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Relationship of Cord Blood Immunoglobulin E and Maternal Immunoglobulin E with Birth Order and Maternal History of Allergy in Albanian Mother/Neonate Pairs

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Abstract

BACKGROUND: Previous studies reported that familial factors such as birth order and mothers atopy might influence cord blood levels and development of allergies.

AIM: The aim of the study was to evaluate the relationship of cord blood IgE and maternal IgE with birth order and mothers history of allergy in Albanian mother/neonate pairs.

MATERIAL AND METHODS: Study population represented 291 mother-infant pairs. Mothers were interviewed with a questionnaire for personal history of allergy and pregnancy history whereas serum IgE levels were determined using sandwich IRMA assay.

RESULTS: The mean level of cIgE in neonates with detectable levels was 1.59 (n = 78). No significant difference in means of cIgE was found between first born and later born neonates (p = 0.232) and between neonates of mothers with a negative and positive history of allergy (p = 0.125). Also, no significant difference was found between means of mIgE by birth order, whereas there was a significant difference of mIgE between mothers with and without a history of allergy (p = 0.01). In a group of neonates with detectable cIgE levels, maternal IgE levels were moderately correlated with cIgE levels.

CONCLUSION: Cord blood IgE is not affected by birth order and mothers history of allergy, whereas mothers IgE are affected by the history of allergy but not by birth order.

Introduction

In the recent years, developed countries have experienced increases in the prevalence of atopic diseases; asthma, eczema and hay fever [1]. Although genetic predisposition is a fundamental factor governing susceptibility to atopic diseases, the rise in atopy has occurred within the too short time frame to be explained by a genetic shift in the population, thus pointing to environmental or lifestyle changes [2, 3].

The cord blood immunoglobulin E (cIgE) has been investigated as a possible early indicator of elevated risk for atopic disease, primarily during childhood [4]. Various studies demonstrated that elevated cIgE are affected by some different factors including maternal, paternal, placenta and fetal characteristics although findings on each factor have been inconclusive [5-12]. There is evidence that the number of siblings and birth order may influence cIgE levels and development of allergies, asthma and immunologic sensitization [13, 14]. The 'hygiene hypothesis' proposed by Strachan suggests that birth order could be associated with frequency of infection, since having older siblings may increase the likelihood of infections leading to a protective effect against childhood allergic disease [15]. Whereas, "in utero programming hypotheses" alternatively proposed that the sibling effect is related to inherent differences in immune function [13].

In Kosovo, there are no data about the prevalence of allergic disease. Taking into account the geographic proximity with Albania and genetic similarities of the Albanian population in Kosovo with Albanian population in Albania, we can assume that prevalence of allergic diseases in Kosovo may be as low as the prevalence of allergic diseases in Albania [16-19]. Also, in Kosovo, there are no data about the factors which can influence cIgE levels.

The aim of the current study was to evaluate the possible influence of birth order and maternal history of allergy on cIgE and maternal immunoglobulin E (mIgE) as well as the correlation between cIgE and mIgE in Albanian mother/neonate pairs.

Material and Methods

Study population

Pregnant women coming to the delivery room in Obstetrics and Gynecology Clinic of the University Clinical Center of Kosovo were screened for eligibility for the study. Women with physiologic pregnancy, vaginal route of delivery and no evidence of multiple gestations and fetal congenital anomaly were eligible. Written informed consent for participation in the study was obtained from 306 pregnant women. In the course of data collection and analysis 15 mother–infant pairs were excluded from the study: four mother–infant pairs due to infants' cord blood IgE greater than 10 kU/L, suspected of possible contamination with maternal blood, two mother–infant pairs because infants cord blood was not obtained, and nine were excluded due to missing data. The remaining 291 mother-infant pairs represented our study population. Considering that the total annual number of newborns in Kosovo is around 35,000, this sample is quite representative.

This study followed the principles of the Declaration of Helsinki and was approved by the University Institutional Review Board.

Data Collection and grouping

After informed consent had been obtained, mothers were interviewed with a detailed questionnaire for personal allergy history and pregnancy history. Pregnancy histories included information about the number and outcomes of all prior pregnancies including those not carried to term. Using this information, neonates were assigned a birth order group: no prior pregnancies were labelled as "first born neonates" and one or more live birth as "later born neonates"; whereas, according to the history of allergy, mothers were assigned as "positive or "negative".

Blood collection

To determine maternal total serum IgE, after delivery, blood samples (5 ml) were collected from the cubital vein into a non-heparinized tube. Neonatal blood (5 ml) was collected from the cord vein by venipuncture at the cut end of the cord attached to the placenta once the placenta was delivered. After centrifugation at 350 g, sera from the blood were aliquoted into 2ml vials for IgE estimation and stored at -20°C till analysis.

