

Cord serum IgE in relation to family history and as predictor of atopic disease in early infancy

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Cord serum IgE was assayed by particle counting immunoassay (PACIA) in an unselected series of European newborns ($n = 190$; geom mean = 0.37 IU/ml) and a cut-off limit established (≥ 1.20 IU/ml) for prediction of atopy. At control follow-up by questionnaire 18 months after birth, 38 infants (20.0%) had developed definite (9.5%) or probable (10.5%) atopy with a significant predominance of boys ($P < 0.03$). Infants with a positive immediate family history (IFH) had a higher risk of developing atopy ($P < 0.0025$) and also had a higher incidence of elevated cord IgE ($P < 0.02$) than infants with a negative IFH. Maternal atopy influenced cord IgE levels significantly ($P < 0.00005$), whereas paternal atopy did not ($P = 0.23$). No fetal IgE antibodies against five common allergens could be demonstrated in 36 cord sera tested. Breast-feeding for 3 months was not sufficient to prevent atopic symptoms. The predictive value of cord IgE was high since 26 of 36 newborns (positive predictive value = 72.2%) with elevated cord IgE had developed atopic symptoms before follow-up. Of the 38 infants who developed atopic symptoms, 26 had elevated cord IgE (sensitivity = 68.4%) compared to only 10 (6.6%) of the 152 atopy-free infants ($P < 0.00005$). The data indicate that elevated cord IgE as determined by PACIA is a good predictor of early-onset atopy, better than family history ($P < 0.008$), and that primarily maternal atopy seems to affect fetal IgE synthesis.

Key words: atopy; antibodies; breast-feeding; cord serum; IgE; infant; newborn; prediction.

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CLINICAL ASPECTS

It is possible to predict atopy by screening for cord serum IgE with a reliable technique since about 75% of newborns with elevated levels will develop atopy in early infancy. However, it should be reminded that a low cord serum IgE does not exclude atopy. Moreover, when interpreting data, one should be aware that several factors, e.g. family history, race, sex, maternal smoking, and contamination, may influence the level of cord serum IgE. Although an elevated level of cord serum IgE may indicate intra-uterine sensitization, technical attempts to find the putative offending allergens have so far been unsuccessful. Highly predictive parameters like cord serum IgE will hopefully contribute to the elucidation of effective preventive programs.

Since the prevalence of atopic disease has a tendency to increase in our society, demands for preventive measures have been put forward. Although the efficacy of such treatments still seems controversial (6, 14, 17, 19), several studies claim the beneficial role of prolonged breast-feeding (7, 9, 10, 18, 21, 48, 59) together

with hypoallergenic diet and allergen avoidance (21, 48, 59). If a sensitive method was available that could predict as early as possible those at high risk of developing atopy it would be possible to apply existent programs at an early stage and by further studies to find new and more effective, preventive programs.

The predictive value of family history alone is low since more than half of the children with a positive family history will probably never develop allergy (40).

Several criteria make cord serum IgE a good candidate for the prediction of atopy: (i) the fetus is capable of synthesizing IgE already at the 11th week of gestation (52), (ii) IgE is considered not to cross the placenta (1, 34), (iii) there is a well-established clinical correlation for adults (27) as well as for infants and children (1, 25, 33, 34, 41) between being a high IgE responder and a proneness to atopic disease, and (iv) early prevention would be possible.

However, it is a prerequisite to have a precise and accurate assay at the level of approx. 1 IU/ml (2.4 ng/ml) (2) to select high IgE producers at birth and, in practice, only a few techniques are capable of this (32, 44, 56).

Several investigators, all using PRIST, have in the last few years shown the high predictive value of neonatal and cord IgE on selected series of newborns (7, 9, 10, 12, 13, 34, 51), as already suggested by preliminary work on infants (1, 13, 20, 27, 33), despite marked differences in the designs of these studies. Recently, similar results were also shown on an unselected series of Swedish newborns using PRIST and cut-off limits of 1.30 and 0.90 IU/ml (11, 37).

