

Prediction of sensitization to inhalant allergens in childhood: evaluating family history, atopic dermatitis and sensitization to food allergens

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Summary

Background A family history of atopy is a poor predictor of sensitization to inhalant allergens and allergic disease during childhood. We recently identified early sensitization to food allergens, especially hen's egg, as a valuable predictor of subsequent sensitization to inhalant allergens.

Objective (1) Whether prediction will be improved by *in vitro* allergy tests at 1 year of age in combination with family history and medical history data. (2) Comparison with the capacities of *in vitro* tests to predict sensitization to aeroallergens.

Methods Of an observational birth cohort study (MAS) 49 children who were sensitized to inhalant allergens at 5 years of age and 116 non-sensitized controls were included in the present study. For the prediction of sensitization to inhalant allergens the following prognostic factors were evaluated: atopic family history (FH), atopic dermatitis (AD) during the first year of life, two *in vitro* allergy tests for specific IgE to common food allergens at 1 year of age (fx5 [Pharmacia] and single allergen specific tests (sIgE) for four allergens) and 'high' total serum IgE, defined by three different cut off points.

Results The combination of medical history data and laboratory tests resulted in the best predictive discrimination. The positive predictive values (PPV) were higher if sensitization to food was detected by single allergen specific tests (PPV: 66%/75%/100% corresponding to the three evaluated risk groups) than by the qualitative fx5 (PPV: 46%/65%/100%). The negative predictive values were equal for both tests (69 and 92% for the two low risk groups). High total serum IgE had low predictive capacity.

Conclusion During infancy the prediction of sensitization to inhalant allergens should be based on medical history data and allergy tests determining sensitization to food allergens. The *in vitro* tests improve the predictive discrimination, but the individual risk profile of the child must be considered for a reliable and valid prediction.

Keywords: food hypersensitivity, inhalant allergens, parental atopy, atopic dermatitis, *in vitro* allergy tests, prediction, early childhood

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Introduction

Because of the increasing prevalence of atopic disorders in children, the prediction of allergic diseases has become an

important issue. Early identification of children at risk is crucial for initiating primary and secondary preventive measures. It is also of interest to determine risk groups in which various preventive strategies can be evaluated in interventional studies. Several studies have demonstrated that early sensitization to food and inhalant allergens must be regarded as a risk for the development of subsequent

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allergic disease [1–4]. Allergic sensitization is frequently asymptomatic but sensitized children are more prone to develop disease in later years [2,3,5,6].

Prediction of allergic diseases is most desirable at birth or in early infancy. Several clinical and immunological measures have been suggested as predictors for allergic diseases including cord blood IgE [7–16]. However, the predictive capacities in terms of sensitivity, specificity and predictive values are generally low for the laboratory parameters investigated. Medical history, especially the atopic family history, has also been evaluated as a possible predictor during childhood [7,12,17,18]. Despite some predictive capacity of medical history data and the negligible costs in comparison with more expensive laboratory tests, the validity of prediction based solely on medical history data is limited.

In addition, available medical history data is often not adequately considered in other studies of the prediction of allergic sensitization or diseases. Such studies have often been conducted within a special risk group, e.g. exclusively in children of atopic families or children that are already sensitized [10,12,16]. This implicit inclusion of a certain prognostic factor does not allow the comparison of risks and predictive values for other groups of children excluded by study design. However, children who are considered at average or low risk *a priori* and are therefore not included in risk evaluation studies will eventually represent — in absolute numbers — the largest group of children who develop an allergic disease [19]. For the recommendation of preventive measures a reliable and comparable estimate for the prognosis is therefore necessary for all children, taking into account individual risk profiles.

In our study children without any *a priori* selected risk profile were followed from birth to the age of 5 years, assessing prognostic factors during the natural course of an atopic or non-atopic 'career'. We investigated whether *in vitro* allergy tests at 1 year of age, especially the multi-allergen test fx5 versus single RASTs, can predict subsequent sensitization to inhalant allergens and whether the combination of these tests with clinical and family history data improve the predictive discrimination.

