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Relationship of cord blood IgE with maternal, fetal, and environmental factors in the Chinese population

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Abstract
Introduction and objectives: Previous studies reported that history of pregnancy and delivery and family environment might influence cord blood IgE (CB-IgE) levels and development of allergies; however, the association between them is not well-established. This study aimed at investigating the IgE level in the newborn's umbilical cord blood and its relationship with maternal, fetal, and environmental factors.
Materials and methods: A total of 989 mothers and their infants were analyzed in this study. Mothers were given a questionnaire that had a series of questions to evaluate demographic information, maternal allergic status, and environmental exposures during pregnancy. Neonatal cord blood samples were taken at the same time for IgE assay.
Results: By univariate analysis, we found statistically significant correlations between CB-IgE levels and gender ($P = 0.000$) and delivery mode ($P = 0.017$). By multivariate analysis, gender was found to have a significant association with CB-IgE levels ($P = 0.001$). No significant difference was found between CB-IgE levels and antenatal complications, the season of birth, birth weight, gestational age, and household income ($P > 0.050$).
Conclusions: In this study, newborn gender was found to be a strong predictor of elevated CB-IgE. The delivery mode was a probable predictor.

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Introduction and objectives

Allergic diseases represent an important health problem worldwide and their prevalence and severity have been increasing in recent decades, leading to profound negative effects on patients' quality of life and becoming a major public health burden in children.[1-3] To prevent these common disorders and reduce the economic burden, the identification of prognostic markers pointing to increased risk of allergy development is of importance.[4]

Cord blood is an easily accessible biological material and has been used for searching prognostic markers for allergies, such as regulatory T cells, gene expression of cytokines, and IgE levels in cord blood. Since the 1970s, cord blood IgE (CB-IgE) has been investigated as a predictive marker for allergic diseases and gained much attention.[4-6] Nowadays, although various studies demonstrated that elevated CB-IgE is affected by some different factors including maternal, paternal, placenta, and fetal characteristics, findings on each factor have been inconclusive and discordant.[7-10] And results remain difficult to compare because of the influence of genetics and different ethnic groups on the CB-IgE.[11,12] Regarding the scarcity of studies about CB-IgE in Chinese Han newborns, more studies are needed to be performed on different populations and situations.

This study aimed at investigating the CB-IgE level in Han newborns in Shanghai China, to specify the relationship between CB-IgE level and maternal, fetal, and environmental factors.

Materials and methods

Study population

In this study, 989 Chinese Han children were enrolled from the Shanghai Allergy Cohort, which was a prospective birth cohort with infants recruited between 2012 and 2013 at two large tertiary hospitals in Shanghai, Xinhua Hospital and the International Peace Maternity & Child Health Hospital. All participants provided written consent form before enrolling. The study was approved by the Ethics Committee of Xinhua Hospital and the International Peace Maternity & Child Health Hospital, and conducted according to the principles in the Declaration of Helsinki.

Epidemiologic information collection

A questionnaire was used to obtain information about newborns (including season of birth, birth weight, gestational age, gender, and delivery mode), mothers (including antenatal complications, maternal atopy, parity, previous pregnancy, maternal age, maternal prepregnancy BMI, and maternal education), and environmental factors [including household income, prenatal pet, and environmental tobacco smoke (ETS) exposures]. Antenatal complications included pregnancy hypertension, diabetes, infection, or intrauterine growth retardation. Maternal atopy was referred to those mothers who had asthma, allergic rhinitis, or atopic dermatitis along with detectable specific IgE. Prenatal pet exposure was defined as keeping cats or dogs at home during pregnancy. ETS included secondhand smoke or active smoking.

CB-IgE measurement

We used the ImmunoCAP Total IgE Low Range Assay to determine CB-IgE levels. Elevation of CB-IgE levels was cut-off at ≥0.5 kU/L.

Statistical analysis

All data were entered into the statistical software package SPSS version 25.0 for Windows. We first determined the percentiles of CB-IgE and the prevalence of elevated CB-IgE in the newborns. Then, we used univariate analysis to examine the correlations of CB-IgE levels with different groups of related factors and performed a multivariable analysis to estimate the independent relationship between CB-IgE levels and the analyzed related factors after adjusting for potential confounders. *P*-Values ≤0.05 were considered statistically significant.

Ethical approval

The study was approved by the Ethics Committee of Xinhua Hospital and the International Peace Maternity & Child Health Hospital, and conducted according to the principles in the Declaration of Helsinki.

Results

CB-IgE levels of the study subjects

This study was performed on 989 mother–newborn pairs. The distribution of CB-IgE level in newborns is presented in Table 1. Data show the quartile values (Q1 = 0.11 kU/L, Q2 = 0.24 kU/L, Q3 = 0.54 kU/L), minimum (0.01 kU/L), and maximum (75.60 kU/L) of CB-IgE. Participants had a mean CB-IgE concentration of 0.94±3.96 kU/L. Overall, 27.10% of Shanghai newborns had CB-IgE levels ≥0.5 kU/L.

Correlations between CB-IgE levels and epidemiologic factors

Table 2 shows that newborn gender and delivery mode were found to have a significant correlation with CB-IgE

Table 1 CB-IgE levels of the study subjects (n = 989).

	CB-IgE
Q1 (kU/L)	0.11
Q2 (kU/L)	0.24
Q3 (kU/L)	0.54
Min (kU/L)	0.01
Max (kU/L)	75.60
Mean ± SD (kU/L)	0.94 ± 3.96
The prevalence of elevated CB-IgE % (CB-IgE ≥ 0.5 (kU/L))	27.10

CB-IgE: cord blood IgE.

