Natural History Of Atopic Disease In Early Childhood: Is Cord Blood IgE A Prognostic Factor?

A Preliminary Report

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Introduction

The natural history of atopic disease in early childhood is poorly defined. Previous studies in selected children suffering from atopic dermatitis, food allergy, or bronchial asthma report improvements ranging from 26% to 90%.[8,15,17,23] These findings are based on the follow-up of affected children, rather than a randomly selected population. Early accessible parameters such as family history (FH) and sex, as well as clinical findings including time of onset, coincidence of different atopic diseases, and severity of the disease have been suggested to be of predictive value for the outcome of atopic dermatitis and bronchial asthma.

It is of particular interest to find factors predicting children at high risk of developing atopy soon after birth to start preventive programs in the immediate postnatal period. Therefore, predictive clinical parameters of established atopy, like time of onset,[20] number of affected systems,[4,20] and severity of the symptoms,[23] might be helpful but are not of great benefit concerning preventive applications.

In this preliminary report, we studied prospectively the natural history of atopy during early childhood and investigated whether cord blood IgE (CB-IgE), FH, and sex are valuable parameters to predict the outcome of atopic disease in early childhood.

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Patients and Methods

Two hundred children born in Munich at the Klinikum rechts der Isar der Technischen Universität München and at the Schwabinger Krankenhaus between September 1984 and February 1985 participated in the present prospective study. To ensure feasibility, only children born between 8 a.m. and 5 p.m. were included, if informed consent by the parents was obtained.

At birth, cord blood from the 200 newborns was collected. Serum for CB-IgE determination was separated and stored at -20°C until assayed. Total IgE was measured by an enzyme immunoassay (Phadezym IgE Prist). All assays were carried out twice. The lower limit of sensitivity was 0.25 kU/L. The coefficient of variation for intra- and interassay variability was below 5.5% for values between 0.25 and 13 kU/L. A cut-off level of greater than 0.9 kU/L was chosen to distinguish between high and low CB-IgE concentrations.[14]

The parents were asked to answer questionnaires at the time of the child's birth, at 13 months (± one month), and at three years (± three months) after birth. At birth, the FH of possible atopic disease was obtained in 200 cases. After 13 months and three years, questionnaires were sent to all parents whose addresses could be traced. About 80% responded: 144 after 13 months (n=181), 124 after three years (n=148), 112 at both time points. Only the data of these 112 children were used for further analysis. The questions covered the family history of atopic disease and the child's own symptoms since the birth regarding skin, conjunctiva, respiratory and gastrointestinal

tracts. Doubtful answers were checked by telephone interviews with the parents as well as the private pediatricians and, in addition, by clinical examination. Without knowledge of CB-IgE, current IgE serum levels, or the results of previous examinations we divided the children into the groups described below. The chi-square test was used in the statistical analyses. P values of <0.05 were considered significant.

Obvious Atopic Disease

Atopic dermatitis: three or more basic features, plus three or more minor features, of the guidelines for the diagnosis of atopic disease by Hanifin and Rajka[11] (not used was the feature "personal or family history of atopy").

Bronchial asthma: three or more episodes of bronchial obstruction, diagnosed at least once by a pediatrician.[12]

Allergic rhinitis: rhinitis and/or conjunctivitis two or more times after exposure to a particular allergen and unrelated to infection.[12]

Urticaria: acute, generalized urticaria two or more times after exposure to a particular allergen.[12]

Food allergy with acute gastrointestinal symptoms: any kind of gastrointestinal symptom (vomiting, diarrhea, abdominal pain, or colic) within two hours after food ingestion, verified by elimination and challenge study of the particular allergen.[13]

To decrease the inevitable misclassification of children based only on symptoms reported by questionnaires, we exclusively accepted children as obvious atopic if their symptoms were independently confirmed by two pediatricians who carried out the clinical examination in this study.