Materials and methods

Subjects

Subjects of the present study were participants of the German Multicentre Allergy Study (MAS). For this prospective and observational birth cohort study [20], 1314 children were followed up to the age of 5 years (at 1, 3, 6, 12 and 18 months, and 2, 3, 4 and 5 years). At each follow-up visit, parents filled in questionnaires and gave structured interviews about atopic symptoms and diseases of their

children. Blood samples were obtained at 1, 2, 3 and 5 years of age. Study participation rate at the fifth birthday was 76%. The study was approved by the local ethics committee. Informed consent was given by all parents.

Inclusion criterion for the present study was a complete follow-up of IgE values at the ages of 1, 2, 3 and 5 years, independent of risk factors such as an atopic family history ($n = 298$). Retrospective screening of a food sensitization by the fx5 test stored blood samples for the first birthday were available from 165 of these 298 children, 75 girls and 90 boys. Of these 165 children, all those sensitized to inhalant allergens at 5 years of age ($n = 49$) were used to evaluate predictive capacities of medical history data and *in vitro* allergy tests. The remaining 116 children who had never been sensitized to inhalant allergens were used as controls.

Definition of allergic sensitization

A child was defined as sensitized to inhalant allergens if specific IgE was detectable for at least one of four tested allergens: house dust mite (Der p 1), cat dander (Fel d 1), mixed grasses and birch pollen (Bet v 1). As described previously [21], the CAP-RAST-FEIA system (Pharmacia, Freiburg, Germany; detection limit: 0.35 kIU/L) was used.

Food sensitization: (1) single allergen specific tests ('sIgE method') — a child was considered sensitized if specific IgE antibody (sIgE) concentrations to *at least one of the four* tested food allergens (hen's egg, cow's milk, wheat or soy) by CAP-RAST-FEIA (Pharmacia) [21] were ≥ 0.35 kU/L; (2) fx5 test — the screening test fx5 from Pharmacia is a qualitative test determining specific sensitization to six food allergens (hen's egg, cow's milk, wheat, soy, cod fish and peanut). The specific IgE antibody levels to the single food allergens are determined by the RAST method. The six food allergens are binded on the same cellulose carrier so that the single specific IgE levels are added up resulting in a positive qualitative test result when 0.35 kU/L is exceeded.

Prognostic factors evaluated

Medical history data during infancy

1 Atopic family history, defined as at least one atopic parent. Parents were considered atopic if at least one of the following conditions were reported: asthma, hay fever, atopic dermatitis or food allergy ($n = 91/165$: 55%).

2 The occurrence of atopic dermatitis in the study child, because the highest incidence of atopic dermatitis is observed during the first year of life ($n = 14/165$: 8.5%). The definition of atopic dermatitis was recently described in detail [17]. Briefly, atopic dermatitis was defined as a combination of at least three typical morphological signs at three or more typical sites.

Table 1. Characteristics of study sample in comparison to total MAS cohort

	Study sample (<i>n</i> = 165)	Total MAS cohort (<i>n</i> = 1314*)
Male	54%	52%
Sensitization to aeroallergens at 5 years	30%	27%
Atopic dermatitis until 1 year	9%	13%
Wheezy bronchitis until 1 year	7%	10%
Parental atopy		
At least one atopic parent	55%	52%
Both parents atopic	11%	13%
Cord blood IgE detectable	30%	36%
Breast feeding more than 4 months	57%	50%
Parental smoking at 18 months	40%	46%
Pets in household at 18 months	34%	30%
Mite allergen exposure by 18 months (median)	270 ng/g	231 ng/g
Cat allergen exposure by 18 months (median)	60 ng/g	64 ng/g

* Due to missing information *n* ≤ 1314. Test for differences in the proportions between the two samples with respect to the listed exposure variables are not statistically significant at *P* < 0.05 level.

In vitro allergy tests at 1 year of age

1 As the incidence of sensitization to food allergens is highest during infancy, we evaluated specific sensitization to food allergens by means of:

a the screening test fx5; and

b the detection of specific IgE to at least one of four tested food allergens (sIgE).

2 Since elevated total serum IgE is a common characteristic in atopics, we included total IgE measures (by CAP-RAST-FEIA, Pharmacia) as an additional test at 1 year of age. As there is no clearly defined threshold for elevated IgE, we considered three different levels according to the percentiles of the total serum IgE distribution in the study sample at 1 year of age: ≥ 50th percentile (6.5 kU/L), ≥ 75th percentile (18 kU/L) and ≥ 90th percentile (57 kU/L).