The aim of the present study was to investigate the relation between cord IgE, family history and infant atopy at 18 months' follow-up in a series of unselected European newborns using a different technology than PRIST to measure cord IgE, i.e. the fully automated particle counting immunoassay (PACIA) (44). Preliminary results have been reported elsewhere (43).

SUBJECTS AND METHODS

Subjects

Initially, 288 unselected European newborns born between December 1979 and June 1981 at the Cliniques Universitaires St. Luc, Brussels, were assayed for their cord serum IgE (44).

Retrospectively, in 1982, an allergy questionnaire was sent to all parents whose addresses could be traced ($n = 217$) and 199 (91.7%) responded.

The parents were asked to fill in, for the infant, siblings and themselves, signs and symptoms indicative of atopic disease in relation to the respiratory tract, eyes, ear, nose, throat, skin, and gastrointestinal tract; whether they were smokers (45), and the type and duration of feeding for the infant. About half of the parents (51.6%) participated by mail and filled in the questionnaire by themselves. The other half (48.4%) was contacted by phone and the signs and symptoms were filled in by a secretary or the author. No infant was subject to any kind of physical examination except for those whose parents had themselves consulted a pediatrician.

Of the 199 participating families, nine newborns were excluded from the study: eight had died for various reasons (46) and one was born at 26 weeks of gestation and the cord blood was suspected contaminated by maternal blood (see Results). Thus, the "net" material in this study consisted of 190 infants followed up at a mean age of 18 months (range: 14 to 28 months). Based on the questionnaire data and the literature (1, 5, 15, 26, 31, 33, 34, 65) the infants were divided into four groups without knowing the cord IgE levels (45): A. The *definite* group when very strong accumulative evidence of atopic disease was present. B. The *probable* group when the infants had at least one (often two or more) probable atopic signs and/or presented with recurrent (≥ 3 times) infections (bronchitis, rhinitis-pharyngitis-conjunctivitis and otitis). C. The *doubtful* group when they had experienced occasional isolated symptoms (≤ 2 times) of doubtful but possible atopic etiology. D. The *negative* group ($n = 119$) when no symptoms at all were stated.

Parents were considered atopic if they had symptoms of asthma, allergic rhinitis, eczema, urticaria, or an etiology strongly suggesting a food allergy.

To simplify statistical analysis of the data, Groups A and B, and Groups C and D, were often fused and are then referred to as the *atopic*

Table 1

Immediate family history (IFH) in relation to cord IgE (IU/ml) and risk of infant atopy at 18 months' follow-up

Family history	n	%	Observed risk		Cord IgE geom. mean	≥ 1.20	
			n	%		n	%
Both parents	15	7.9	7	46.7	0.87	5	33.3
Only one parent atopic	66	34.7	17	25.8	0.50	16	24.2
Only mother atopic	37	19.4	12	32.4 ⁶	0.74	15	40.5 ³
Only father atopic	29	15.3	5	17.2 ⁶	0.30 ⁶	1	3.4 ³
No parent atopic	109	57.1	14	12.8	0.28 ⁶	15	13.8
Sibling atopic	23	21.5	8	34.8	0.50 ⁵	5	21.7
Sibling non-atopic	84	78.5	11	13.1	0.31 ⁵	14	16.7
Positive IFH	84	44.2	25	29.8 ¹	0.56 ⁴	22	26.2 ²
Negative IFH	106	55.8	13	12.3 ¹	0.27 ⁴	14	13.2 ²
Total	190	100.0	38	20.0	0.37	36	18.9

¹ $P < 0.0025$; ² $P < 0.02$; ³ $P < 0.003$; ⁴ $P < 0.00005$; ⁵ $P < 0.05$; ⁶ $P > 0.10$

Table 2

Atopic symptoms of infants at 18 months' follow-up in relation to immediate family history (IFH), sex and cord IgE (IU/ml)

