

Atopic family history. Validation of instruments in a multicenter cohort study

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In order to identify newborns at risk for atopic diseases, we developed a family questionnaire and selected specific answers which were suitable to identify atopic family members. The validity of the questionnaire was evaluated by the Phadiatop test results of 793 mothers and 353 fathers. As both screening instruments do not measure the same, the Phadiatop test identifies sensitization to inhalant allergens and the history reflects the clinical manifestation of atopic disease, the agreement between sensitization and manifestation is incomplete. Sensitivity and specificity of the questionnaire screening conditions to reproduce the Phadiatop test result was 64% and 84% for mothers, and 58% and 88% for fathers, respectively. The relative risk for lifetime prevalence of atopic manifestations in Phadiatop positive over negative mothers was calculated to be 3.88 (95% confidence interval = 3.12 to 4.81), and for Phadiatop positive over negative fathers to amount 4.84 (95% confidence interval 3.25 to 7.23). A few relevant answers of 20 were identified by logistic regression analysis to predict the Phadiatop test result nearly, as well as the total questionnaire.

**R. L. Bergmann¹, J. Forster², J. Schulz⁴,
K. E. Bergmann⁴, C. P. Bauer³,
U. Wahn¹**

Departments of Pediatrics, ¹Free University Berlin, ²University of Freiburg, ³Technical University of Munich, ⁴Institute of Social Medicine and Epidemiology, Federal Health Office, Berlin, Germany

Renate L. Bergmann, Department of Pediatrics, Free University Berlin, Heubnerweg 6, 1000 Berlin 19, Germany

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Atopic diseases run in families, their inheritance is probably multigenic. The ability to produce high total IgE (1) and to respond with specific IgE antibodies (2) are regulated by different genetic control mechanisms. Bronchial hyperreactivity (3) and dry skin (4) are probably also inherited independently. Genetic traits, allergens and non-specific environmental factors add up to form a "sufficient cause" (5) for the emergence of atopic disease. The heterogeneous contributing causes produce multiple phenotypes of atopic diseases. Whether or not a person is classified atopic, therefore, not only depends upon the definition of atopy, but also on the markers and instruments applied. Accordingly, the prevalence of atopic diseases will differ for definition, markers, and instruments used (6, 7).

Family history is considered to have a high predictive value at birth for later atopic diseases (8, 9). In order to screen newborns to be enrolled in a prospective cohort study on the etiology and course of atopic diseases, we developed a family questionnaire to identify atopic family members. Whether the answers were correct and the questionnaire conditions valid to identify atopic status

was evaluated by applying an accepted specific IgE antibody-screening test in parents. But both screening instruments do not measure the same, therefore the different results will be discussed. Also, we will suggest core questions that might be as predictive as the total questionnaire.

Material and methods

Probands and procedures

To prepare a large prospective multicenter cohort study on atopic diseases in early childhood, a questionnaire was developed by pediatric allergologists and epidemiologists based on expert knowledge and lay comprehensibility. The aim was to screen parents and siblings of newborns for atopic diseases. The questionnaire asks for typical allergic symptoms after exposure, for atopic diagnoses, allergy tests and results, smoking status, education, occupation, and for the person who had filled in the questionnaire. Questions concerning severity, quality and time course of atopy were not asked for.

Out of the questionnaire an array of specific questions was then chosen to define atopic status.

