Factors associated with cord blood IgE levels

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Summary

Background: **The cord blood IgE level is thought to be a predictor of allergic disorders in childhood. It is not well understood how this marker is influenced by the fetal environment, such as maternal, paternal, placenta, and fetal characteristics.**

Objective: **We aimed to investigate the association between cord blood IgE levels and various genetic and environmental factors.**

Methods: **This was a cross-sectional study including a total of 181 neonates and their mothers. A questionnaire asking about demographic data, delivery characteristics, maternal past medical history and information on exposure to known environmental allergens was distributed to pregnant women. Blood samples from them and neonatal cord blood samples were taken at the same time for IgE assay.**

Results: **By univariate analysis we found an association between cord blood IgE levels and higher number of previous pregnancies, delivery season, type of delivery, history of allergy during pregnancy, but not the type of allergic disease and history of allergic disease before pregnancy, were associated with elevated cord blood IgE levels. The maternal blood level of IgE was correlated with its level in cord blood. By multivariate analysis, the number of previous pregnancies, the type and season of delivery and a history of allergy during pregnancy and maternal age and blood IgE levels were variables which had a significant association with cord blood IgE levels.**

Conclusion: **Among the evaluated factors, the presence of any kind of allergic disorder in the mother or her family and elevated maternal blood IgE level are associated with the cord blood IgE of the child. Maternal age and smoking, neonatal gender, type of delivery, season of birth and parity are probable predictors.** ***(Asian Pac J Allergy Immunol 2013;31:157-62)***

Key words: *cord blood, IgE, predictor*

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Submitted date: 1/5/2012

Accepted date: 17/10/2012

Introduction

Epidemiologic data suggest that the prevalence of atopy has increased dramatically in recent decades.[1,2] Immune development and predisposition to atopy begins during the gestational period and atopic diseases are often diagnosed in the early years of life.[3,4] Based on these facts, there is growing interest in primary prevention of atopic disorders. Early detection of high-risk groups in the perinatal period is the first essential step for prevention and for providing a better strategy for treating such disorders.[5]

IgE in cord blood is thought to be a product of the fetus and is secreted by the fetus by the 11th week of gestation.[6] Since the 1970s, the role of cord blood immunoglobulin E (IgE) levels in predicting the development of atopy has been widely discussed and it has been proposed as a valuable tool for identifying neonates with a high risk of developing atopy in later life.[7,8] However, there are also conflicting studies regarding the accuracy of cord blood IgE in predicting childhood atopy [9-11] and it is not well understood how cord blood IgE levels are influenced by the fetal environment, including maternal, paternal, placenta, and fetal characteristics.[12-17]

DOI 10.12932/AP0234.31.2.2013

In order to achieve a better understanding of the role of this predictive marker, we aimed to further investigate the association between cord blood IgE levels and a variety of genetic, environmental and psychosocial factors in a cross-sectional study including 181 cases.

Methods

Subjects and population

This was a descriptive and analytic cross-sectional study carried out during 2006 and 2007. A total of 181 cord blood samples were obtained from neonates of mothers who were referred to the Amir-al-momenin Hospital of Semnan, Iran for delivery. The mother's blood samples were obtained at the same time. Samples were immediately sent to the laboratory for refrigeration and serum isolation procedures.

A self-administered questionnaire was distributed to the study participants and was completed by them. The first part of questionnaire included demographic data (mother's age and sex of neonate), the second part asked about delivery characteristics (number of previous pregnancies, mode and season of delivery). The third part asked about the mother's past medical history (underlying cardiac, pulmonary or neurologic condition), past drug history, family history of allergy, and history of allergic disease before pregnancy and the presence and type of allergic disease during pregnancy. The last part consisted of information on exposure to known environmental allergens.

IgE assay

After performing centrifuge and freezing procedures, samples were tested for total IgE level using IgE Elisa kit (product of Pishtazteb Company, Iran). Normal values for IgE levels for the mother's blood was equal or less than 160 IU/ml and for cord blood was equal or less than 10 IU/ml.

The study protocol was approved by the ethics committee of Semnan University of Medical Sciences and each participant gave informed consent before enrollment.

Statistical analysis

All data were entered into the statistical software package SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL). Nominal and categorical variables were presented as frequency (percent) while scale variables were presented as mean ± Standard Deviation (SD). Analysis was carried out using Spearman's correlation, the Mann-Whitney and Kruskal-Wallis non-parametric tests and linear regression analysis was also used. $P < 0.05$ was considered statistically significant. To meet the assumptions of linear regression, the equation $\sqrt{Ln(IgECord)+1}$ was used and then the relationships between variables were investigated.