Symptoms of atopy	Total		IFH		Boys		Cord IgE ¹		≥ 1.20	
	n	(%)	n	(%)	n	(%)	Geom. mean	+ 2SD	n	(%)
A. Definite	18	(9.5)	13	(72.2)	13	(72.2) ²	3.18	25.2	16	(88.9)
B. Probable	20	(10.5)	12	(60.0)	13	(65.0)	1.26	8.87	10	(50.0)
C. Doubtful	33	(17.4)	21	(63.6)	19	(57.6)	0.32 ³	1.46	1	(3.0)
D. Negative	119	(62.6)	38	(31.9)	56	(47.1) ²	0.23 ³	1.56	9	(7.6)
A + B. Atopics	38	(20.0)	25	(65.8) ⁴	26	(68.4) ⁵	1.96 ⁶	17.5	26	(68.4) ⁶
C + D. Non-atopics	152	(80.0)	59	(38.8) ⁴	75	(49.3) ⁵	0.24 ⁶	1.51	10	(6.6) ⁶
Total	190	(100)	84	(44.2)	101	(53.2)	0.37	4.62	36	(18.9)

¹Analysis of variance on groups A, B, C and D; $P < 0.00005$ ² $P < 0.04$; ³ $P = 0.05$; ⁴ $P < 0.0025$; ⁵ $P < 0.03$; ⁶ $P < 0.00005$

group ($n = 38$) and the *non-atopic* group ($n = 152$), respectively. There was no significant difference ($P > 0.10$) in the incidence of family history or atopic infants whether the data were obtained by mail or phone. Only immediate family history (IFH; parents and siblings) was considered and no attention was paid to drug-associated allergies.

IgE assays

Cord serum IgE was automatically assayed in duplicate by PACIA combined with pepsin

digestion (44). The practical sensitivity was 0.10 IU/ml and the coefficients of variation of intra- and inter-assays did not exceed 7.6 % for values between 0.40 and 10 IU/ml.

IgE antibodies in cord sera were assayed against five common relevant allergens: *Phleum pratense* (g6), *Dermatophagoides pteronyssinus* (d1), cat epithelium (e1), egg white (f1) and cow milk (f2), with the PACIA IgE antibody test (42) using allergen-coated discs purchased from Pharmacia AB, Uppsala, Sweden. The standard curve was from the Phadebas RAST standard kit (birch pollen) in which the last standard D

(0.35 PRU/ml) was diluted 3 times further in normal rabbit serum to reach 0.12 PRU/ml of IgE. In PACIA 1 PRU was approximately equal to 1 IU (42), and 4% agglutination was chosen as the limit of detection, which in serum corresponded to 0.12 IU/ml of IgE antibody.

Statistics

Mean values in the text always refer to geometrical means. Medians were compared by the non-parametric Mann-Whitney U-test and frequencies by Fisher's exact test (2×2 -tables). Two-tailed P -values ≤ 0.05 were considered significant. All data were processed in an IBM 370/158 computer using the SPSS-program (53).

RESULTS

Family history at 18 months' follow-up

The incidence of atopy in parents and siblings in the 190 families and the observed risk to the infants according to IFH agree with the literature (Table 1).

In this series, 38 newborns (20.0%) developed either definite ($n = 18$; 9.5%) or probable ($n = 20$; 10.5%) atopic disease before 18 months of age (Table 2) with a significant ($P < 0.03$) predominance of boys ($n = 26$; 23.8%) over girls ($n = 12$; 13.5%). The most common cumulative symptoms in the definite group were eczema ($n = 13$; 72.2%), diagnosed asthma ($n = 4$; 22.2%) and strongly suggested food allergy ($n = 9$; 50%). Infants in the probable group presented with eczema ($n = 8$; 40%), suspected food allergy with repeated rashes, vomiting, diarrhoea and food dislikes to the same food ($n = 9$; 45%). Also, 14 (70%) infants had recurrent infections, one had recurrent croup and five had rashes of unknown etiology. Doubtful symptoms were reported in 33 (17.4%) cases, and 119 (62.6%) infants had no reported symptoms at all.