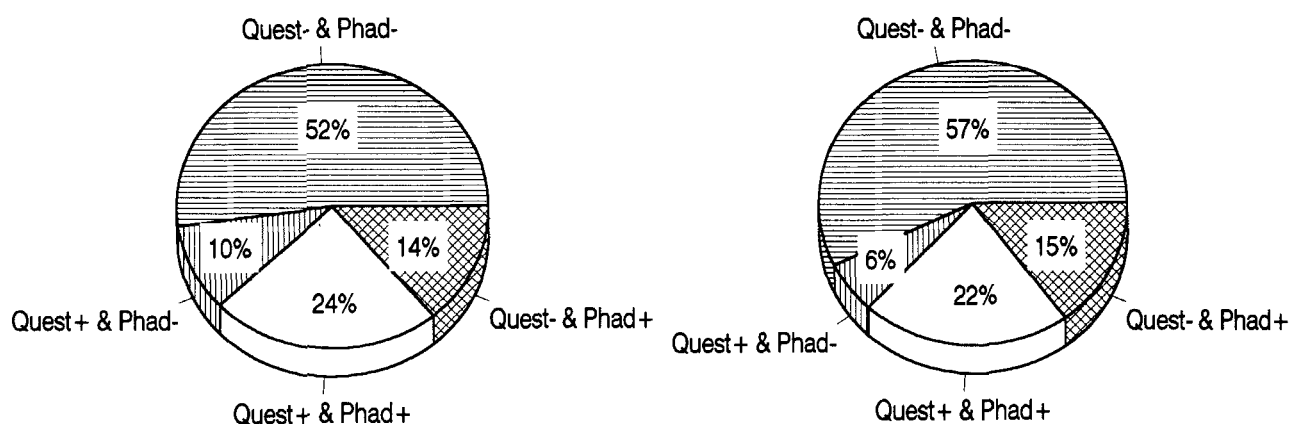


Fig. 1. a) Prevalence of atopic mothers according to history by questionnaire (QUEST) or according to Phadiatop test (PHAD). $n = 793$; b) Prevalence of atopic mothers according to 3 relevant answers from questionnaire (QUEST) and according to Phadiatop test (PHAD). $n = 736$.

Either lifetime prevalence for atopic diseases or for typical symptoms after exposure were accepted; some of the less specific answers were only accepted together with a report of a positive allergy test result. If at least one of these screening conditions turned out to be positive, the family member was considered atopic (appendix).

6019 (79%) mothers and 5819 (77%) fathers of 7609 infants born in 6 obstetric departments of West Germany between January and December 1990, filled in the questionnaire, 22% of the mothers and 21% of the fathers were classified atopic according to the questionnaire; 64% of all families invited, participated in the study: 499 infants with double-positive family history and/or cordblood-IgE values above 0.9 kU/l were recruited as cases and 815 infants, who were selected at random and simultaneously from the remaining newborns, participated as controls.

In 78% of families, mothers and fathers answered the questions concerning their own disease either together or each one for himself, 22% of mothers filled in the questionnaire for the father. Data for mother and father were, therefore, treated separately.

Of the 1314 participating families, 793 mothers and 353 fathers were willing to have a RAST-multiantigen-screening-test applied within the first six months after the interview. There was no significant difference in atopic status (by questionnaire) in the mothers tested, compared to the mothers of the total cohort, i.e. 35%, and 36%, respectively. The same was true for fathers: 30% were atopic in the total cohort and 27% of those tested. The mean age of mothers was 29.0 (± 4.9) years, the mean age of fathers 32.7 (± 5.9) years.

The Phadiatop IgE-antibody screening test (Pharmacia, Freiburg) was used. It is a two-step sandwich radioimmunoassay, based on the reaction between a balanced mixture of 8 inhalant al-

lergens (house dust mite, cat dander, dog dander, ragweed, birch, rye, timothy grass, cladosporium herbarum) and specific serum IgE of the person to be tested. In other countries, the composition of the test is slightly different. Its sensitivity and specificity in identifying the atopic status has been established in patients with clinically and immunologically proven inhalant allergies, and in similarly identified non-allergic controls (10, 11), i.e. under highly selective conditions.

Statistical analysis

Statistical analyses in this paper were performed using the Statistical Package of the Social Sciences (SPSS/PC), Version 4.01. Measures of validity (e.g. sensitivity and specificity) are given in percentages derived from 2 by 2 cross-tabulations. When p-values for an association (e.g. Phi correlation coefficient) are reported, they refer to the Pearson χ^2 of the underlying crosstable. The 95% confidence limits of the relative risk (RR) were computed via an approximation formula.