Probable Atopic Disease

Atopic dermatitis: pruritus and dry, squamous dermatitis.[12]

Bronchial asthma: two episodes of bronchial obstruction at least once diagnosed by a pediatrician and/or four or more episodes of bronchitis, pneumonia, or persistent coughing.[12]

Allergic rhinitis: nasal obstruction, episodes of sneezing more than five to 10 times in a row, rhinorrhea during at least four weeks unrelated to infection.[21]

Food allergy with acute gastrointestinal symptoms: four or more episodes of vomiting, diarrhea, abdominal pain, or colic within two hours after ingestion of a particular food.[13]

Positive Family History of Atopy

Previous or present symptoms of bronchial asthma, allergic rhinitis, atopic dermatitis, or allergic urticaria in first-degree relatives. To verify the accuracy of the answer, we registered a positive FH only if it was mentioned in at least two out of three questionnaires.

Results

Out of the 200 newborns participating in this study, 110 (55%) were male, 90 newborns (45%) were female. In 59 cases (29.5%) a family history of atopy was reported. An increased level of CB-IgE (>0.9 kU/L) was determined in 21 infants (10.5%).

During the first year of age, 144 children were available for follow-up analysis. Nineteen percent developed an obvious atopy, and 34% manifested a probable atopic disease (data not shown). After three years, 112 children remained in the study. Out of these, 16% suffered from an obvious atopic condition and 8% from a probable atopic disorder, while 76% had no atopic symptoms at three years of age (Table 1). Dropouts and children remaining in the study did not significantly differ regarding

Table

AGE				al
			)	112
	[illegible]	9 (8%)	)	112

Table 2

OBVIOUS, PROBABLE, OR NO ATOPIC DISEASE AT 3 YEARS OF AGE IN RELATION TO CORD BLOOD IgE (CB-IgE), FAMILY HISTORY, AND SEX

	DIAGNOSIS	
	Obvious atopy	Probable atopy
Elevate	8 (53%)	4 (27%)
Norm	26 (27%)	26 (27%)
Positiv	14 (45%)	11 (36%)
No FH	20 (25%)	19 (23%)
Male	18 (31%)	13 (23%)
Female	16 (29%)	17 (31%)

sex, FH, or CB-IgE (respectively, p >0.1).

Children with increased CB-IgE or a FH of atopy developed obvious atopic disorders significantly more often during the first three years of age (respectively, p <0.025, p <0.01). Atopy was equally as frequent in both sexes (p >0.1) (Table 2).

The patterns of the different atopic disorders determined after the first and third year are listed in Table 3. Ninety-six percent of all one-year-old children with an obvious atopic disease suffered from atopic dermatitis alone or in association with other atopic manifestations. In the third year, atopic dermatitis was still predominant, but decreased to 61% of all obvious cases, while bronchial asthma increased in incidence from 17% to 33%. Urticaria was only observed in three-year-old children.

Of all children with an obvious or probable atopy in the first year of age (n=58), 64% (n=37) recovered at the end of the study. On the other hand, only 11% (n=10) of healthy or probable-atopic one-year-old children (n=88) developed an obvious atopy during the next two years (Table 4). It is remarkable that 70% (n=7) of these children (n=10) already had a classification of probable atopic disorder at one year of age. Out of all children who showed obvious atopic symptoms at any time during this three-year study period (n=34), only three children (9%) developed the initial signs of atopy after one year of age.

Regarding the outcome of atopic diseases, we tested CB-IgE, FH, and sex as prognostic parameters. From all obvious or probable atopic one-year-old infants who had a normal CB-IgE (CB-IgE <0.9 kU/L) at birth (n=47), 19% (n=9) had an obvious and 6% (n=3) a probable atopic disorder at three years of age. Seventy-five percent (n=35) had recovered and showed no further symptoms of atopy. In contrast, only two children (18%) with obvious or probable atopy at one year of age and elevated CB-IgE at birth became healthy during the follow-up period, while nine children (82%) continuously suffered from an obvious (55%)or probable (27%) atopic disease (Table 5). Although we could only study a small number of atopic one-year-old patients with elevated CB-IgE, the association between CB-IgE and outcome of atopy was significant (p <0.05).

