------|------|
|                | P+  | P-  | P+  | P-  | PMF+ | PMF- | PMF+ | PMF- |
| <i>n</i>       | 34  | 142 | 10  | 7   | 41   | 132  | 3    | 17   |
| Clinical atopy |     |     |     |     |      |      |      |      |
| CA             | 32  | 26  | 6   | 4   | 36   | 23   | 2    | 7    |
| NCA            | 2   | 116 | 4   | 3   | 5    | 109  | 1    | 10   |
| Atopy          |     |     |     |     |      |      |      |      |
| A              | 26  | 5   | 0   | 5   | 26   | 4    | 0    | 6    |
| NA             | 8   | 137 | 10  | 2   | 15   | 128  | 3    | 11   |

+ = positive result of test; - = negative result of test; CA = children with clinical signs/symptoms of atopic disease; NCA = children with no clinical signs/symptoms of atopic disease; A = children with positive ( $\geq 2$ ) SPT to common food and/or inhalant allergens; NA = children with no positive ( $\geq 2$ ) SPT to common food and/or inhalant allergens.

the combined parameter (PMF) and PP was 90% (173/193; Table 4). A positive combined test but a negative PP was found mainly (65%;  $n = 11/17$ ) in children classified as nonatopic (NA).

### Concordance between results of Phadiatop Paediatric, Phadiatop, mixed-food RAST, and SPT

There was an acceptable concordance between the SPT results to food allergens and PP and MF (Table 1). Thus, among 20 children with at least one positive food skin prick test, 15 had positive PP and MF. Interestingly, 18 of the 20 children with positive summarized SPT to food allergens had positive P. Moreover, all 17 clinically atopic children with positive SPTs toward the selected food allergens (CA group) had positive P. In contrast, two and three of these children were missed by PP and MF, respectively. Furthermore, one child with a positive SPT score to food allergens and positive MF has no symptoms of atopic disease (NCA group). Of 10 children with positive SPT to hazelnut, all 10 had positive P while only seven had positive PP (Table 2).

Of the 32 children with positive SPT reactions to inhalant allergens, 24 (75%) had positive PP (Table 1). The corresponding figure for MF was 16 (50%), while almost all children – i.e., 29 (91%) – had positive P. In the last group, 93% (27/29) belonged to the CA group. All children with positive PP and positive SPTs to inhalant allergens ( $n = 24$ ) were clinically atopic.

Except for cat, there was complete concordance between the SPT results to animal danders and timothy pollen and the corresponding PP and P results. Both PP and P were negative for the same two children with positive SPTs to cat dander.

However, among 15 children with positive SPT to

Table 3. Diagnostic value of Phadiatop Paediatric (PP), Phadiatop (P), mixed-food RAST (MF), combination of Phadiatop and mixed-food RAST (PMF), and total IgE. Results are given as sensitivity, specificity, and efficacy of these tests in diagnosing atopy in 193 children

|                 | <i>n</i> | PP | P  | MF | PMF | IgE* |
|-----------------|----------|----|----|----|-----|------|
| Sensitivity (%) |          |    |    |    |     |      |
| CA group        | 68       | 56 | 53 | 38 | 63  | 81   |
| A group         | 36       | 72 | 86 | 53 | 89  | 86   |
| Specificity (%) |          |    |    |    |     |      |
| CA group        | 68       | 95 | 96 | 92 | 88  | 48   |
| A group         | 36       | 89 | 94 | 89 | 83  | 44   |
| Efficacy (%)    |          |    |    |    |     |      |
| CA group        | 68       | 81 | 81 | 73 | 79  | 60   |
| A group         | 36       | 85 | 92 | 92 | 84  | 52   |

\* Based on number of serum samples with raised IgE levels ( $> 24.3$  kU/l).

CA = children with clinical signs/symptoms of atopic disease; A = children with positive ( $\geq 2$ ) SPT to common food and/or inhalant allergens; sensitivity = true positive/(true positive + false negative); specificity = true negative/(true negative + false positive); efficacy = (true positive + true negative)/all infants.

birch, 11 had positive PP, while all were positive in the P analysis. Three of four children with positive SPTs to birch pollen but negative PP had positive SPTs to hazelnut at the same time, but none of them had positive SPTs to other food or inhalant allergens. The fourth child had positive SPT to *D. pteronyssinus*. Three of these four children were classified as clinically atopic, while the fourth child had no clinical manifestations of atopy. The allergic respiratory symptoms in the first-mentioned three children were strictly correlated to the tree-pollen season. The remaining 11 children with positive SPTs to birch pollen and positive PP also had positive SPTs to other inhalant and/or food allergens, and they showed allergic symptoms when exposed to a variety of allergens.