Statistics

The statistical analysis was performed using SPSS/pc, version 1995 (SPSS Inc., Chicago, IL, USA). Tests for differences in the proportion of exposure variables between the total cohort and the analysed subcohort were computed as described by Kramer [22]. To evaluate the predictive discrimination of the prognostic factors we computed and compared the risks (equal to the probability) of sensitization to inhalant allergens at 5 years of age for different characteristics of the prognostic factors. The single risks were calculated as the proportion of sensitized children in the evaluated risk groups. If the determination of these factors is interpreted as a 'diagnostic test' for subsequent allergic

sensitization to inhalant allergens the observed risks correspond with the positive predictive values (PPV: probability that a subject with a positive test result will be sensitized). The other validity parameters for the prediction of a sensitization to inhalant allergens were defined as follows: negative predictive value (NPV) as probability that a subject with a negative test result will not be sensitized; sensitivity (SE) as probability that a sensitized subject has a positive test result and specificity (SP) as probability that an unsensitized subject has a negative test result.

Results

Characteristics of subjects in the analysed subgroups and the overall MAS cohort are listed in Table 1. The analysed group did not differ significantly from the MAS cohort regarding these characteristics. Participation rates in blood exams were also not significantly related to either low risk or high risk subjects (considered risk factors: atopic family history, elevated cord blood IgE [≥ 0.35 and ≥ 0.9 kU/L], occurrence of clinical symptoms in early childhood [wheezy bronchitis and atopic dermatitis]).

Prediction on the basis of the medical history data

The calculated risks of sensitization to inhalant allergens at 5 years of age (*n* = 49) on the basis of the medical history data only are shown in Fig. 1. Children of non-atopic parents had a 16% risk of developing subsequent sensitization to inhalant allergens. Children with one or two atopic parents

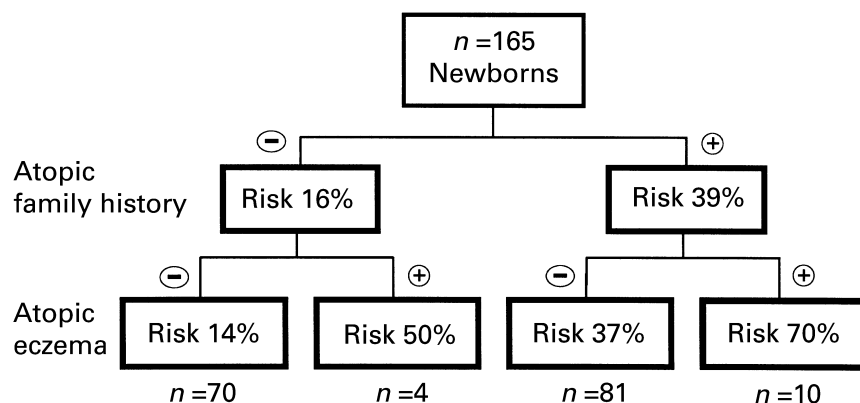


Fig. 1. Risk (percentage) of sensitization to inhalant allergens at 5 years of age based on medical history data during infancy. If the respective prognostic factor is present ('positive') the risk corresponds to the positive predictive value.

had a risk of 39% of becoming sensitized to aeroallergens. As a second medical history factor the occurrence of an atopic dermatitis during infancy was considered. For children with negative atopic family history and no atopic dermatitis the risk of later allergic sensitization was only 14%, increasing up to 70% if the two prognostic factors were positive.

Prediction including the additional information of the allergy test results

Sensitization to food allergens was detected in 30 children (18%) by means of the qualitative fx5 test, and 24 children (14%) were found to be sensitized to at least one of the four tested food allergens (by four single allergen specific tests). The results of the two *in vitro* tests (Table 2) show no complete concordance and different positive predictive values. The sensitivity of the fx5 was slightly higher (37%) than the sensitivity of the sIgE tests (35%), specificity

Table 2. Comparison of two *in vitro* tests for sensitization to food allergens (fx5 test vs separate determination of sepecific IgE to four tested food allergens*).