A logistic regression technique was applied to build up an optimal prediction equation of the Phadiatop test outcome. Important items of the questionnaire were chosen as predictors. Because of a close relationship between these items a multivariate approach was necessary to take these intercorrelations into account. Starting with a full model of 20 predictors a backward selection algorithm was used to sort-out irrelevant predictors by computing the significance level of the model if a predictor was removed from it. A residual analysis of the final model was performed to examine its adequacy. Cases with a Studentized residual greater than 2 were excluded and the computation of the final model was repeated. The analysis was done with the procedure Logistic Regression in SPSS/PC.

Table 1. Agreement between positive Phadiatop test results and answers to the questionnaire items. 793 mothers and 353 fathers

Symptom or disease (questionnaire item)	Percentage of positive Phadiatop tests in persons with positive history			
	Mothers		Fathers	
	%	Phi	%	Phi
A1: asthma symptoms after animal contact	79	0.25	82	0.18
A2: asthma symptoms during summer + TEST pollen	86	0.24	94	0.23
A3: asthma symptoms at night & morning + TEST house dust	74	0.15	83	0.11
A: allergic asthma	86	0.30	82	0.23
R1: rhinoconj. symptoms after animal contact	78	0.33	90	0.29
R2: rhinoconj. symptoms during spring & summer + TEST pollen	88	0.36	91	0.32
R3: rhinoconj. symptoms at night & morning + TEST house dust	74	0.19	83	0.16*
R: allergic rhinoconjunctivitis	78	0.49	85	0.51
D: atopic dermatitis	64	0.13	64	0.08°
U: urticaria after animal contact + TEST animals	71	0.17	100	0.17*
F: symptoms food allergy + TEST food	85	0.17	100	0.17*
Atopic	70	0.48	78	0.49

Associations between Phadiatop test results and questionnaire answers are all significant at $p < 0.001$ except for * $p < 0.05$ and ° non significant

Results

About half of the 793 mothers and 353 fathers in the cohort tested were non-atopic by either Phadiatop or questionnaire screening, 48% of mothers in our sample would be classified atopic if either instrument was accepted independently to define atopy (Fig. 1a). The respective figure in fathers is 50%. However, if both, history and Phadiatop test, had to be positive to define a person atopic, then the prevalence of atopics in our sample would be halved to 24% (Fig. 1a) in mothers and 25% fathers, respectively.

Clinical manifestations and immunological markers are two different categories of indicators to identify atopy. Accepting the history as a standard, then the validity of the Phadiatop test was explored: the sensitivity of the Phadiatop test to identify mothers rated atopic according to the history was 70%, and in fathers 78%. The specificity in classifying non-atopic mothers was 79%, and fathers 74%, respectively.

Taking every single screening condition of the questionnaire as the standard to define atopy and comparing the Phadiatop test results with each one showed a significant concordance for positive and negative outcomes in each condition, except for atopic dermatitis in fathers, (Table 1). Of all screening conditions, the results of the Phadiatop test agreed best with a diagnosis of allergic rhinoconjunctivitis.

If an illness is being reported, then non-differential misclassification and even reporting bias can occur. Therefore, as another view, the Phadiatop test was used as the standard to test the validity of the answers to the questionnaire. In this direction, the sensitivity of the questionnaire was 64% for

mothers, and 58% for fathers. The specificity was higher, i.e. 84% in mothers and 88% in fathers, respectively.

Of the mothers, who underwent a Phadiatop testing, 289 reported of having had an allergy test at some time in the past. Again, taking the Phadiatop test as the standard, 86% of mothers with a positive Phadiatop test reported, that their allergy test had been positive in the past. But 62% with a negative Phadiatop test also reported having had a positive test result in their history. Of the 84 fathers who had a Phadiatop test done and also reported an allergy test in the past, 90% reported a positive test outcome. But of the Phadiatop negative fathers 47% also had a positive test in their history. Concordance of reported test results and Phadiatop test outcomes are highly significant in mothers and fathers ($p < 0.001$).

Considering the particular inhalant allergens reported, concordance was highest for pollen, house-dust and animals ($p < 0.001$ in the mothers and fathers), and not significant for moulds.

