

Neonatal IgA and IgE levels among infants with paternal heredity for atopic disease

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Serum IgA and IgE levels were studied in the postnatal period in 21 infants having a paternal heredity of atopic disease. Three different sampling techniques were used, aspirated cord blood (CB), gravity-collected cord blood, and capillary collected blood at 4–5 days of age. Significant differences among the three sampling techniques were recorded for IgA ($P < 0.01$), but not for IgE. The IgA levels decreased from birth to 4–5 days of age in 90% (19/21) of the infants ($P < 0.01$). The corresponding decrease in IgE levels was 20%. This postnatal difference in the frequency of decreasing increasing IgA and IgE levels was significant ($P < 0.05$). An analysis of CB IgA to detect maternal contamination of CB was found to be of questionable value, since only 50% (2/4) of the cases with an elevated CB-IgA level could be considered contaminated. The results of this study further emphasize that aspiration of CB and capillary collection of blood at 4–5 days of age are the best sampling techniques to avoid contamination. The general finding that paternal heredity had no significant influence on infant IgE contrasts with the strong influence of maternal heredity. Further studies will show whether the explanation lies in genetic or transplacental factors, or in both kinds of factors.

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The fetus is considered capable of IgE production from week 11 of gestation (26), and IgE is believed not to pass the placental barrier (3, 4). The presence of IgE in cord blood (CB) is therefore thought to be a sign of fetal IgE synthesis. IgE is a marker of atopy, and an increased CB-IgE level has been reported to predict atopic disease during childhood (7, 9, 19, 24, 25). However, in recent years, several studies have shown conflicting results concerning the usefulness of CB IgE for predicting atopic allergy (16, 21, 22, 28). One cause of the divergent results may be that the risk of maternal contamination of CB has not been given enough consideration (15, 20–23, 28). However, even after the exclusion of CB samples with maternal contamination, a positive correlation between maternal IgE levels and CB-IgE levels has been observed (21, 23). Recently, we have also shown increasing IgE levels from birth to 4–5 days of age in blood samples of infants with a family history of atopic disease (23). Taken together, these observations indicate that, besides the possibility of maternal contamination of CB, other factors, genetic or congenital, may influence fetal IgE synthesis.

The present study investigated the changes in IgA

and IgE levels at birth and in the postnatal period in selected infants at risk of atopic disease because of paternal heredity. In this way, we hoped to reduce the previously observed strong influence of maternal atopy on these parameters (3, 5, 6, 23–25). The effect on the neonatal IgA and IgE levels of three blood-sampling techniques – i.e., aspiration of CB with a needle in the cord vein, letting the CB flow freely from the cord into a tube (gravity collection), and capillary blood sampling at 4–5 days of age – was assessed.

Material and methods

The participating families ($n = 20$) were selected consecutively while they were in the maternity ward at Nacka Hospital, Stockholm, Sweden. Only families where the father had clinical symptoms of respiratory allergies (rhinoconjunctivitis and/or bronchial asthma caused by pollens and/or animal danders) were enrolled in the study. Paternity was verified only from the case history, and not by any genetic markers – e.g., human leukocyte antigen (HLA).

Parents

The fathers had a mean age of 33 (range 23–47) years. Sixteen had a history of respiratory allergy to pollens (tree and/or grass pollen) and 14 to animal danders (cat and/or dog). Eighty-five percent (17/20) of the fathers suffered from allergic rhinoconjunctivitis and 40% (8/20) from bronchial asthma. The mothers had a mean age of 31 (range 21–40) years, and none of them reported clinical symptoms of atopic diseases.

Infants

Twenty-one infants, 15 boys and six girls, including one pair of twins, were born at full term. The pair of twins was heterozygous and therefore considered as two subjects in all data evaluations. All the infants were healthy during the postnatal period.

Serum samples

CB was collected first by aspirating blood from the umbilical vein with a needle. The blood from a segment of the umbilical cord was thereafter allowed to flow freely into a tube (gravity collection). At 4–5 days of age, a capillary blood sample was taken from each infant by heel puncture. Blood samples were collected from the mothers at delivery and from the fathers during the follow-up. The serum samples from the mothers and fathers and three from each infant were stored at -20°C , pending analyses. All three serum samples from each infant were analyzed simultaneously with regard to IgA and IgE concentrations to minimize assay variations.