The highest incidence of positive IFH (Table 2) was in the definite group (72.2%) and the lowest in the negative group (31.9%), whereas it was intermediate and similar in the doubtful (63.6%) and the probable group (60%). Note-

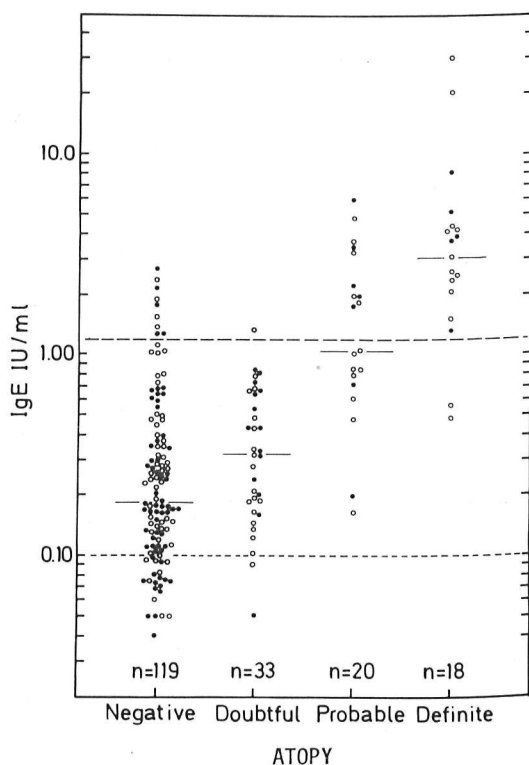


Fig. 1. Cord serum IgE (IU/ml) of infants followed up at 18 months of age for atopic symptoms (boys = $\circ$, girls = $\bullet$). The lower dashed line indicates the practical sensitivity of the IgE assay and the upper the cut-off limit used for prediction of atopy (≥ 1.20 IU/ml). The light bars represent the geometrical means).

worthy is that atopic mothers had more often ($P < 0.005$) sons (36/52; 69.2%) than non-atopic mothers (65/138; 47.1%).

Cord IgE as predictor of atopy

Mean cord IgE levels were higher in the definite (3.18 IU/ml) and the probable (1.26 IU/ml) groups compared to the doubtful (0.32 IU/ml) and negative (0.23 IU/ml) groups (Fig. 1 and Table 2). Analysis of variance on the four groups was highly significant, also for each sex analyzed separately ($P < 0.00005$). There was no significant difference in cord IgE between the two sexes in any of the four groups despite such a difference ($P = 0.047$) in the total material ($n = 190$).

For prediction a cut-off limit of 1.20 IU/ml was obtained by adding 2 SD to the geometrical mean of cord IgE calculated on only those infants in the negative group D (Fig. 1) whose IFH were negative ($n = 81$; 0.20 IU/ml). Thus, elevated cord IgE was found in 36 (18.9%) newborns of whom 26 (positive predictive value = 72.2%) had developed definite (16/18; 88.9%) or probable (10/20; 50%) atopy before 18 months (Fig. 1, Tables 2, 3). In comparison, IFH offered a positive predictive value of only 29.8% ($P < 0.008$).

Of the 38 infants who developed allergy, 26 (sensitivity 68.4%) had elevated cord IgE, 25 (65.8%) had positive IFH and 34 (89.5%) had either positive IFH or elevated cord IgE. In comparison, among the 152 infants of the non-atopic group only 10 (6.6%) had elevated cord IgE ($P < 0.00005$) and 59 (38.8%) had positive IFH ($P < 0.0025$). All predictive parameters are outlined in Table 3.

As shown (Fig. 2), positive IFH together with elevated cord IgE added no significant information ($P = 0.32$) to the predictive value ($n = 17/22$; 77.3%) as compared to elevated cord IgE and negative IFH ($n = 9/14$; 64.3%). Moreover, the latter was more predictive ($P = 0.015$) than positive IFH (25/84; 29.8%). Among newborns with low cord IgE

positive IFH had some informative value ($P = 0.05$).