## Discussion

This study shows that the preschool period is one in which the identification of atopic allergy is highly dependent on the choice of *in vitro* test. P was better than PP and MF in sensitivity, specificity, and efficacy in the identification of atopy (i.e., children in the A group with at least one positive SPT to food and/or inhalant allergens). This observation indicates that the IgE-ab patterns even at 5–6 years of age are rather similar to those of adults. Earlier studies have also shown that in this age group the levels of IgE-ab to food allergens usually start to decline, while the levels of IgE-ab to inhalant allergens increase (9, 18, 19, 21, 25).

The difference between the capacities of P and PP to identify atopy among our children was further confirmed by showing the discordance of the two tests (Table 4). One explanation of this difference may be that the two *in vitro* tests only partly overlap with respect to allergen composition. This hypothesis is supported by the observation that a child with an isolated tree-pollen-induced respiratory allergy, with or without a concomitant food allergy to nuts, may be missed by PP but not by P. Such a finding is important, since birch pollen is an important inhalant allergen (5, 6) in northern Europe, in northern Japan, and in North America.

When P and MF were combined in a new parameter (PMF), the specificity and efficacy for atopy detection became lower than those observed for P alone (Table 3). The marginal increase in sensitivity achieved by combining the result of two tests meant that 32 instead of 31 children were correctly identified as atopic (Table 3). On the other hand, the decrease in specificity from 94%, to 83%, corresponded to 16 children with positive PMF but negative SPT. These differences can be attributed to the presence of low levels of IgE-ab to food allergens which are often found in the skin and in the serum, without any

obvious connection to clinical symptoms of atopic allergy (8, 9, 12).

The limited usefulness of adding MF to P for the identification of atopy has also been reported by others (14). However, it conflicts with the results of Zimmerman & Forsyth (25). Furthermore, the ability of PP (sensitivity of 72%, specificity of 89%, and efficacy of 85%) to detect atopy was lower than that reported by Wood et al. (24). Our children had a narrow age range, 4.7–5.9 years, while Wood et al. (24) and Zimmerman & Forsyth (25) studied children with a wider age range who were mainly below 5 years of age. This probably explains the greater influence of food sensitization in their studies.

Another explanation of the difference may be sought in the classification of atopy. According to Pepys, the word "atopy" should be used without clinical implication (17). We used only the SPT results to establish atopy. In previous studies (24, 25), the definition of atopy was established by combining the case history with the physical examination and a positive SPT and/or RAST test. We believe that when RAST is used to classify for atopy, the results will be biased if a similar *in vitro* test (i.e., P or PP) is evaluated for its ability to detect the cases of atopy. On the other hand, we agree with Wood et al. (24) and Zimmerman & Forsyth (25) that when using an *in vitro* test for atopy screening of IgE antibodies, one must also use a test for IgE sensitization in the classification of atopy. In this study, the number of children in the CA group was reduced by approximately 50%, when the SPT results were included in the classification of atopy (Table 2). The decrease in numbers was most pronounced among children with clinical signs/symptoms of atopic dermatitis and bronchial asthma. Furthermore, Pepys' classification increased the efficacy of identifying atopy by PP and P from 81%, to 85%, and 81%, to 92%, respectively (Table 3).

When studying the capacity of the four tests (P, PP, MF, and PMF) to identify a child in the CA group – i.e., children with all types of clinical signs/symptoms of atopic diseases – we found that sensitivity and efficacy decreased to 63% and 81%, respectively. However, as P in particular, but also PP, was of great value for identifying children in the A group, both tests provide the general physician who has a limited experience of allergies with "a good means" of distinguishing between children with and without an atopic component in the disease; i.e., to distinguish between IgE-mediated allergy and nonallergic hypersensitivity.

In conclusion, our results indicate that for atopy screening of 5–6-year-old children:

- Phadiatop is useful and, at these ages, better than Phadiatop Paediatric.
- Phadiatop Paediatric might be useful at younger

ages, but the upper age limit should not exceed 5 years; otherwise, tree-pollen-induced respiratory allergy may be overlooked.

- The combination of Phadiatop with mixed-food RAST may be an alternative, but further studies are needed to evaluate the interpretation of a positive combination test in children with negative SPTs.

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