Serum IgE immunoradiometric assays (IRMA)

Serum IgE levels were determined using sandwich IRMA assay (Total IgE IRMA, Immunotech, Marseille, France) with a detection level of 0.5 kIU/L.

Statistical analysis

Statistical analyses were done for the population of 291 mother-child pairs. Cord blood IgE levels were analysed as dependent variable whereas maternal IgE levels were analysed as a factor which can affect cIgE levels but also as a variable which can be affected by birth order and history of allergy. Cord blood IgE levels were dichotomized at the detection limit of 0.5 kIU/L as undetectable (<0.5 kIU/l) and detectable (≥ 0.5 kIU/L), whereas mIgE were dichotomized at the limit of 100 kIU/L as negative (< 100 kIU/l) and positive (≥ 100 kIU/l). However, cIgE and mIgE were mostly used as continuous values. According to birth order, neonates were categorized as first born neonates and as later born neonates (2+).

To explore the relationship of cord blood IgE and mothers, IgE with birth order and mothers history of allergy, frequencies, means and correlation between cIgE and mIgE were analysed. Frequencies of cIgE were analysed for the whole sample of neonates (n=291), whereas the means were analysed only in the group with detectable levels of cIgE, since we were not inclined to work with values assigned to undetectable samples. Statistical differences in frequencies were tested by Pearson's Chi-square test, whereas differences in means were analysed by one-way ANOVA. To test for correlation between categorical and continuous variables Spearman's correlation method was used whereas statistical significance was put on $p = 0.05$. Statistical analyses were carried out using SPSS statistical package, version 23.

Results

Study population

Two hundred and ninety-one mother-infant pairs represented our study population. From 291 mothers in our study population, 74 (24.7%) were in age group 16-23 years, 187 (62.3%) age group 34-33 years and 39 (13%) were in group 34+, with no

statistically significant difference between the frequencies of detectable and non-detectable cIgE by mothers' age groups.

Table 1: Frequencies and means of cIgE

		Birth order		Mothers history of allergy	
		Birth 1	Birth 2+	Negative	Positive
a) Frequencies of cIgE	Total N (%)	N (%)	N (%)	N (%)	N (%)
All neonates	291 (100.00)	123 (42.27)	168 (57.73)	261 (89.69)	30 (10.31)
cIgE < 0.5	215 (100.00)	90 (41.86)	125 (58.14)	197 (91.63)	18 (8.37)
cIgE ≥ 0.5	76 (100.00)	33 (43.42)	43 (56.58)	64 (84.21)	12 (15.79)
		p = 0.458		p = 0.068	
b) Means of cIgE					
Neonates with cIgE ≥0.5					
Mean (N)	1.59 (76)	1.83 (33)	1.41 (43)	1.47 (64)	2.20 (12)
		p = 0.232		p = 0.125	
Neonates of mothers with mIgE < 100					
Mean (N)	1.47 (58)	1.88 (25)	1.16 (33)	1.49 (50)	1.36 (8)
		p = 0.04		P=0.807	
Neonates of mothers with mIgE ≥ 100					
Mean (N)	1.98 (18)	1.67 (8)	2.22 (10)	1.43 (14)	3.89 (4)
		p = 0.5		p = 0.02	

Table 1a presents frequencies of dichotomized neonates analysed by birth order and maternal history of allergy. From 291 neonates, 76 (26.12%) had detectable levels of cIgE (≥ 0.5 kIU/L) with no significant differences in percentages of detectable and non-detectable cIgE by birth order (p = 0.458) and history of allergy (p = 0.068).

Table 1b shows means of cIgE only for the group of neonates with detectable levels of cIgE analysed by birth order and maternal history of allergy. The mean level of cIgE in neonates with detectable levels was 1.59 (n = 78). Although first born neonates had higher mean cIgE compared to later born ones (1.83 vs. 1.41), no significant difference was found between the means of the two groups (p = 0.232). Whereas neonates of mothers with a positive history of allergy had higher mean cIgE compared to neonates of mothers with a negative history of allergy (2.20 vs. 1.47), the difference between the means of two groups was non-significant (p = 0.125).

To find exactly which group of neonates stratified by mothers IgE affects the relationship of cIgE and birth order/history of allergy; the means of cIgE between parameters were analysed. It was observed that mean cIgE level was higher in neonates born by mothers with mIgE ≥ 100 than in neonates born by mothers with mIgE < 100 (1.98 vs. 1.47) but with no significant difference (p = 0.218, data not included in the Table).