Results

Descriptive characteristics

The mean maternal age (±SD) at delivery was 26.6±5.5 and neonates' gender was female in 86 (47.5%) and male in 95 (52.5%) deliveries. The median (Interquartile) level of cord blood IgE level was 1.8 (4.25) in neonates and was and 67.00 (92.00) in mothers. Table 1 shows the descriptive data from our study. Table 2 shows the frequency of specific types of allergic disorders before and during pregnancy among mothers. The frequency of exposure to different environmental allergens during pregnancy is shown Table 3.

Univariate analysis

The effect of maternal age, the sex of the neonate, the number of previous pregnancies, the mode and season of delivery, past medical history, past drug history, family history of allergy, and history of allergic disease before pregnancy and the presence and type of allergic disease during pregnancy and the effect of exposure to known environmental allergens was evaluated on cord blood IgE levels separately. Non-parametric tests were used for this purpose. Neonate sex, maternal age, family history of allergy, presence of underlying medical conditions, past drug history and exposure to known environmental allergens were not associated with elevated cord blood IgE levels. By contrast, higher number of previous pregnancies, delivery during spring or winter, Ceasarean type of delivery, a history of allergy during pregnancy, but not type of allergic disease and history of allergic disease before pregnancy, were associated with elevated cord blood IgE levels. None of the specific types of allergic disorders were associated with elevated cord blood IgE levels before or during pregnancy (P-value = 0.113). Exposure to none of the known environmental allergens had a statistically significant association with elevated cord blood IgE levels. The maternal blood level of IgE was correlated with its level in cord blood (p value <0.001, correlation coefficient = +0.415). Results of univariate analyses are presented in Table 1 and 3.

DOI 10.12932/AP0234.31.2.2013

Table 1. The frequency of different factors that may affect cord blood IgE level and median cord blood IgE levels

Variable	Frequency (percent)	Median cord blood IgE level (Interquartile) IU/ml	*P*-value
Neonatal sex			0.553
Male	86 (47.5)	1.70 (4.03)	
Female	95 (52.5)	1.80 (5.00)	
Maternal age			0.796
< 30	123 (68)	1.80 (4.02)	
≥30	58 (32)	1.50 (5.55)	
Number of pregnancies			0.009
≤2	133 (73.5)	1.80 (4.01)	
>2	48 (26.5)	1.75 (6.75)	
Season of delivery			<0.001
Spring	47 (26)	2.00 (4.80)	
Summer	34 (19)	1.45(4.63)	
Autumn	54 (30)	1.20 (1.08)	
Winter	46 (25)	4.00 (6.65)	
Type of delivery			0.044
C/S	108 (60)	2.00 (5.93)	
NVD	73 (40)	1.40 (2.00)	
Allergic disorder during pregnancy			0.006
Present	88 (48.6)	2.00 (4.80)	
Absent	93 (51.4)	1.40 (4.17)	
Allergic disorder history before pregnancy			0.034
Present	48 (26.5)	2.55 (5.67)	
Absent	133 (73.5)	1.60 (3.58)	
Family history for allergy			0.754
Positive	40 (22)	1.90 (4.98)	
Negative	141 (78)	1.70 (4.00)	
Underlying cardiac, pulmonary or neurologic condition			0.645
Present	9 (5)	1.20 (5.10)	
Absent	172 (95)	1.80 (4.00)	
Drug history			0.0907
Positive	8 (4.4)	1.50 (7.85)	
Negative	173 (95.6)	1.80 (4.25)	

Multivariate analysis

After introducing all the assessed variables into the multivariate analysis regression model, number of previous pregnancies, type and season of delivery, history of allergy during pregnancy, maternal age and blood IgE level were variables which had a significant association with cord blood IgE levels and were predictive factors for the cord blood IgE level. There was a significant inverse relationship between maternal age, season of delivery and type of delivery and cord blood IgE levels. In other words these three variables had odds ratios less than one and had a protective role against an increase in cord blood IgE levels. Other factors including number of previous pregnancies, maternal blood IgE levels and the presence of allergic disorders during pregnancy had a significant direct relation with blood IgE levels. These three variables had odds ratios greater than one and so were independent predictors of cord blood IgE levels. The rtesults of regression analysis are presented in table 4.

Discussion

In this cross-sectional study we evaluated effect of variable factors on cord blood IgE levels. by univariate analysis, we found statistically significant associations between cord blood IgE levels and higher number of previous pregnancies, delivery during spring or winter, Ceasarean type of delivery, a history of allergy during pregnancy, but not the type of allergic disease or a history of allergic disease before pregnancy, were associated with elevated cord blood IgE levels. Maternal blood levels of IgE was also correlated with its level in cord blood. Neonate sex, maternal age, a family history of allergy, the presence of underlying medical conditions, a past drug history and exposure to known environmental allergens were not associated with elevated cord blood IgE levels. By multivariate analysis the part; number of pregnancies the mother has had, the type and season of delivery, a history of allergy during pregnancy, maternal age and blood IgE level were variables which had a significant association with cord blood IgE levels.