In this study, the prognosis of atopy in early childhood was not influenced by the presence or absence of a positive FH (p >0.1) (Table 5).

The outcome of atopy was significantly influenced by the sex of the children. Fifty-two percent of the boys with an obvious or probable atopic disease at one year of age showed continuously obvious or probable atopic symptoms, whereas 81% of the girls recovered (p <0.001) (Table 5).

Discussion

In this preliminary report we followed 200 newborns from birth up to three years of age; 112 children could be followed over the whole period.

The observed frequency of atopy in first-degree relatives and the frequency of increased CB-IgE levels are in agreement with previous reports.[6,14] Our data strongly support the predictive value of these two parameters for subsequent development of atopy.[6,14,16]

Atopic disorders are common in early childhood. In the present study, the cumulated incidence of obvious atopy for the first three years of age was 30%. Previous studies reported an incidence ranging from 24% to 34% in the first two years of life.[7,18] A rather wide range of numbers is found in

Table 3

PATTERN OF ATOPIC MANIFESTATION AT 1 AND 3 YEARS OF AGE

DIAGNOSIS	AGE	
	1 year of age	
Atopic dermatitis	22 (9.1%)	
Bronchial asthma		
Rhinitis		
Immediate food allergy		
Urticaria		
Double manifestation		
Triple manifestation		

the literature from studies with longer follow-up periods.[1,6,14] This range might be due to different criteria and methods used to define atopy, as well as to differences in the geographical and social background of the populations evaluated. In this study, all diagnoses of obvious atopic disease were confirmed by physical examination to reduce inevitable misclassification of symptoms merely based on questionnaires.

The pattern of atopic manifestation observed in this preliminary report is typical for the investigated age group.[22] Atopic dermatitis was the predominant feature of atopy during the first and third year of age. At the third year, the number of children suffering from bronchial asthma and urticaria increased, whereas the prevalence of atopic dermatitis was diminished.

The natural history of atopic dermatitis,[5,17,23] bronchial asthma,[4,9,10] and food allergy[2,8] has been studied only in preselected populations. There are no studies on unselected children and few on the natural history of the overall picture of atopic disease.[22] Our data suggest that the risk of developing atopic diseases in early childhood is highest during the first year of age. Out of all children who developed an obvious atopic allergy at any time in the three-year study period, over two thirds showed obvious, and one fifth had probable, symptoms during the first year of age. In contrast, less than 10% of all observed children developed initial signs of atopy after one year of age. This is in agreement with other studies which report a mean onset of atopy during the first year of age.[7,17] An explanation for this finding might be that the transient IgA deficiency occurring during the first months of infancy allows increased intestinal permeability and the access of ingested allergens to the immune system.[19]

There is an extreme variation in the literature concerning the outcome of atopic dermatitis, bronchial asthma, and food allergy. Reports of improvement ranged between 26% and 90%.[15,17,23] Most studies reported recovery in about 50% of the cases.[5,8-10,19] In our study, two thirds of all obvious or probable atopic one-year-old infants recovered by three years of age. Explanations for this variation might be due to different study designs, as mentioned above.

Since the onset of atopic disease is most frequent during the first year of age, parameters to predict subsequent development of atopic disease and, more importantly, parameters to predict the outcome of the disease should be available as soon as possible after birth. Cord

			Total
Obvious atopy			24
Probable atopy			34
No atopy		3	54
Total	18	9	112

blood IgE can be determined immediately after birth. The measurement of IgE is sensitive, specific, reproducible, and of low cost. In addition to the well-established usefulness of CB-IgE for the prediction of subsequent development of atopic disorders,[6,14,16] our data support the value of CB-IgE as a prognostic parameter for the outcome of atopic disease. Children with normal CB-IgE recovered significantly more frequently than children with elevated CB-IgE levels during the three-year observation. However, it is difficult to get definite evidence regarding the duration of atopic diseases in childhood with the present follow-up period, since there is the possibility that healthy children at three years of age could later drop back into the atopic disease group. Nevertheless, in our present study CB-IgE predicts the outcome of atopy during the first three years of age. To clarify these results, a multicenter study with a longer follow-up period is in progress.

