

Atopic dermatitis in early infancy predicts allergic airway disease at 5 years*

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Summary

Background Screening tests for atopy risk in newborns have a low predictive value. If early atopic symptoms and signs could be used as predictors for the next expected atopic disorder then secondary prevention could be employed. The aim of this study was to evaluate the capacity of early atopic dermatitis to predict aeroallergen sensitization and the manifestation of respiratory atopic disorders at 5 years of age.

Methods 1314 children of a German prospective birth cohort study MAS-90 were followed from birth up to 5 years of age. Atopic dermatitis, asthma and rhinoconjunctivitis were diagnosed from symptoms and signs at physical examinations and by interviews of the parents. Blood was drawn at 1, 2, 3, and 5 years of age. Aeroallergen sensitization was diagnosed by a specific IgE value of at least 0.35 kU/L (CAP class ≥ 1) against any of five respiratory allergens (mite, cat, dog, birch, grass).

Results Atopic dermatitis in the first 3 months was a risk factor for aeroallergen sensitization at 5 years. The risk increased with a positive family history for atopic diseases. Seventy-seven per cent of children with two atopic parents and early atopic dermatitis were sensitized against aeroallergens at 5 years, i.e. could have been predicted in early infancy without any laboratory tests. Although these risk factors were also significantly associated with the manifestation of allergic airway disease, the positive predictive value for this outcome at age 5 years was not yet as high, i.e. 50%.

Conclusion Infants with very early signs of atopic dermatitis and a positive family history are candidates for early intervention measures against respiratory allergies.

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Introduction

There are no powerful screening tests for atopy risk in newborns for selective primary prevention. For example, cord blood IgE and family history have been shown to have only a moderate predictive value [1–4]. Most children who developed early atopic symptoms would not have been considered as having a high atopy-risk at birth [4]. Therefore, primary preventive measures, such as dietetic intervention, might not have been necessary for

most infants, while others in need would not have received them. Selective screening for secondary prevention of respiratory atopy risk in infants who had already developed first signs or symptoms of other atopy might be more promising [5]. Sensitization against egg protein, for example, is predictive of later respiratory sensitization [6]. But inhalative sensitization is also more prevalent in school-children who had suffered from atopic dermatitis in their first 2 years of life [7]. Of infants with severe atopic dermatitis, 93% were found to be sensitized against inhalant allergens by the age of 3, and 79% also had clinical symptoms of respiratory allergy [8]. Since preventive measures should start as early as possible, the aim of this study was to evaluate the predictive capacity of atopic dermatitis in the first 3 months of life for respiratory

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sensitization or manifestation of allergic airway disease at 5 years of age.

Materials and methods

Study subjects

For a prospective cohort study 1314 infants were recruited out of 7609 newborns at six obstetric departments in five German cities (Berlin, Düsseldorf, Freiburg, Mainz, Munich) between 1 January and 31 December 1990. From a questionnaire comprising diagnoses, relevant symptoms of atopic diseases and allergy tests 11 validated screening parameters [9] were used to determine the atopic status of parents and siblings. Cord blood IgE of the newborns was determined by Pharmacia CAP RAST FEIA with a detection limit of 0.35 kU/L.

At birth, 1986 infants and their families were invited to participate in the study, 1314 of whom agreed. Of this cohort 499 (38%) belonged to a 'high risk' group with at least two atopic family members and/or a cord blood IgE value above 0.9 kU/L [10]. The 'control group' comprised 815 infants (62%), who had been chosen at random, but matched for birth date and gender, from all the newborns left after the high risk group had been removed. Control infants had either one or no atopic family member and a cord blood IgE value less than 0.9 kU/L. The attrition rates from the invited 1986 families to the 1314 participating cohort families were not biased with respect to atopy risk or social status. Parents participating in the study gave their written informed consent. The study was approved by the Ethics Committee of the university.

Follow-up

The infants were examined at five paediatric clinics at the ages 1, 3, 6, 12, 24, 36, 48 and 60 months. By the age of 5 years the number of participating children had decreased to 76% of the original ($n = 1004$). A small, though significant difference ($P \leq 0.05$) was found in the participation rate between children with atopic family history (80%), and those without atopic family history (74%). At follow-up visits parents filled in a questionnaire and gave a structured interview. Physical examinations were conducted by physicians in a standardized manner, special attention was paid to the skin.