IgA

The IgA levels were analyzed in duplicate with a sandwich ELISA (20). The upper normal level for cord IgA was set at 14 mg/l, calculated as the geometric mean (GM) plus three standard deviations (SD) in 20 newborn infants with maternal atopic heredity who had CB IgE $<0.125\text{ kU/l}$ (20, 23). An IgA level above this limit was taken to indicate maternal contamination (20, 23).

IgE

The parental IgE levels were analyzed in duplicate by PRIST (Pharmacia Diagnostics, Uppsala, Sweden). A modified PRIST method, with an increased sensitivity (i.e., 0.125 kU/l), was used for the CB and 4–5-day samples (20). The intra- and interassay variations of the sensitive PRIST assay were 5% and 13%, respectively (21). A neonatal IgE level $\geq 0.9\text{ kU/l}$ was considered elevated (19). In the sta-

tistical analyses, all values below the threshold of sensitivity were given the value of 0.125 kU/l . The presence of IgE antibodies against pollens and/or animal danders in the maternal and paternal serum samples was determined by Phadiatop (Pharmacia Diagnostics, Uppsala, Sweden) (11)). The result of the test was either positive or negative.

Ethical aspects

The study was approved by the ethics committee at Söder Hospital, Stockholm, Sweden. Informed consent was given by all families before entering the study.

Statistical analyses

Wilcoxon's paired signed rank sum test (WILC), the Mann-Whitney U-test (MW), the Kruskal-Wallis one-way analysis by ranks (KW), Fisher's exact test (FISHER), and the Spearman rank correlation test (r_s) were used to analyze the results. A P value (two-tailed) <0.05 was considered significant.

Results

Parental IgA

The individual values of paternal IgA ($n=19$; two cases not available for analysis) and of maternal IgA ($n=21$) are presented in Table 1. The geometric means (GM) were 3.4 g/l (range 2.0–6.2) and 2.6 g/l (range 1.4–5.9), respectively. The paternal IgA levels were significantly ($P<0.01$; MW) higher than the maternal IgA levels.

Infant IgA

The IgA levels in gravity-collected CB (CB-IgA_{grav}) varied between 3.1 and 25.7 mg/l ($n=21$; GM = 7.2 mg/l ; Table 1). The GMs in aspirated CB (CB-IgA_{asp}) and in capillary blood samples collected at 4–5 days of age (IgA_{4–5}) were 5.6 mg/l and 4.1 mg/l , respectively. There were significant ($P<0.01$; KW) differences in IgA levels among the three blood-sampling techniques.

IgA_{4–5} levels and CB-IgA_{asp} levels were highly correlated ($n=21$; $r_s=0.81$, $P<0.001$), but differed significantly ($n=21$; $P<0.01$, WILC), since the former levels were lower (GM = 4.1 mg/l) than the latter (GM = 5.6 mg/l). In fact, IgA levels decreased in 90% (19/21) of the cases after birth, the mean decrease being 27% of GM.

An increased IgA level, defined as $\geq 14\text{ mg/l}$, was found in four (19%) CB_{grav} samples (nos. 11, 17, 18, and 21). In two of these cases (nos. 11 and 17), the corresponding CB-IgA_{asp} levels, as well as the IgA_{4–5} levels, were below 14 mg/l , indicating a possible ma-

Table 1. IgA and IgE levels in maternal (M) and paternal (P) serum samples and corresponding infant immunoglobulin (IgA/IgE) levels in aspirated cord blood (CB_{asp}), gravity-collected cord blood (CB_{grav}), and capillary-collected blood on days 4-5