When mean cIgE levels were analysed by birth order, there was the statistically significant difference between the means of cIgE of neonates born by mothers with mIgE < 100, with the values higher in first born neonates (p = 0.04). But the opposite is true for neonates of mothers with mIgE ≥100, where the mean levels of cIgE were higher in later born neonates (p = 0.5). On the other hand, when analyzed by history of allergy, the means of cIgE were significantly different in neonates born by mothers with mIgE ≥ 100 (p = 0.02), being higher in neonates of mothers with positive history of allergy, but with no significant difference in neonates born by mothers with mIgE < 100 (p = 0.807).

Table 2: Frequencies and means of mIgE

		Birth order		Mothers history of allergy	
		Birth 1	Birth 2+	Negative	Positive
a) Frequencies of mIgE	Total N (%)	N (%)	N (%)	N (%)	N (%)
Mothers	291 (100.00)	123 (42.27)	168 (57.73)	261 (89.69)	30 (10.31)
mIgE < 100	242 (100.00)	101 (41.74)	141 (58.26)	221 (91.32)	21 (8.68)
mIgE ≥ 100	49 (100.00)	22 (44.90)	27 (55.10)	40 (81.63)	9 (18.37)
		p = 0.399		p = 0.042	
b) Means of mIgE					
All mothers					
Mean (N)	52.83 (291)	54.71 (123)	51.46 (168)	49.68 (261)	80.12 (30)
		p>0.05		p=0.01	
Mothers of neonates with cIgE<0.5					
Mean (N)	47.13 (215)	47.70 (90)	46.72 (125)	45.09 (197)	71.23 (18)
		p>0.05		p>0.05	
Mothers of neonates with cIgE≥0.5					
Mean (N)	68.13 (76)	72.59 (33)	65.23 (43)	63.73 (64)	93.47 (12)
		p>0.05		p>0.05	

Table 2a shows that 49 mothers from 291 (16.84%) had levels of IgE ≥ 100 kIU/L, with no statistically significant difference between dichotomised frequencies of mIgE by birth order (p = 0.399), but with statistically significant difference of dichotomised frequencies of mIgE by history of allergy (p = 0.042). The means of mIgE are presented in Table 2b. The means of mIgE levels were 29.97 in mothers with mIgE < 100 and 165.23 in mother's mIgE ≥ 100. Comparing the means of mIgE by birth order no significant differences between means were found. Whereas, when means of mIgE were compared by mothers history of allergy statistically significant difference was found (p = 0.01).

On the other hand, when mIgE levels stratified by levels of cIgE were analysed no significant statistical differences between birth order and history of allergy were observed either in mothers of neonates with undetectable cIgE or mothers of neonates with detectable cIgE levels.

In the whole sample of mother/neonate pairs (n = 291), positive maternal IgE contributed significantly to the positivity of cord blood IgE (r_S = 0.231, p = 0.000, data not included in the table). Fig. 1A presents the levels of IgE in mothers of neonates with detectable levels (68.4 kIU/L, n = 76) and the levels of cIgE in neonates with detectable levels (1.6 kIU/L, n = 76). In this group of neonates (cIgE ≥ 0.5) maternal IgE levels were moderately correlated with cord blood IgE levels (r_S = 0.296, p = 0.009) (Figure 1B).

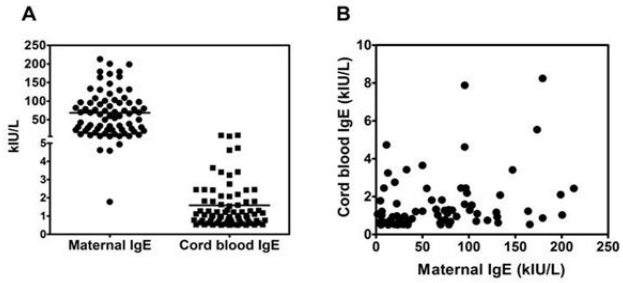

Figure 1: IgE levels in the serum of mothers (mIgE) and cord blood IgE (cIgE). A) Maternal IgE levels were significantly higher than levels of cIgE (P<0.0001). B) A medium correlation was found between maternal IgE and cIgE (p<0.01)

Discussion

In this study, we found that cIgE levels were not normally distributed and that most cIgE levels were below 0.5 kIU/L, as stated in previous reports [20, 21]. The frequency of newborns with detectable levels of cIgE was 26.12% which is higher than frequencies reported in several studies which used the same cut-off values of 0.5 kIU/L [21, 22], but lower than in some other [7, 23, 24] and similar to results of Edenharter et al [25]. Whereas, the mean cIgE level among detectable samples was 1.59 IU/l, with a range of 0.51 to 8.24 kIU/l, similar to findings from Nabavi et al. [10] but lower than the one reported by Goldstein which resulted from a sample taken from a community cohort with high prevalence of asthma [23].