Cord IgE in relation to family history

Of the 36 newborns with elevated cord IgE, 22 (61.1%) had positive IFH, whereas 62 (40.3%) of the 154 newborns with low cord IgE had such history ($P < 0.02$). Elevated cord IgE was most common among newborns with bi-parental (33.3%) or uni-maternal history (40.5%) (Table 1). With a negative bi-parental history still 13.8% (15/109) of the newborns had elevated cord IgE. When uni-paternal atopy was present ($n = 29$) only one newborn (3.4%) had elevated cord IgE as compared to 15 (40.5%) when uni-maternal atopy ($n = 37$) was present ($P < 0.0003$).

The level of cord IgE parallels well with atopic heredity and, logically, with the incidence of elevated cord IgE (Table 1). Thus, newborns to atopic mothers ($n = 52$) had significantly ($P < 0.00005$) higher cord IgE levels than newborns to non-atopic mothers ($n = 138$), i.e. 0.77 IU/ml and 0.28 IU/ml, respectively. Also, newborns with atopic siblings ($n = 23$; 0.50 IU/ml) had significantly higher cord IgE levels ($P = 0.049$) compared to those with non-atopic siblings ($n = 84$; 0.31 IU/ml), whereas no significant difference was observed ($P = 0.23$) whether the

Table 3

Immunoglobulin E in cord blood of unselected newborns as predictor of atopic disease

Author	Croner	Kjellman	Magnusson	
Year	1982	1984	this study	
Method	PRIST	PRIST	PACIA	
Cut-off limit (IU/ml)	≥ 1.30	≥ 0.90	≥ 0.90	≥ 1.20
Follow-up (years)	1.5	7	1.5	1.5
n	1701	1651	190	190
Atopic infants (%)	8	37	20	20
Elevated cord-IgE (%)	5	13	22	19
Pos. pred. value (%) ¹	70	82	67	72
Neg. pred. value (%) ²	95	70	93	92
Sensitivity (%) ³	44	28	74	68
Specificity (%) ⁴	98	97	91	93
Accuracy (%) ⁵	94	71	87	88

¹True positives/(true positives + false positives)

²True negatives/(true negatives + false negatives)

³True positives/(true positives + false negatives)

⁴True negatives/(false positives + true negatives)

⁵(True negatives + true positives)/total number of cases

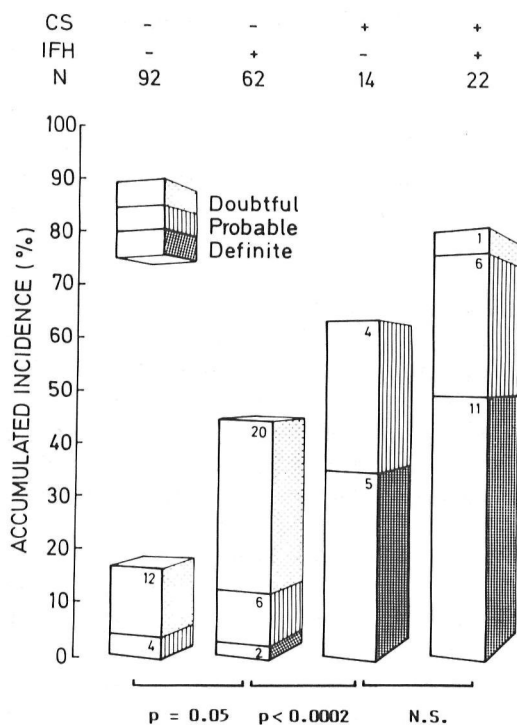


Fig. 2. Comparison of immediate family history (IFH) and elevated cord IgE (CS; ≥ 1.20 IU/ml) as predictors of atopy in infants at 18 months' follow-up. The figures in the columns indicate the number of infants within each group. *P*-values refer to Fisher's exact test between the frequencies of atopic and non-atopic infants.

father was atopic ($n = 44$; 0.43 IU/ml) or not ($n = 146$; 0.36 IU/ml), neither after controlling for maternal atopy (Table 1).

In an attempt to see whether contamination of cord blood by mother's blood could account for the observed influence of maternal atopy on cord IgE levels, atopic infants ($n = 38$) of atopic mothers ($n = 19$) were compared to those of non-atopic mothers ($n = 19$). However, neither the incidence of elevated cord IgE ($P = 0.15$) nor the mean cord IgE levels ($P = 0.50$) of the two groups were significantly different (Fig. 3).