Fam. no.	M IgA g/l	P IgA g/l	CB-IgA _{asp} mg/l	CB-IgA _{grav} mg/l	IgA ₄₋₅ mg/l	M IgE kU/l	P IgE kU/l	CB-IgE _{asp} kU/l	CB-IgE _{grav} kU/l	IgE ₄₋₅ kU/l
1	2.5	3.8	4.1	3.6	2.8	52	265	0.16	0.16	0.20
2	2.6	2.9	4.6	4.4	3.0	28	75	<0.125	<0.125	<0.125
3	4.3	3.3	4.8	5.5	3.4	11	24	<0.125	<0.125	<0.125
4	2.5	2.0	5.5	6.5	4.9	7.8	60	<0.125	<0.125	<0.125
5	1.4	3.4	5.4	7.7	4.8	5.1	63	<0.125	<0.125	<0.125
6	4.6	3.7	8.9	8.2	6.2	38	2000	<0.125	<0.125	<0.125
7	1.7	3.8	2.4	8.6	2.1	17	285	<0.125	<0.125	<0.125
8	2.5	3.7	3.2	2.6	2.2	14	419	<0.125	<0.125	<0.125
9 ^b	1.4	3.4	3.1	4.4	1.8	4.9	128	<0.125	<0.125	<0.125
10 ^b	1.4	3.4	2.7	5.2	2.3	4.9	128	<0.125	<0.125	<0.125
11	5.9	n.a.	7.9	15	2.6	62	n.a.	0.14	0.14	0.15
12	2.6	2.7	5.1	7.6	7.8	9.8	6.6	<0.125	<0.125	<0.125
13	3.7	2.7	7.5	9.2	6.2	22	212	<0.125	0.18	0.13
14	1.6	5.3	5.5	5.3	3.2	883	75	2.4	2.3	3.0
15	3.0	3.0	8.1	8.6	5.0	0.8	51	0.40	0.33	0.39
16	2.7	3.7	8.5	11	6.1	17	195	<0.125	<0.125	<0.125
17	2.7	4.7	3.7	19	2.7	8.3	15	0.23	0.22	0.31
18	3.0	3.5	28	26	18	43	263	0.35	0.35	0.39
19	2.3	6.2	4.4	4.4	3.2	11	502	0.29	0.31	0.35
20	2.1	n.a.	3.7	2.2	2.1	25	n.a.	<0.125	<0.125	<0.125
21	3.7	3.1	18	16	24	11	134	1.9	1.1	1.1
Median	2.6	3.4	5.1	7.6	3.2	14	128	<0.125	<0.125	0.13
Geom. mean	2.6	3.4	5.6	7.2	4.1	16	103	0.20	0.19	0.21
±1 SD	1.7-3.8	2.6-4.5	3.1-10.1	3.9-13.2	2.1-8.1	12.0-216	28.5-375	<0.125-0.47	<0.125-0.43	<0.125-0.48

n.a.=not available; ^b=pair of twins.

ternal contamination of the gravity-collected CB. However, in the other two infants (nos. 18 and 21), the IgA level was increased on all three testing occasions, suggesting that the IgA was mainly of fetal origin. When the two CB samples (nos. 11 and 17) with suspected maternal contamination were omitted, the CB-IgA_{grav} (GM = 5.6 mg/l) and CB-IgA_{asp} (GM = 5.0 mg/l) levels did not differ significantly (WILC), and they were highly correlated ($n=19$; $r_s=0.73$, $P<0.01$).

There were no significant correlations between paternal IgA levels and any of the levels of CB-IgA_{asp} ($n=19$), CB-IgA_{grav} ($n=19$), or IgA₄₋₅ ($n=19$). However, there were significant correlations between maternal IgA levels and CB-IgA_{asp} ($n=21$; $r_s=0.66$, $P<0.01$), CB-IgA_{grav} ($n=21$; $r_s=0.57$, $P<0.05$), and IgA₄₋₅ ($n=21$; $r_s=0.55$, $P<0.05$), respectively.

Parental IgE

Paternal IgE levels showed a wide range, 6.6-2000 kU/l, with a GM of 103 kU/l (Table 1). In 89% (17/19), Phadiatop was positive, confirming the atopic state in most of the fathers. The two fathers (nos. 4 and 12) with a negative Phadiatop reported bronchial asthma when exposed to animal danders. There was no significant correlation between paternal IgE and IgA levels.

Maternal IgE levels had a GM of 16 kU/l (range

0.8-883) which was significantly ($P<0.001$, MW) lower than the paternal IgE levels (Table 1). Phadiatop was positive in two women (nos. 11 and 18), in spite of a negative history of atopic disease and IgE levels within the normal range (i.e., <125 kU/l (31)). On the other hand, one woman (no. 14) with an increased IgE level (883 kU/l) had a negative Phadiatop. No significant correlation was found between maternal IgA and IgE levels.

Infant IgE

The individual IgE levels in gravity-collected CB (CB-IgE_{grav}), aspirated CB (CB-IgE_{asp}), and capillary-collected blood at days 4-5 (IgE₄₋₅) are presented in Table 1. The corresponding GMs were 0.19, 0.20, and 0.21 kU/l, respectively, without any significant difference between the three groups (KW). Two CB samples (nos. 14 and 21) showed elevated (≥ 0.9 kU/l) levels of both CB-IgE_{grav} and CB-IgE_{asp}, and neither of these seemed to be due to maternal contamination, since the CB-IgA_{grav} and CB-IgA_{asp} levels were similar. Moreover, in infant no. 14, the IgA levels were below 14 mg/l and in infant no. 21 above 14 mg/l on all three testing occasions.