We could not find any association between neonatal gender and cord blood IgE levels. This finding is in contrast to results of previous studies that showed higher levels of IgE in the cord blood of male infants.[13,15-19] This association in so strong that some studies have proposed setting higher cut-off values in male babies for levels of cord blood IgE level.[17] We concluded that, despite the results of our study, neonatal male gender is associated with higher cord blood IgE levels. We could not determine why this association was been present in the results of our study.

In this study maternal age was not associated with cord blood IgE levels according to univariate analysis, but multivariate analysis indicated that higher maternal age was associated with lower cord blood IgE levels. Results regarding the effect of maternal age on cord blood IgE are controversial. In a study by Scirica et al.[15] the level of cord blood IgE was shown to be lower in older mothers. Two other studies have also indicated an insignificant decrease

DOI 10.12932/AP0234.31.2.2013

Table 2. The Frequency of allergic disorders before and during pregnancy in the study population

Specific type of allergic disorder	Before pregnancy Frequency (percent)	Mean cord blood IgE level (SD) (IU/ml)	Median cord blood IgE (IU/ml)	During pregnancy Frequency (percent)	Mean cord blood IgE level (SD) (IU/ml)
Asthma	2 (1)	6.65 (6.15)	6.65	5 (2.8)	7.06 (5.26)
Allergic rhinitis	19 (10.5)	4.71 (4.37)	2.80	30 (16.6)	3.97 (4.28)
Urticaria	10 (5.5)	3.43 (3.61)	2.50	18 (9.9)	3.75 (3.88)
Eczema	7 (4)	6.20 (5.71)	3.00	12 (6.6)	5.06 (4.87)
Food allergy	2 (1)	3.45 (2.89)	3.45	5 (2.8)	1.82 (1.10)
Drug allergy	2 (1)	7.80 (2.54)	7.80	1 (0.6)	16.50
More than one type of allergic disorder	5 (3)	2.04 (2.78)	0.56-7.00	17 (9.6)	3.84 (4.13)

in cord blood IgE as maternal age increases.[19,20] However, the results of another study by Kaan et al. indicated an opposite relationship between these two factors i.e. increase in maternal age was associated with an increase in neonatal cord blood IgE levels.[18] Based on the results of previous studies and our findings, it seems that the evidence is in favor of decrease in cord blood IgE level with increase in maternal age. However further studies in this area are needed.

The cord blood IgE level was shown to be elevated with increasing parity in our study. Some previous studies have shown reduced IgE levels with increasing birth order.[13,20,21] However the results of other studies[15,18,19] with stronger methodology, especially the one by Wegineka et al.[14] which specifically investigated this topic, suggest that there is no association between birth order and cord blood IgE levels. These studies propose that finding an association between these two factors might be the result of confounding factors or errors in methodology. These errors might have been ignored in our study. In conclusion; despite stronger evidence ofor the absence of an association between birth order and cord blood IgE levels, definite comment on this subject should be postponed untill results of further studies are available.

We found a seasonal variation in the level of cord blood IgE, with lowest values in autumn and the highest value in spring and winter. The results of most other studies investigating this topic are in agreement with our findings.[19,22,23] This seasonal variation may indicate the effect of environmental allergens on cord blood IgE levels. The effect of delivery route on the development of atopy later in neonates who have been delivered via Ceasarean section [24,25] while some others did not find such an association. [26,27] Previous studies investigating the association between cord blood IgE levels and delivery route did not find such an association.[15,19] We found a significantly higher level of IgE in cord blood of neonates delivered via Ceasarean section. This difference might be result of changes in intestinal flora, a marker of neonatal stress or both.[15] At this time, information on this part is not enough for coming to a conclusion.

Considering our results, by univariate analysis a positive history of allergic disorders before and during pregnancy, but not positive family history for such disorders, were associated with elevated cord blood IgE levels. No specific type of allergen could be found to be associated with elevated cord blood IgE levels. By multivariate regression analysisonly a positive history of allergic disorders during pregnancy was associated with elevated cord blood IgE levels.