Blood samples were taken at 12, 24, 36 and at 60 months of age. Because not all parents agreed to blood sampling at each follow-up; the number of samples ranged from 574 to 723. At age 5 years 641 blood samples were obtained, 52% of children from atopic families, and 46% of those without atopic family history ($P \leq 0.05\%$). Total IgE and specific IgE against four common food allergens (cow's milk f 2,

egg f 1, soy f 14, wheat f 4) and 5 aeroallergens (mite d 1, cat e 1, dog e 2, grass b 6, birch t 3) were determined by the Pharmacia CAP assay.

Definitions of atopic diseases

Family history, clinical manifestations of atopic diseases, and atopic sensitization were treated separately. For the preceding observation period a negative, probable or obvious diagnosis of atopic dermatitis, asthma and rhinoconjunctivitis was given, based on four different sources of information. 1. The reported diagnosis by the family physician (in nearly all cases a paediatrician), 2. the examining doctor's opinion on reported relevant symptoms, 3. the diagnosis given by the examining doctor, and 4 a. in the case of atopic dermatitis, a computer algorithm which was used to construct a diagnosis from a meticulous description of morphological skin phenomena at follow-up, or 4 b. in the case of asthma recurrent wheezing and shortness of breath. The consistency and plausibility of the diagnoses for each case by each source were checked by a paediatrician (RLB), and some reclassifications were required. For the analysis in this study, cases with only a probable (suspected) diagnosis at follow-up were added to the negative cases.

Obvious atopic dermatitis (AD) was diagnosed from a combination of 'dry skin' and at least three out of nine typical signs (itching, erythema, red papules, vesicles, rhagades, excoriation, squamæ, lichenification, perifollicular accentuation) in at least three out of 26 typical anatomical sites (e.g. cheeks, infra-auricular, extensor or flexural areas). In the first month of life the diagnosis of an obvious AD was not given to any child, only of probable AD. Obvious asthma at 5 years of age required at least four wheezing episodes (expiratory stridor) in the preceding 12 months. Obvious rhinoconjunctivitis at age 5 years required a blocked and/or running nose without a cold, lasting for at least 2 months but no longer than 8 months by the preceding year. For the analysis in this study, obvious cases with asthma or rhinoconjunctivitis were added up to the entity 'allergic airway disease', which did not require sensitization.

An infant was considered sensitised against aeroallergens when the IgE concentration against at least one of the five test allergens was equal or greater than 0.35 kU/L ($\geq$ CAP class 1).

Statistical evaluation

Odds ratios and (approximate) 95% Cornfield's confidence intervals were computed as a measure of association between the outcome variables, prevalence of aeroallergen sensitization at 5 years, prevalence of allergic airway

disease at 5 years, and the influential variables, early atopic dermatitis up to 3 months and family history. The predictive performance of early atopic dermatitis up to 3 months and family history was evaluated by computing specificity, sensitivity, positive and negative predictive values. For all statistical computations we used SPSS for Windows, Version 6.1.

Results

Food and aeroallergen sensitization

Up to the age of 3 years food sensitization rates exceeded aeroallergen sensitization rates. No blood samples were taken at age 4 years. At age 5 years, aeroallergen sensitization rate outnumbered food sensitization rate with 28.0% vs 22.3%.

Occurrence of AD, asthma, rhinoconjunctivitis and allergic airway disease

The period prevalence of AD in the first 3 months of life amounted to 4.8% (59 infants). The period prevalences of asthma and rhinoconjunctivitis began to rise from 2 years onward. At age 5 years the period prevalence of rhinoconjunctivitis slightly exceeded that of asthma with 11.2% vs 10.5%. The period prevalence of allergic airway disease (either or both) at 5 years amounted to 18.1% (182 children).

Sensitization and early atopic dermatitis

There was no difference in the prevalence of AD at 5 years of age between children who had blood samples taken compared with those who did not (63% in either groups). Figure 1 gives an overview of the risk of developing sensitization against at least one of nine allergens at the ages 1, 2, 3 and 5 years in those children diagnosed as having AD at the age intervals 1–3 months, 18–24 months or 4–5 years, compared with a control group of children with no atopic manifestation at the same ages. For infants who had an obvious AD in the first 3 months, the sensitization rate increased from 44% at age 1 years to 69% at age 5 years. When atopic dermatitis was prevalent at the age of 2 or 5 years, the observed upward trend of sensitization risk at the ages 1, 2, 3 and 5 years was similar, but the corresponding sensitization rates were lower than in infants with AD in the first 3 months of life (Fig. 1). In the control group with no atopic symptoms at 3 months, 2 and 5 years of age, we also observed an increase of the sensitization rates but at much lower levels.