Maternal contamination was suspected in two infants (nos. 11 and 17) on the basis of an increased CB-IgA_{grav} level. However, this did not affect their

Table 2. Spearman rank correlations (r_s) between maternal IgE (M-IgE), paternal IgE (P-IgE), and infant IgE levels in aspirated cord blood (CB-IgE_{asp}) and in capillary-collected blood on days 4–5 IgE_{4–5}¹

	M-IgE	P-IgE	CB-IgE _{asp}	IgE _{4–5}
M-IgE (<i>n</i> =21)	–	0.56	0.20	0.25
P-IgE (<i>n</i> =19)	0.02	–	–0.13	–0.20
CB-IgE _{asp} (<i>n</i> =21)	0.37	0.56	–	0.93
IgE _{4–5} (<i>n</i> =21)	0.27	0.40	<0.001	–

n=number of serum samples available.

Lower left values refer to *P* values and upper right values to rank correlations (r_s).

CB-IgE_{grav} levels, probably because of the low levels of maternal IgE. Nevertheless, after omission of these two infants, the CB-IgE_{grav} and CB-IgE_{asp} levels were highly correlated ($n=19$; $r_s=0.95$, $P<0.001$) and not significantly different. There were also significant correlations between CB-IgE_{grav} and IgE_{4–5} ($n=19$; $r_s=0.93$, $P<0.001$) and between CB-IgE_{asp} and IgE_{4–5} ($n=21$; $r_s=0.93$, $P<0.001$) (Table 2). There were no significant correlations between the levels of IgA and IgE on any sampling occasion.

Among 10 infants with detectable CB-IgE_{asp} (≥ 0.125 kU/l), eight (80%) had IgE_{4–5} levels that were the same or higher. The increase in IgE levels after birth contrasted with the decrease observed in IgA levels during this period. The difference in frequency of decreasing concentrations between the two isotypes was significant ($P<0.05$, FISHER).

There were no significant correlations between the levels of parental IgE and infant IgE (Table 2).

The influence of parental heredity on all the results presented above have been based on the questionnaire data. However, in order to make a more restricted group of infants with a well-defined unipaternal heredity, we also calculated all the statistics, taking into account parental Phadiatop and total serum IgE. In this way, six infants were excluded from the original 21. Phadiatop was positive in two mothers (nos. 11 and 18), and Phadiatop was negative in two fathers (nos. 4 and 12). Serum IgE was increased in one mother (no. 14), and two paternal sera were not available (nos. 11 and 20). Despite these considerations, there were no major changes in the significance of the correlations or in the group comparisons.

Discussion

The results of the present study on infants with a paternal heredity of atopic disease confirm many of our previous findings in infants with maternal heredity (23). Thus, irrespective of parental heredity, postnatal IgA and IgE levels were influenced by the blood-sampling technique. A few cases of maternally contaminated CB samples were observed, as judged by an increased CB-IgA_{grav}, but not by the corre-

sponding CB-IgA_{asp} level. Hence, both our studies indicate that aspiration of CB or capillary collection at days 4–5 is the best blood-sampling technique to avoid contamination (14, 21, 23, 28). Moreover, the IgA levels decreased significantly from birth to days 4–5 of age, but the IgE levels did not. Indeed, more than 90% of the infants had lower IgA_{4–5} than CB-IgA_{asp} levels in both studies. In contrast, IgE decreased in just 20% of the infants in the present study and in 60% in the previous one (23). This difference between the two isotypes is significant whatever the heredity. We have previously speculated that the capillary sampling technique might be of partial importance, but also that there is an active synthesis of IgE in early postnatal life (23). Furthermore, CB-IgE_{asp} and IgE_{4–5}, as well as CB-IgA_{asp} and IgA_{4–5}, were highly correlated, irrespective of the parental history of allergy.