To find out which smallest set of answers in the questionnaire would be sufficient to predict the Phadiatop test result, we applied a logistic regression analysis. In the final model, just three answers from the mothers and two answers from the fathers could predict the Phadiatop test result nearly as well as the whole set of screening conditions.

These questions were:

- Do you or did you ever suffer from allergic rhinoconjunctivitis?
- Do you or did you suffer from allergic asthma?
- Do you or did you suffer – in the absence of a cold – from an itchy, stuffed or running nose and/or from swollen, itching eyes, especially

- * when handling fur- or featherbearing animals?
- * regularly during spring and summer?

The sensitivity of these three answers to predict the Phadiatop test result was slightly lower than that of the total questionnaire conditions, i.e. 60% instead of 64% in mothers, and 53% instead of 58% in fathers. The specificity in the prediction of the Phadiatop test result was 90% in mothers and 92% in fathers, i.e. higher than in the total questionnaire.

The prevalence of non-atopic mothers was 52%, when using either the screening conditions or the Phadiatop test for the definition (Fig. 1a). A slightly higher number, i.e. 57% was found, when only the relevant answers beside the Phadiatop test outcome were used to define atopy (Fig. 1b). The respective percentages in fathers were 50% and 55%.

The relative risk (RR) of a sensitized, i.e. Phadiatop test positive person of this age group to ever having (had) an atopic manifestation was estimated: the RR of a sensitized over a non-sensitized mother is 3.88 (95% confidence interval = 3.12 to 4.81), the RR in fathers is 4.84 (95% CI = 3.25 to 7.23), respectively. Obviously, the values are highly significant.

Discussion

The validity of a questionnaire about manifestations of atopic disease was tested by applying a different instrument: the Phadiatop test screens sensitization against the inhalant allergens, which play a predominant role in atopy after 3 years of age (12). Because only a small portion of adults is sensitized exclusively against food allergens the Phadiatop test has been used successfully to identify most atopic adults: evidence for its suitability has been given in several clinical settings (11), and in a mass screening of 600 recruits in Italy (13). Its sensitivity and specificity in distinguishing persons with or without atopic disease was high, mainly between 85 and 100% (11). But in these studies those adults were selected, who in their history had specific symptoms of atopy, had typical signs on physical examination, and also had specific antibodies by skin prick tests (SPT). Controls were non-atopics, excluded by these instruments.

Specific IgE-screening in population based studies performed with SPT or RAST, showed much weaker associations between manifestation and sensitization. In children aged 6 to 17 years in the NHANESII survey in USA, at least one positive SPT-result was found in 45%, who according to questionnaire data, had symptoms of asthma, compared with 21% in the non-asthmatic popula-

tion (14). In New Zealand 66% of 13-year-old children with asthma symptoms (by questionnaire) had at least one positive SPT compared with 45% of the total population (15).

In a population-based study Vervloet et al. examined the validity of a standardized questionnaire by applying the Phadiatop test (16), 75% of male adults below 30 years of age reporting of asthma manifestations, had a positive Phadiatop test result. In female asthmatics of the same age only 45% had a positive result. Agreements declined with increasing age and with questions concerning hay fever or perennial rhinitis to 27%. Several factors could explain the better agreement in the present study: in our questionnaire the exclusion of common colds, producing rhinoconjunctivitis symptoms, and the inclusion of questions on positive allergy tests for some of the conditions, probably increased the validity of answers concerning hay fever and perennial rhinoconjunctivitis. Also, the age of parents in our study was younger, i.e. 29 (± 5) years in mothers and 33 (± 6) years in fathers.

But even the study of Vervloet et al. (16) does not use the Phadiatop test as the standard to validate the questionnaire, but rather examines the validity of the Phadiatop test in predicting the answers to the questionnaire. To our knowledge, our report addresses this more reasonable direction for the first time: when specific IgE antibodies, discovered by Phadiatop test, are considered the necessary marker of the atopic state, then our presented questionnaire has been shown to have a modest sensitivity and a good specificity. Apparently, our screening conditions were somewhat more suitable for recognizing non-atopics than atopic persons. This is even more true for the shorter questionnaire (with only three questions).