It has been suggested that the prognosis of atopic dermatitis and bronchial asthma is worse among children with a positive FH.[4] In the present study, we did not find an association between FH and the outcome of atopy. Our findings are in agreement with Businco et al,[5] who concluded from their data that a positive FH was not a prognostic factor for atopic disease in childhood.

In this study the prognosis was affected by the sex of the child. Girls had a significantly better prognosis compared with boys. Previous reports indicate a better prognosis for boys,[19] as well as for girls,[17] or could not find any differences between sexes.[10]

The severity of symptoms at the onset,[4] as well as the association of several atopic manifestations,[4,19] are claimed by some investigators to indicate the outcome of atopy. Other studies have examined several other parameters, such as skin reactivity to allergens,[5,9,15] and total[5,15] and specific IgE,[15] for their value to predict the prognosis of atopy, but no correlation was found.

In summary, the present prospective study in randomly selected children presents evidence that the natural history of atopic disease is usually favorable and that CB-IgE is a valuable parameter to predict the outcome of atopic disease in early childhood. Cord blood IgE could be useful to select children at high risk of developing prolonged atopy for entry into preventive programs in the immediate postnatal period. In addition, knowing CB-IgE levels might be helpful in determining the intensity of the therapy and need of controls by the treating physician. To confirm the results of this preliminary report, a multicenter study is in progress.

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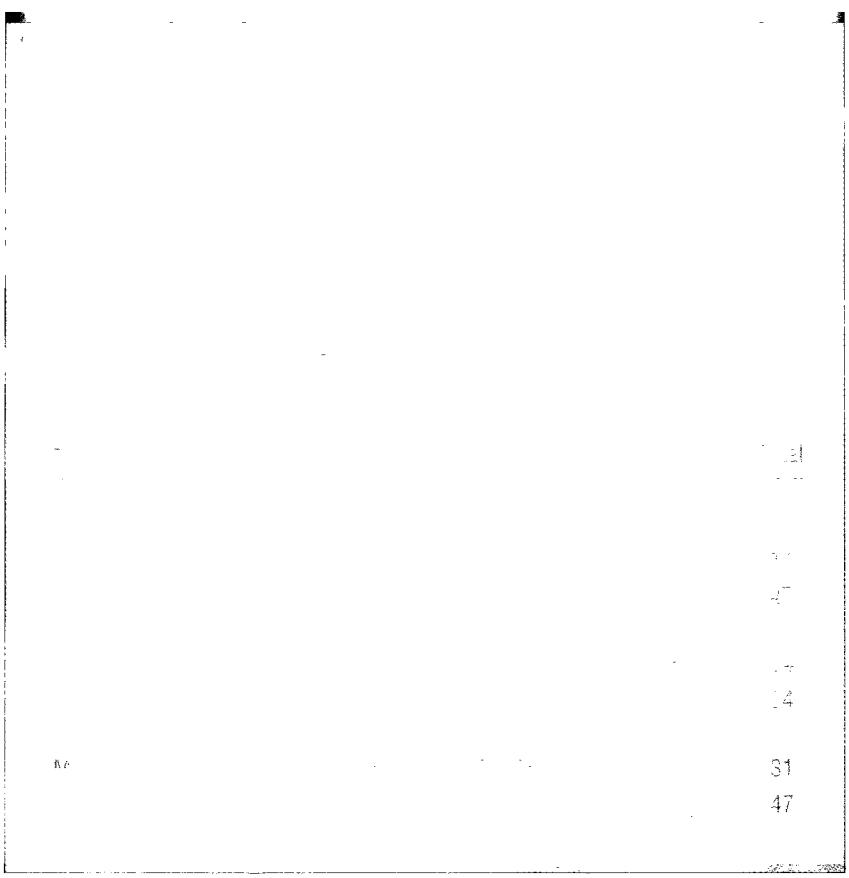

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