There are many studies evaluating the effect of parental and familial history of allergy on cord blood IgE levels. However, few studies failed to find any association between cord blood IgE levels and a history of allergy in parents or other family members,[17] while many of them confirmed the presence of such a relationship, especially in the maternal side of family.[15,16,28] Although maternal smoking history is associated with cord blood IgE levels in some studies,[29-30] maternal smoking history is not associated with this level in many other studies.[16,19, 31-33] Data on the effect of other specific allergen types on cord blood IgE values are limited. In a study conducted by Sthernthal et al. evaluating the effects of interpersonal trauma on cord blood IgE levels, a significant association between cord blood IgE levels and exposure to cockroachs in the

DOI 10.12932/AP0234.31.2.2013

Table 3. The frequency and exposure to variable known environmental allergens, comparing two groups with and without exposure

Specific type of allergen	Frequency (percent)	Median cord blood IgE level (Interquartile) IU/ml	p-value
Cigarette smoking			0.316
Negative	113 (62.4)	1.50 (4.53)	
Positive	68 (37.6)	2.00 (4.38)	
Pets			0.963
Negative	158 (87.3)	1.80 (4.13)	
Positive	23 (12.7)	1.70 (5.00)	
Birds			0.291
Negative	162 (89.5)	1.70 (4.00)	
Positive	19 (10.5)	2.00 (6.80)	
Humid environment			0.124
Negative	134 (74)	1.95 (5.00)	
Positive	47 (26)	1.40 (2.03)	
Open kitchen			0.970
Negative	102 (56.4)	1.70 (4.00)	
Positive	79 (43.6)	1.80 (5.03)	
Inappropriate cleaning			0.185
Negative	136 (75.1)	1.85 (5.00)	
Positive	45 (24.9)	1.50 (2.44)	
Feather or wool pillow			0.730
Negative	57 (31.5)	1.90 (5.01)	
Positive	124 (68.5)	1.70 (4.00)	
Fluffy toy			0.180
Negative	84 (46.4)	1.30 (5.15)	
Positive	97 (53.6)	1.90 (3.90)	
Environmental pollutant			0.994
Negative	124 (68.5)	1.80 (4.90)	
Positive	57 (31.5)	1.70 (4.00)	
Canned foods			
Negative	144 (79.5)	1.80 (4.00)	
Positive	37 (20.5)	1.70 (5.08)	
Cockroach			0.906
Negative	113 (62.4)	1.70 (4.01)	
Positive	68 (37.6)	1.80 (5.00)	
Old building			0.989
Negative	114 (63)	1.80 (4.05)	
Positive	67 (37)	1.70 (5.00)	
Garden near house			0.675
Negative	111 (61.3)	1.70 (3.00)	
Positive	70 (38.7)	1.85 (5.05)	

home was identified. However, they could not find such an association in relation to exposure to house dust mite.[12] In the study by Lin et al. maternal sensitization to dog dander and carpets at home were risk factors for an increase in cord blood IgE levels. [16] Finally; we think that a positive history of allergy in mothers or maternal family members is associated with an increase in cord blood IgE levels. Results regarding effect of cigarette smoking are controversial. It may depend on many factors, such as the amount and interval of smoking and the predisposition of neonates. Information on other environmental allergens is limited and inconclusive. Both

Table 4. The results of linear regression analysis assessing the effect of various factors on cord blood IgE levels

Factor	β coefficient	SE*	t	*p*-value
Paraty	0.094	0.027	3.49	0.001
Maternal age	-0.018	0.006	-3.14	0.002
Type of delivery**	-0.169	0.052	-3.27	0.001
Maternal blood IgE level	0.002	< 0.001	4.82	<0.001
Presence of allergic disorders during pregnancy	0.153	0.052	2.92	0.004
Season of delivery***	-0.227	0.056	-4.09	<0.001

* SE: Standard Error ** cod 1 for C/S and code 0 for NVD *** code 1 for winter and code 0 otherwise

univariate and multivariate analysis found an association between cord blood and maternal blood IgE level in our study. Many previous studies investigating determinants of cord blood IgE level have found such an association.[13,18,19,33] Specifically, a study by Bonnelykkeet et al. investigated this subject. In addition to proving this relationship, this study showed that this association is the result of maternofetal transfer and in half of the cases with elevated cord blood IgE, signs of this kind of transfer were present.[34]

We tried to evaluate all factors likely to be relevantto cord blood IgE levels and this made our study less specific. A smaller sample size in comparison to similar previous studies was another weakness of our study.

In conclusion; among the evaluated factors, the presence of any kind of allergic disorders in the infant's mother or her family and elevated maternal blood IgE level are strong predictors of increased levels of cord blood IgE. Maternal age and smoking, neonatal gender, type of delivery, season of birth and number of pregnancies are probable predictors. Other evaluated factors are less likely to have any association.

Acknowledgment

The study was supported by a grant from Research Deputy at Semnan University of Medical Sciences. We would like to express our sincere gratitude to Farzan Institute for Research & Technology for technical assistance.

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DOI 10.12932/AP0234.31.2.2013

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DOI 10.12932/AP0234.31.2.2013