In our previous study on infants with a maternal history of atopy, we observed that CB-IgE and maternal IgE levels correlated strongly (23), in contrast to the present findings on infants of nonatopic mothers (i.e., atopic fathers). Moreover, there was no influence of paternal atopy on the infant IgE level on any sampling occasion. Although the number of infants in our study was small, a compilation of our data (Fig. 1) from the present and the previous study (23), using infant groups with a strict uni- and biparental heredity for atopy, supports the view that CB-IgE is higher among infants with maternal and biparental heredity (3, 5, 6, 24, 25) but contradicts results where no difference in maternal and paternal influence was found (9). No such effect was noticed for CB IgA. Clinical observations also indicate that infants with a maternal history of atopic disease run a greater risk of developing atopic disease than infants with a paternal history (1, 29). The cause of this pronounced maternal influence on both CB-IgE levels and the risk of developing atopy may lie in genetic factors (1, 2, 6, 8, 32), but the cause may also be the close contact between the mother and child during pregnancy and lactation. An atopic mother may, via her placenta and later via breast milk, transfer factors affecting the immune system of the infant in various ways (17, 27, 30). An influence of maternal anti-idiotypic antibodies on fetal newborn antibody production has recently been reported (12, 13). In the case of CB IgE, we have previously argued for a transplacental effect in addition to fetal IgE synthesis, since the influence of maternal atopy on the infant IgE level seemed to decline at 4–5 days of age (23). Moreover, there was no difference in IgE_{4–5} levels between infants of atopic mothers and those of atopic fathers. More research on the putative mechanisms governed by maternal influence seems warranted.

An elevated CB-IgE level has been reported to be

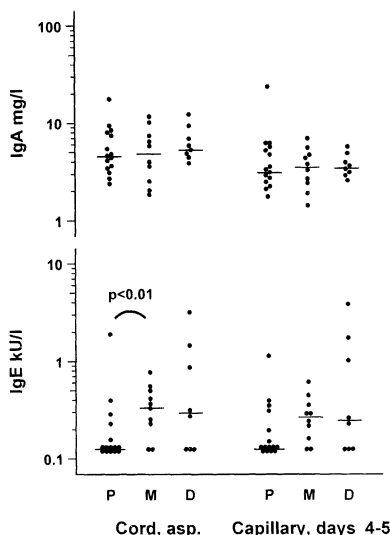


Fig. 1. Comparison of IgA (mg/l) and IgE (kU/l) levels in aspirated cord blood (CB_{asp}) and in capillary-collected blood at 4–5 days of age among infants with unipaternal atopy (P-group; $n=15$), unimaterial atopy (M-group; $n=10$), and biparental atopic heredity (D-group; $n=8$). M- and D-groups are taken from previous study (23). Horizontal bars represent geometric means. Only statistically significant difference among groups was found for CB-IgE_{asp}, i.e., M-group vs P-group ($P<0.01$; MW).

a good predictor of the development of atopy during infancy (7, 9, 19, 24, 25). However, several recent studies fail to confirm such findings (16, 21, 22, 28). One reason for discrepancies may be that contamination of CB by maternal blood obscures the results by causing too many falsely elevated CB-IgE levels (15, 20–23, 28). To overcome this problem, a screening for elevated IgA in all CB with elevated IgE levels has been proposed (15, 20–23, 28) since IgA, like IgE, is believed not to pass the placental barrier (3, 10). Thus, serum samples with CB-IgA levels exceeding a certain cutoff point, 14 mg/l (15, 20) or 32 mg/l (5, 18), should be considered maternally contaminated and therefore be excluded. However, our data reveal that only two (50%) of four infants with an elevated CB-IgA_{grav} (i.e., >14 mg/l) could be considered contaminated. This casts doubt on the value of CB-IgA level as a marker of contamination (14, 21). One infant (no. 21) of the two who had a markedly elevated CB-IgE level, as judged by our CB-IgE_{asp} and IgE₄₋₅ data, would thus erroneously have been excluded as contaminated. Moreover, a

CB-IgA level below 14 mg/l does not exclude minor contamination from mothers with high IgE levels. Our few cases of increased CB-IgA levels persisting at 4–5 days of age may well indicate a stressed immune system in some newborn infants, a finding that would be consistent with the fetal IgA synthesis observed in some studies (12, 13).

In summary, we have confirmed, on the basis of several blood-sampling techniques, that the maternal influence on CB-IgE level is much stronger than the paternal one. Besides genetic factors, transplacental factors may be important. An elevated CB-IgA level seems of limited value for detecting maternally contaminated CB, since a low CB-IgA level does not exclude contamination and an increased level may lead to the erroneous exclusion of immunologically hyperreactive infants. Our results also indicate that either aspiration of CB or capillary collection on days 4–5 is the right sampling technique to avoid contamination.

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