Several studies have been conducted to investigate the effect of parity on cIgE levels and to determine whether the sibling effect might be mediated in part by *in utero* programming rather than postnatal exposure [26]. Data from several investigations show that birth order is associated with lower IgE levels in cord blood [14, 20, 26-28] but also, there are other studies which found no association between birth order and cIgE levels [7, 22, 23]. We came across only one study which found that birth order is associated with higher cIgE levels [10].

After the Bergmanini report [20], Karmaus et al. were the first ones to analyse the birth order effect on cIgE. In 2001 they reported that children born third or later were less likely to be in a higher cIgE group than first-born children [13]. In another publication, Karmaus et al. reported a statistically significant correlation between cIgE and birth order of live offspring although the correlation they reported was very weak (r_s = - 0.092, P = 0.008) [29]. The correlation found by Karmaus et al. was assumed to be the result of changes in the utero environment from infections during pregnancy and endocrine changes which override the effect of the hygiene hypothesis.

In contrast to reports from some other regions in the world, we did not find a statistically significant birth order effect in cIgE. Our results are in line with the results reported by Bergmanini [20] and several other authors [7, 22, 23] who found a nonsignificant relationship between these parameters. Significant differences in cIgE levels by birth order were found only in neonates born by mothers with mIgE < 100 and, non-significant difference in neonates born by mothers with mIgE > 100. Our results do not support the finding by Karmaus et al. that birth order effect on cIgE is transmitted through maternal IgE [29]. Despite all investigations done so far on the effect of birth order on the immune response of neonates, there is no exact explanation for mechanisms which underlie the relationship between birth order and cIgE. The nonsignificant birth order effect on cIgE in our sample from a low-income country could explain the low prevalence of allergic diseases in our country by hygiene hypothesis theory rather than by *in utero* programming hypothesis.

The mean level of cIgE in a group of neonates with cIgE > 0.5 was higher in neonates from mothers with a history of allergy but with no significant difference with neonates from mothers without a history of allergy which is in line with results reported by Liu et al. [21]. When neonates with detectable levels were stratified by mIgE, we observed significantly elevated levels of cIgE only in the group of mothers with IgE ≥ 100 kIU/L, with positive allergy history, and this is in line with the results of Shah et al. [11, 30]. This indicates that the newborns of these mothers should be assessed for elevated levels of cIgE, to undertake pre-emptive measures against the onset of atopic diathesis**.**

In the current study, no significant differences were found either by frequencies or using mIgE levels between mothers of first born neonates and later born neonates. The absence of association of mIgE and birth order in this study as those found from other authors [26, 28] do not support the findings from Karmaus et al. who reported that maternal IgE decreases with increasing birth order [29]. More studies are required to verify the effect of birth order on mothers immune response and through that on the fetal immune response.

Many previous studies have reported an association between mIgE and cIgE that is comparable with our findings suggesting the factors from family can induce production of IgE [10, 11, 21, 23, 26-29, 31]. But, also there is one study which did not find a correlation between these two variables [32]. A significant difference of mIgE between mothers with a history of allergy and mothers without a history of allergy and a correlation found between mIgE and cIgE in this study show that mIgE was predictive for detectable levels of cIgE and suggests that the maternal IgE may influence fetal IgE. One approach to explain the correlation assumes that cIgE levels are

genetically determined [33] whereas other approaches go through in utero programming [13, 29].

In the group of neonates with cIgE ≥ 0.5 maternal IgE levels were moderately correlated with cIgE levels. The correlation found is unlikely to be due to contamination of the neonatal blood with maternal blood. However, to rule out maternal contamination of the cord blood we did not perform any testing knowing that maternal IgE does not cross the placenta [35] and because when measured cord blood IgA, the rates of contamination were very low [31,36]. Also, the very low cIgE in our sample of neonates from mothers with mIgE >100 indicate than there is no contamination of cord blood with maternal blood.

In conclusion, the current study found that cIgE were not affected by birth order and mothers history of allergy, whereas mIgE were affected by the history of allergy but not by birth order. Also, we conclude that newborns of mothers with allergy history with mIgE > 100 should be assessed for elevated levels of cIgE, to undertake pre-emptive measures against the onset of atopic diathesis**.**

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