IgE antibodies in cord sera

The PACIA IgE antibody test was performed on 28 sera from the atopic group and 10 sera

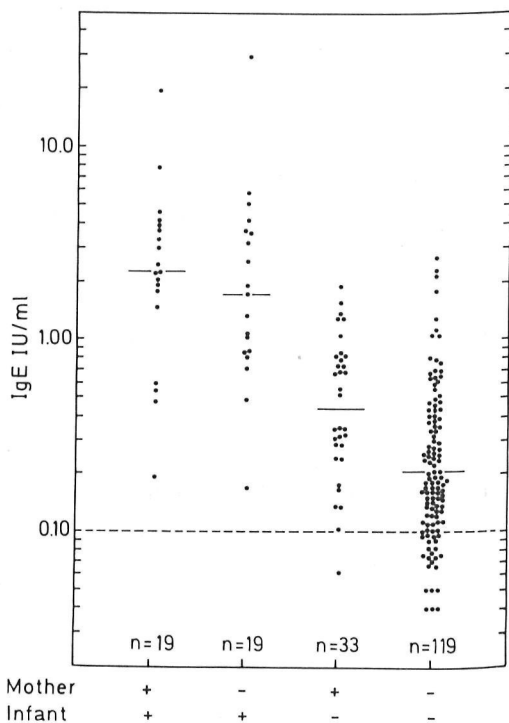


Fig. 3. Cord serum IgE of atopic (+) and non-atopic (-) infants in relation to atopic (+) and non-atopic (-) mothers. The dashed line indicates the practical sensitivity of the IgE assay and the light bars the geometrical means.

from the non-atopic group. For the five allergens tested only one cord serum was positive (≥ 0.12 IU/ml) having 0.18 IU/ml and 0.86 IU/ml of IgE antibody against *Phleum pratense* and cat epithelium, respectively. Since, in the questionnaire, the mother reported reactions to the same allergens and the baby was prematurely born (26 weeks), this sample was excluded from study due to a possible contamination of the cord blood by mother's blood during labor or sampling. Total cord IgE was 5.85 IU/ml and at follow-up the infant had doubtful symptoms.

Cord IgE and milk feeding

Newborns who before follow-up have had problems related to cow milk ($n = 26$; 0.87 IU/ml), e.g. vomiting, diarrhoea, eczema, dislike or

reflux; had significantly higher ($P < 0.00005$) cord IgE levels than infants without such problems ($n = 164$; 0.32 IU/ml).

Only 48 (25.3%) mothers breast-fed for more than 3 months giving a weak tendency that these newborns developed definite and probably atopy less frequently (8/48; 16.7%) than those breast-fed less than 3 months (30/142; 21.1%). Although still non-significant, this trend became clearer for newborns to atopic mothers, i.e. (4/15; 26.7%) and (15/37; 40.5%), respectively.

DISCUSSION

The results of this study with PACIA on an unselected series of 190 European newborns add further support to the high value of cord serum IgE in predicting atopy as previously shown by others with PRIST for both unselected (11, 37) and selected newborns (7, 10, 12, 34, 51). Only one report is in discord (25). Minor discrepancies between the results in these studies are probably related to their different designs since most parameters have varied, e.g. the age of the infant at follow-up; the criteria and methods used to define the atopic state; the food regimens; the populations studied, which implies social, ethnical and geographical differences; the methodology used for IgE measurements and the cut-off point chosen. For a comparison of studies on selected newborns confer Bousquet et al. (4).