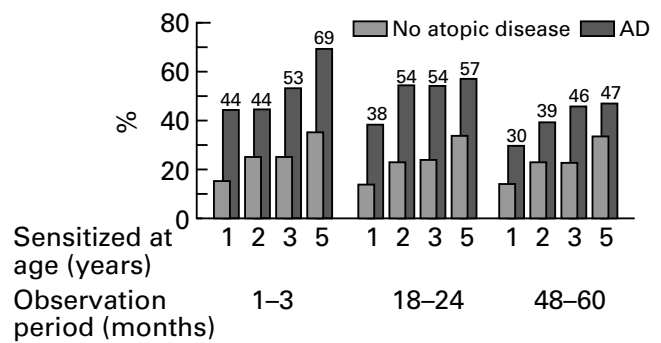


Fig. 1. Sensitization rates at the ages 1, 2, 3, and 5 years in children who were diagnosed as having had AD compared with those with no atopic manifestations at 1–3 months, at 18–24 months, at 48–60 months of age, respectively. Sensitization was defined as a CAP-value of ≥ 0.35 kU/L against at least one of nine allergens (food and inhalants). The number of children in the cohort having blood samples taken at these ages ranged from 574 to 723.

Risk factors for and prediction of outcome variables

Tables 1 and 2 summarize the evaluation of cord blood IgE, early atopic dermatitis and/or a positive family history as risk factors and predictors for two outcomes at the age of 5 years: aeroallergen sensitization, and manifestation of allergic airway disease. While cord blood IgE is not a significant

Table 1. Risk and predictive value of single and combined risk (exposure) factors for aeroallergen sensitization at 5 years of age.

Outcome and risk factors	Odds ratio	(95% CI)	SE%	SP%	PPV%	NPV%
Outcome 1.						
Aeroallergen sensitization at 5 years ($n = 181$, 28% of blood samples)						
Risk factors						
Cord blood IgE ≥ 0.9 kU/l	0.95	(0.63–1.54)	18.9	80.9	28.0	71.8
At least two atopic family members	1.78	(1.19–2.67)	27.6	82.4	37.9	74.5
Atopic dermatitis first 3 months	4.10	(2.07–8.09)	12.2	96.7	59.5	73.6
Atopic dermatitis first 3 months and at least two atopic family members	8.87	(2.41–32.61)	5.5	99.3	76.9	72.7

SE, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value.

Table 2. Risk and predictive value of single and combined risk (exposure) factors for allergic airway disease (manifestation) at 5 years of age.

Outcome and risk factors	Odds ratio	(95% CI)	SE%	SP%	PPV%	NPV%
Outcome 2: Allergic airway disease at 5 years (<i>n</i> = 182, 18.1% of children)						
Risk factors						
Cord blood IgE ≥ 0.9 kU/L	1.15	(0.76–1.75)	20.0	82.2	19.4	82.7
At least two atopic family members	1.82	(1.26–2.62)	29.1	81.6	26.0	83.8
Atopic dermatitis first 3 months	1.81	(0.96–3.43)	7.8	95.5	28.1	82.3
Atopic dermatitis first 3 months and at least two atopic family members	4.64	(1.72–12.55)	4.5	99.0	50.2	82.3

SE, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value.

risk factor for sensitization or manifestation of airway diseases at 5 years, a family with at least two atopic members is significantly associated with aeroallergen sensitization of the child at five years (OR 1.78, 95% CI [1.19,2.67]), and with allergic airway disease at 5 years (OR 1.82, 95% CI [1.26,2.62]). AD in the first 3 months is strongly associated with aeroallergen sensitization at 5 years of age, (OR 4.10, 95% CI [2.07,8.09]). When a positive family history is present in addition to early AD, this association shows a further increase, and the positive predictive value increases to 76.9%. For the manifestation of allergic airway disease the association with early AD is not significant, e.g. the odds ratio amounts to 1.81 and the 95% CI to 0.96–3.43. But with two atopic members the odds ratio increases to 4.64 (95% CI [1.72,12.55]), while the positive predictive value amounts to 50.2%.

Figure 2 contrasts only the positive predictive values for aeroallergen sensitization, and allergic airway disease in a low risk group, an intermediate risk group and a high risk group. With aeroallergen sensitization as the outcome variable an increase from 17.6% to 59.6% is observed when the group with neither early AD nor atopic family is compared with the early AD group. A further substantial increase up to 76.9% can be observed when at least two family members have an atopic history. The rise is not as steep when allergic airway disease is used as the outcome variable, i.e. from 12.1% over 28.1% to 50.2%.