<i>In vitro</i> allergy test		Sensitization to at least 1 of 4 food allergens	
		negative	positive
fx5 Test	negative	133	2
	positive	8	22
Predictive value		NPV	PPV
fx5 Test		77%	60%
sIgE to at least 1 of 4 allergens*		77%	71%

*Egg, cow's milk, soy and wheat, determined by single RASTs. NPV: negative predictive value, PPV: positive predictive value.

was lower for the fx5 (90 vs 94%). As described in the methods section, the tests differ in the tested allergen spectrum and the test system itself. The predictive discrimination of atopic family history, atopic dermatitis and the *in vitro* test results are shown in Table 3. In comparison with each single prognostic factor, the consideration of medical and family history data as well as *in vitro* tests will improve the prediction of subsequent sensitization to inhalant allergens. For children without atopic dermatitis, the positive predictive value is increased by the tests for sensitization to food allergens: (1) in children of non-atopic families the risk (PPV) for subsequent sensitization increases with a positive test result from 14% (medical history data only, Fig. 1) to 46 to 66% depending on the food test (Table 3); (2) with a positive atopic family history the PPV increases from 37 to 65% (fx5) and 75% (four allergen specific tests).

Since only four children with a negative atopic family history developed an atopic dermatitis, the evaluation of the prognostic values is limited by the small sample size. If atopic family history and atopic dermatitis were present, all children with a positive test developed a sensitization to inhalant allergens, resulting in a PPV of 100% (Table 3).

The different levels of the total serum IgE, however, resulted in much lower predictive values compared with the food allergy tests. For children without atopic family history and atopic dermatitis (FH⁻/AD⁻) the PPVs for the 50th, 75th and 90th percentile ranged from 23 to 70% (sensitivity: 40%). In the group of children with a positive atopic family history the PPVs ranged from 42% to 47% (sensitivity: 23%).

The evaluation of the prognostic factors for allergic airway disease (rhinitis and wheezy bronchitis) is limited at the time of follow-up of our cohort because a certain proportion of the children as yet unaffected will probably develop an allergic airway disease in later years. Combining medical history data and *in vitro* tests we determined positive predictive values up to 50% for prediction of allergic airway disease at 5 years of age.

Table 3. Validity parameters for the prediction of a sensitization to inhalant allergens at 5 years of age on the basis of medical history data and allergy tests during infancy. The four evaluated risk groups correspond to the four groups in Fig. 1.

Risk factor profile according to medical history data				
	FH– AD– (n = 70)	FS– AD+ (n = 4)	FH+ AD– (n = 81)	FH+ AD+ (n = 10)
<i>Test</i>	<i>fx5 Test</i>	<i>fx5 Test</i>	<i>fx5 Test</i>	<i>fx5 Test</i>
PPV	46%	1 of 4 children	65%	4 of 4 children with
NPV	92%	with positive	69%	positive fx5 test are
Sensitivity	50%	fx5 test result	30%	sensitized (100%)
Specificity	90%		90%	
<i>Test</i>	<i>4 food allergens*</i>	<i>4 food allergens*</i>	<i>4 food allergens*</i>	<i>4 food allergens*</i>
PPV	66%	1 of 4 children	75%	2 of 2 children with
NPV	93%	with positive	69%	positive food test
Sensitivity	60%	fx5 test result	30%	are sensitized
Specificity	95%		94%	(100%)

*Egg, cow's milk, soy and wheat, determined by single RASTs. FH: atopic family history, AD: atopic dermatitis during infancy.

Discussion

Our results suggest that during infancy the prediction of a subsequent sensitization to inhalant allergens should be based on relevant medical history data and tests determining sensitization to food allergens. In comparison with each single prognostic factor, the combination of atopic family history, atopic dermatitis and *in vitro* tests improved the predictive discrimination and resulted in a more differentiated prediction considering the individual risk profile. Both of the *in vitro* tests used to determine sensitization to food allergens improved the prediction for subsequent sensitization to inhalant allergens, whereas total IgE measurements resulted in only low predictive capacity. Assuming the medical history is available to the physician before laboratory testing is performed, a combination of early medical history data and *in vitro* allergy tests, i.e. during the first year of life, seems to be the most reasonable strategy to predict allergic disorders. However, our results also showed that the prediction must be differentiated according to the individual risk profile of the child. An allergy test does not have the same predictive value for every patient without considering important medical history information. In our study the differences between the 'overall' predictive values of allergy tests and the predictive values according to the individual risk profile are evident. All relevant information must be considered to achieve the most reliable and valid prediction. In other studies not all accessible data was included in the analysis, resulting in a less accurate prediction which cannot be generalized to the 'average' patient. One aim of our study was to focus on this problem. It is difficult to interpret and compare different