The present study is compared to the extensive continual Swedish study (11, 37) being the only one on cord serum of unselected newborns. The cut-off points, obtained similarly, were remarkably close as were most of the predictive parameters at 18 months' follow-up (Table 3). Thus, before this age approx. 70% of the newborns with elevated cord IgE had developed probable or definite atopic disease. In contrast, less than 10% of the infants without atopic symptoms had elevated cord IgE. An elevated cord IgE could thus imply at least a 10 times greater risk of developing atopy before 18 months of age than a low cord IgE. This figure is very close to those previously observed for children at different ages (33). The test sen-

sitivities (Table 3) show that about 50% of the newborns who developed atopy before 18 months of age will have elevated cord IgE. As illustrated in the Swedish study at a 7-year follow-up, it is highly probable that the number of false positives (elevated cord IgE and no allergy) will diminish with increasing age but unfortunately the number of false negatives (low cord IgE and allergy) will also increase (37). A similar trend is discernable in the present study. The doubtful group might hide atopy-prone infants, despite a low incidence of elevated cord IgE, since a positive IFH was relatively common. The sporadic symptoms might be early warnings that are compatible with a later onset and a milder expression of atopy in this group (37). As shown here, and by others (11, 37, 51), cord IgE predicts atopy better than IFH. However, while cord IgE mainly seems to predict early-onset and perhaps more severe disease, IFH gains more value with increasing age (37) indicating that also environmental factors are important in triggering atopic disease and not only the IgE genotype (8, 16, 45, 64).

In the present study, there was a high cumulative incidence of atopic disease (Table 1) and consequently a positive IFH of the newborns was common (44%). This is higher than the 31–32% reported by Kjellman and colleagues (11, 37) but close to other reports (19, 24, 26, 29, 58, 59). Likewise, the cumulative incidence of atopy in the 18-months old infants (20%) was both higher (11, 19) and lower (26, 29, 58, 59) than previously reported. The most common symptoms in the atopic group were eczema, recurrent infections and gastro-intestinal manifestations in agreement with previous reports (11, 26, 61). These anamnestic data were fairly consistent despite being based on questionnaires which inevitably leads to misclassifications, even if the reliability of this procedure is reported over 80% (11, 41). Moreover, as much attention was paid to probable atopic signs associated with recurrent infections the probable group must be fairly heterogeneous and probably overestimated in terms of atopic infants. However, the prevalence of atopic disease in children is approx. 15–20%

(19, 35, 36) with a cumulative incidence sometimes as high as 40% at 12 months (26) and 36% at 7 years of age (37). In view of these considerations and as in a majority of the cases atopic symptoms appear already in early infancy (19, 41), a cumulative incidence of 20% at 18 months of age, although high, seems realistic. Moreover, in the present study, prolonged breast-feeding was not common, a fact which might influence the onset of atopy (19, 64). In any case, misclassifications would further reduce the accuracy of the statistics.

The significant predominance of boys in the atopic group confirms previous observations (11, 19, 63), a fact which probably also explains the here and elsewhere observed sex difference in elevated (9, 11, 44) and mean cord IgE (44). The finding that atopic mothers often have sons is interesting and merits further attention.

When comparing studies, one should also consider a possible influence of the method used for the assay of IgE. PRIST tends to give lower values than other technologies, (44, 49) thus perhaps explaining the lower incidence of elevated cord IgE obtained with PRIST (11) compared to PACIA in this study. Also, PRIST appears to be susceptible to variations, as suggested by the variety of cut-off points chosen for predictive purposes, i.e. 0.5, 0.7, 0.8, 0.9, 1.0, 1.3 IU/ml (7, 9, 10, 11, 37, 51) and that the signal-to-noise ratio at the highest cut-off points is much better for PACIA (20 to 1; expressed as percentage agglutination) (44) than for PRIST (3 to 1; expressed as cpm) (3), probably because in PACIA the cut-off point lies on the linear part of the standard curve (44). This fact may partially explain the lower sensitivity of predictions obtained by Croner et al. (11) because of poor discrimination at 1.3 IU/ml with PRIST. Good discrimination by PACIA is further suggested by the marginal effects that changing the cut-off point to 0.90 IU/ml has on the positive predictive value, incidence of elevated cord IgE and sensitivity (Table 3). Recently, Kjellman & Croner (37) changed the cut-off point with PRIST to 0.90 IU/ml since many infants with "intermediate cord IgE" had developed atopy before 7 years of age. Whether this is due to the technique is uncertain but it has an apparent

effect on the incidence of elevated cord IgE (Table 3). PACIA besides being non-isotopic offers many advantages (42, 44), including full automation (> 50 samples/h) and rapidity (50 min/sample) that facilitate screening and immediate prevention.