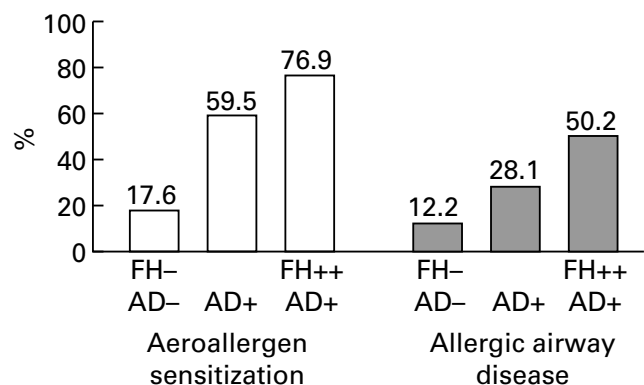


Fig. 2. Percentage of children with aeroallergen sensitization or with manifestation of allergic airway disease at age 5 years according to risk constellation in infancy: AD +/AD-, infants with AD vs infants with no AD in the first 3 months of life. FH + +/FH-, infants with at least two atopic family members or no atopy in their family.

Discussion

A multicentre cohort study design was chosen because the number of high risk cases to be observed longitudinally could otherwise not be collected within one year. The participation of different observers requires careful standardization and strict criteria.

As expected, the cases lost to follow-up, and the attrition rates for blood sampling were more pronounced in families without atopy than in those with atopic history. However, the magnitude of this difference is considered irrelevant with respect to the results.

While several textbooks still state that an inflammatory skin lesion observed in the first trimester is more likely due to seborrhoeic dermatitis than to atopic dermatitis, which by them is considered to emerge after the first three months of life, there is now ample evidence that the highest incidence of AD is observed in the first 3 months of life [11–13].

To avoid prejudices, strict diagnostic criteria were therefore necessary for the diagnosis of AD in this multicentre study. The basic diagnostic features for atopic dermatitis in Hanifin and Rajka's classical publication [14], in Hanifin's version for children [15] or those of Sampson [16] require a chronically relapsing course, a family history, and an own history. In a study starting at birth and intended to evaluate risk factors for AD, neither of these three factors could be applied for diagnosis. Even many of the minor features may not be present in very early AD [5,17,18]. Therefore a computerized system was developed in this study for the diagnosis of AD. The diagnostic criteria were based on several information sources, which were checked for consistency. Since very mild or questionable cases of AD were subordinated to the cases with no AD a clear cut-off line between mild and moderate AD may not have been achieved.

The low predictive capacity of risk factors at birth [4] initiated a search for early atopic symptoms and signs which could qualify children for secondary prevention. According to the dynamics of the atopic march [5], the clinical manifestations of atopic dermatitis and gastrointestinal allergy were to be expected first, accompanied or succeeded by specific food antibodies. The observation that aeroallergen sensitization not only succeeded sensitization against food allergens [7] but also followed early AD in most children, made early AD a candidate for the prediction of later aeroallergen sensitization. Additionally, it could be demonstrated that a higher proportion of children with very early AD than with AD at 2 or 5 years developed antibodies, which suggests (and is in line with other observations) that AD starting early in life is more often extrinsic or atopic than later AD [7]. Infants with AD in the first 3 months had a nearly 60% chance to become sensitized against aeroallergens at 5 years of age. An atopic family history of two members added 17% to the predictive value. But simultaneously, the sensitivity of these risk constellations dropped from about 12% to nearly 6%, which indicates that most children developing aeroallergen sensitization would not have been recognized by these predictors.

Similar considerations would apply when looking at infants with only severe forms of AD. The positive predictive value for aeroallergen sensitization would probably be even higher, as might be concluded from the observations of Guillet and Guillet [8], and the sensitivity even lower, i.e. fewer children would be classified as being at high risk.

In any case, beside early AD additional predictors will be helpful to identify children whose families should definitely receive preventive recommendations against allergic airway disease, e.g. children with sensitization against food antigens in early life [6,19]. Since early exposure to indoor allergens is associated with atopic sensitization against these allergens, preventive measures probably should be started in early infancy [20], at an age when specific food antibodies in serum routinely are not screened for. Although in infancy, the accuracy of specific serum IgE determinations is thought to be superior to skin-prick tests, these could be utilized alternatively to identify infants with food sensitization,

Because there is little overlap between the high risk groups identified by different early indicators, these groups together, could constitute a larger sample of high risk children, who, with reasonable sensitivity, are candidates for secondary prevention. This suggests that AD observed in the first months of life, in combination with a positive family history for allergic diseases, should initiate preventive measures against aeroallergen sensitization and asthma at least in these infants [21–23]. Physicians are well advised to take notice of symptoms and signs of AD in early life, and to observe the development of other early signs of

atopic disease in order to commence secondary preventive measures.

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