investigations of prediction of allergy if the analysed subjects differ in their risk factor profile. Therefore, in our study children at risk and children without a specified risk were included and followed-up from birth to 5 years of age to observe the natural course of an atopic 'career'.

The main interest of this study was the evaluation of the predictive capacity of the prognostic factors, especially the qualitative multiallergen test fx5 and the presence of food sensitization determined by single allergen specific tests to four tested allergens.

Prediction of allergic sensitization does not necessarily predict clinical disorders. Sensitization, however, is a prerequisite for the development of allergic airway disease and sensitized children must be regarded at risk of developing subsequent allergic disease. In our birth cohort children are followed-up until the fifth birthday. At that time-point the prevalence rate of allergic airway disease will probably still be relatively low because a certain proportion of the children as yet unaffected will develop an allergic airway disease in later years. Therefore our aim was to predict allergic sensitization as a risk for the occurrence of clinical disease in older children.

It could be argued that the first birthday is already too late to implement effective preventive measures. We chose the first birthday for the application of the allergy tests because of the availability of blood tests according to our study design and because the incidence of food sensitization is highest during infancy. Testing for sensitization to food allergens before the age of 12 months, however, might substantially decrease the sensitivity of this valuable predictor. The prevalence of food sensitization during the first months of life is possibly too low to include a sufficient

number of children at risk. The dilemma of choosing between the earliest possible application of secondary preventive measures but with low sensitivity and a time-point too late for interventions remains unresolved.

For predictive purposes the most important validity parameter is the risk of developing such an outcome, corresponding with the positive predictive value. In infants without atopic dermatitis the positive predictive value was mainly higher if sensitization to food was detected by the combination of single sIgE tests than by the qualitative 'screening' test fx5. The negative predictive values which are most important for the low risk group, i.e. children without any of the evaluated risk factors present, are the same for both food tests. A negative test result in that group suggests that the risk of sensitization to inhalant allergens is so low that inconvenient and expensive preventive measures do not have to be taken into consideration. In addition, because of their high specificity, the predictive factors are useful as inclusion criteria for interventional studies.

The validity parameters of the prediction can hardly be compared with those of other studies because of the described differences in inclusion criteria and therefore examined risk groups [6,9,10,12,16]. With regard to our data, the total IgE cannot be recommended as a predictor of sensitization to inhalant allergens. A decision in favour of one of the two food tests must also be based on costs, and their sensitivity and specificity. The partly different validity parameters of the prediction may be due to the difference in the tested allergen spectrum and in the test system itself. The lower costs of the fx5 test contrast with the better predictive capacity and the slightly better sensitivity and specificity values of the single determination of specific IgE. The high PPVs of both tests in the children with atopic dermatitis have to be interpreted cautiously because of the small sample size. It is known that children with an atopic dermatitis have a high risk of allergic sensitization [19]. But our results indicate that the predictive discrimination for this group of children can also be increased by a positive food test result.

However, our main interest was the prediction in apparently healthy children without atopic dermatitis. Firstly, the risk estimated solely by the medical history data is low compared with the diseased children, so a further discrimination will be helpful to select children at risk. Secondly, healthy infants will eventually represent, in absolute numbers, the majority of children who will develop sensitization to inhalant allergens and subsequently allergic airway disease.

We conclude that during infancy the prediction of sensitization to inhalant allergens should be based on relevant medical history data and allergy tests determining sensitization to food allergens. However, for a reliable and valid prediction the individual risk profile of the child must be always considered. For children at risk, e.g. with a positive

atopic family history, we recommend an *in vitro* test for determining sensitization to food allergens to improve the prediction. The sample size of the risk group of children with an additional atopic dermatitis was too small for definite recommendations. But our results suggest that the application of an *in vitro* test also improves the predictive discrimination for these children.

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