Because PACIA detected IgE down to 0.05 IU/ml, it was possible to calculate and compare in detail the mean cord IgE levels according to the family history of the newborns. The genetic influence on IgE was confirmed (22) since the highest levels were found when both parents were allergic and the lowest when both were non-allergic. In agreement with some previous investigators (12, 13, 34, 51) but in contrast to others (7), maternal atopy significantly influenced cord IgE. As suggested by statistics, this influence could not be attributed to a major contamination of cord blood by maternal blood. Furthermore, Michel et al. (51), using direct needle aspiration of the cord vein to avoid contamination at sampling, made the same observation. Even though one would expect, because of heredity, higher cord IgE levels in newborns to atopic mothers, a minor transplacental leakage of maternal IgE during labor cannot be excluded (66). It is also likely that various humoral maternal and external factors, e.g. related to progesterone treatment (51) and smoking (45), may pass the placenta and influence *in utero*, the IgE producing system of the fetus. Even though occasional significant materno-fetal admixtures are possible (13, 37, 54) they do not seem to jeopardize the overall predictive value of cord IgE. Sample contamination could be avoided by using serum at 5 days of age (9, 13). However, this is less practical and would delay prevention.

The finding that maternal but not paternal atopy influenced cord IgE confirms previous observations (51). Discrepancy with others (11) may be due to misclassifications, materno-fetal serum admixtures, differences in the technologies for IgE measurements or the populations studied. Nevertheless, it is interesting to note that in family studies on serum IgE (39, 57, 60), the IgE levels of the children correlated better with maternal than paternal serum IgE, with the best concordance between mother-son

($P < 0.0005$) and the worst between father-son ($P > 0.17$). These data agree with the results of the present study since mainly boys were atopic, had elevated cord IgE and maternal IFH. Even though paternal atopy apparently does not influence cord IgE, but still a high percentage of infants with such history develop allergy, it is tempting to speculate on other genetic factors. One possibility would be paternal transmission of a deficiency in a subset of T-cells (28), a defect perhaps penetrating first after birth.

In favor of intra-uterine sensitization, low amounts of specific IgE antibodies to cow milk have been found in cord sera (7, 51). However, in previous studies with RAST (11, 12, 24, 34), as in the present one with PACIA, no allergen-specific IgE of fetal origin could be detected. Even though one might question the reliability of the positive RAST results technically (50), there is suggestive evidence of sensitization *in utero* (38, 47) and subsequent IgE production (30, 62). The negative results could be related to improper allergen selection, IgE of low affinity, only a locally distributed IgE, rapid clearance, or masking of the small amount of IgE Ab in immune complexes.

Several studies have shown that cow milk as a food regimen has a negative effect on IgE production (9, 10, 48, 58) and on the outcome of newborns at high risk of developing atopy (7, 9, 48). It is therefore interesting that those infants who manifested problems associated with cow milk in the present study also had higher IgE levels in cord serum. This strengthens the highly allergenic capacity of cow milk in atopy-prone infants. Although breast-feeding was not of any significant benefit, perhaps because very few mothers breast-fed their infants for as long as the recommended 6 months (8, 21, 59), there was such a trend, which was strongest among infants to atopic mothers (18, 59).

In conclusion, cord IgE as a good predictor of atopy in early infancy was confirmed in the present study on unselected newborns using a new automated assay technique, i.e. PACIA (44). To be really efficient and ethically acceptable a large screening program should comprise all newborns (9, 13) and not only those with

uni- or bi-parental IFH (11, 37) considering that 30–40% of atopic children have negative IFH. Even though a few existing studies support a favorable cost-benefit ratio (9, 13) and demonstrate encouraging prophylactic measures (7, 9, 21, 23), further evaluation seems necessary before making a definitive decision about a generalized cord IgE screening program. In the meantime, families at high risk should try to follow existing recommendations (8, 21, 45, 59).

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