Although subjective reports of positive allergy test results refer to past events, we found a good agreement of reported positive tests against pollen, housedust and animal dander with positive Phadiatop test results.

However, the percentage of mothers, and less so of fathers, who reported a positive allergy test result, but had a negative Phadiatop result, was unexpectedly high. This could be due to positive patch tests, misinterpreted as IgE-specific sensitizations.

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Appendix

11 validated screening conditions for atopic status in parents of newborn infants

Mother or father were considered atopic, if they gave a positive answer to one of the following questions or question combinations:

- | | |
|--|---|
| <p>A1 * Do you or did you ever suffer from attacks of cough, wheezing and/or breathlessness, especially after contact with fur- or featherbearing animals?</p> <p>A2 * Do you or did you ever suffer from attacks of cough, wheezing and/or breathlessness, especially during spring and summer?</p> <p style="margin-left: 20px;">* Did you ever have an allergy test?</p> <p style="margin-left: 20px;">* If yes, did the test confirm the allergy?</p> <p style="margin-left: 20px;">* If yes, against which of the following substances did you have a positive test result?</p> <p style="margin-left: 40px;">* pollen of grass, trees, flowers, herbs.</p> <p>A3 * Do you or did you ever suffer from attacks of cough, wheezing and/or breathlessness, especially at night or early in the morning?</p> <p style="margin-left: 20px;">* Did you ever have an allergy test?</p> <p style="margin-left: 20px;">* If yes, did the test confirm the allergy?</p> <p style="margin-left: 20px;">* If yes, against which of the following substances did you have a positive test result?</p> <p style="margin-left: 40px;">* house dust (mites).</p> <p>A * Do you or did you suffer from allergic asthma?</p> | <p>R1 * Do you or did you suffer – in the absence of a cold – from an itchy, stuffed or running nose and/or from swollen, itching eyes, especially after contact with fur- or featherbearing animals?</p> <p>R2 * Do you or did you suffer – in the absence of a cold – from an itchy, stuffed or running nose and/or from swollen, itching eyes, especially during spring and summer?</p> <p style="margin-left: 20px;">* Did you ever have an allergy test?</p> <p style="margin-left: 20px;">* If yes, did the test confirm the allergy?</p> <p style="margin-left: 20px;">* If yes, against which of the following substances did you have a positive test result?</p> <p style="margin-left: 40px;">* pollen of grass, trees, flowers, herbs.</p> <p>R3 * Do you or did you suffer – in the absence of a cold – from an itchy, stuffed or running nose and/or from swollen, itching eyes, especially at night or early in the morning?</p> <p style="margin-left: 20px;">* Did you ever have an allergy test?</p> <p style="margin-left: 20px;">* If yes, did the test confirm the allergy?</p> <p style="margin-left: 20px;">* If yes, against which of the following substances did you have a positive test result?</p> <p style="margin-left: 40px;">* house dust (mites).</p> <p>R * Do you or did you ever suffer from hay-fever (allergic rhinitis, allergic conjunctivitis)?</p> |
|--|---|

- D * Do you or did you ever suffer from neurodermatitis (endogenous eczema or atopic dermatitis)?
- U * Did you repeatedly suffer from urticaria with hives and/or swelling of lips and eyelids after contact with fur- and feather-bearing animals?
 - * Did you ever have an allergy test?
 - * If yes, did the test confirm the allergy?
 - * If yes, against which of the following substances did you have a positive test result?
 - * animals.
- F * Do you have an allergy against foods?
 - * If yes, which foods are concerned:
 - * milk and milk products.
 - * eggs.
 - * nuts.
 - * fish.
 - * Did you ever have an allergy test?
 - * If yes, did the test(s) confirm the allergy?
 - * If yes, against which of the following substances did you have a positive test result?
 - * milk and milk products.
 - * eggs.
 - * nuts.
 - * fish.