Table 2 Correlations between CB-IgE levels and epidemiologic factors.

CB-IgE	N	Median	Interquartile range	P-value[a]
Newborn gender				
Female	466	0.20	0.34	0.000*
Male	499	0.28	0.54	
Delivery mode				
Vaginal	229	0.21	0.32	0.017*
Cesarean section	737	0.24	0.47	
Antenatal complications[b]				
No	763	0.23	0.41	0.458
Yes	177	0.25	0.54	
Maternal atopy[c]				
No	824	0.23	0.41	0.098
Yes	129	0.29	0.56	
Parity				
None	868	0.24	0.43	0.754
≥1	98	0.21	0.42	
Previous pregnancy				
None	629	0.24	0.42	0.555
≥1	337	0.23	0.45	
Prenatal pet exposure				
No	857	0.23	0.43	0.830
Yes	105	0.27	0.45	
Prenatal ETS exposure				
No	577	0.24	0.43	0.789
Yes	387	0.23	0.45	
Birth weight (g)				
<2500	24	0.24	0.88	0.966
2500–4000	857	0.23	0.42	
≥4000	85	0.22	0.42	
Gestational age (weeks)				
<37	33	0.15	0.32	0.080
37–39	686	0.24	0.49	
≥40	247	0.22	0.36	
Season of birth				
Summer (Jun–Aug)	170	0.25	0.44	0.287
Autumn (Sep–Nov)	451	0.26	0.43	
Winter (Dec–Feb)	337	0.22	0.39	
Maternal education				
Middle school or lower	28	0.18	0.24	0.524
High school	112	0.22	0.38	
College or higher	825	0.24	0.44	
Maternal age (years)				
<25	62	0.25	0.60	0.866
25–29	500	0.22	0.39	
30–34	325	0.25	0.50	
≥35	77	0.21	0.64	
Maternal prepregnancy BMI (kg/m^2)				
<18.5	150	0.23	0.51	0.390
18.5–24.9	694	0.23	0.41	
25–29.9	92	0.29	0.76	
≥30	26	0.30	0.49	
Household income				
<100K	273	0.25	0.45	0.524
≥100K	540	0.22	0.41	
Unknown	176	0.24	0.42	

CB-IgE: cord blood IgE; ETS: environmental tobacco smoke.
[a]*P*-values for Mann–Whitney U-test or Kruskal–Wallis H-test.
[b]Antenatal complications included pregnancy hypertension, diabetes, infection, or intrauterine growth retardation.
[c]Maternal atopy was referred to those mothers who had asthma, allergic rhinitis, or atopic dermatitis along with detectable specific IgE.
*$P \leq 0.05$.

Table 3 Correlations between CB-IgE elevation and epidemiologic factors.

Variable	Elevated CB-IgE, n (%)	Crude OR	95% CI	P-value[a]	aOR	95% CI	*P*-value[a]
Newborn gender							
B Female	105 (22.5)	1.000			1.000		
Male	156 (31.3)	1.564	(1.172,2.086)	0.002*	1.642	(1.212, 2.224)	0.001*
Delivery mode							
Vaginal	50 (21.8)	1.000			1.000		
Cesarean section	212 (28.8)	1.446	(1.017,2.055)	0.040*	1.342	(0.914,1.969)	0.133
Antenatal complications[b]							
No	206 (27.0)	1.000			1.000		
Yes	51 (28.8)	1.094	(0.762,1.572)	0.626	1.064	(0.718,1.576)	0.757
Maternal atopy[c]							
No	219 (26.6)	1.000			1.000		
Yes	41 (31.8)	1.287	(0.861,1.923)	0.218	1.217	(0.793,1.868)	0.369
Parity							
None	235 (27.1)	1.000			1.000		
≥1	27 (27.6)	1.024	(0.642,1.635)	0.920	1.013	(0.582,1.763)	0.964
Previous pregnancy							
None	169 (26.9)	1.000			1.000		
≥1	93 (27.6)	1.037	(0.771,1.396)	0.808	1.001	(0.699,1.433)	0.995
Prenatal pet exposure							
No	234 (27.3)	1.000			1.000		
Yes	28 (26.7)	0.968	(0.612,1.530)	0.890	1.077	(0.662,1.752)	0.765
Prenatal ETS exposure							
No	158 (27.4)	1.000			1.000		
Yes	105 (27.1)	0.987	(0.739,1.319)	0.932	0.976	(0.711,1.341)	0.882
Birth weight (g)							
<2500	8 (33.3)	1.000			1.000		
2500–4000	231 (27.0)	0.738	(0.312,1.748)	0.490	0.427	(0.132,1.374)	0.154
≥4000	23 (27.1)	0.742	(0.280,1.966)	0.548	0.378	(0.104,1.364)	0.137
Gestational age (weeks)							
<37	7 (21.2)	1.000			1.000		
37–39	196 (28.6)	1.486	(0.634,3.479)	0.362	2.170	(0.686,6.862)	0.187
≥40	59 (23.9)	1.166	(0.481,2.823)	0.734	1.891	(0.571,6.261)	0.297
Season of birth							
Summer (Jun–Aug)	46 (27.1)	1.000			1.000		
Autumn (Sep–Nov)	131 (29.0)	1.104	(0.744,1.638)	0.625	1.079	(0.697,1.673)	0.732
Winter (Dec–Feb)	85 (25.2)	0.909	(0.598,1.381)	0.656	0.882	(0.556,1.399)	0.593
Maternal education							
Middle school or lower	6 (21.4)	1.000			1.000		
High school	27 (24.1)	1.165	(0.428,3.170)	0.765	1.125	(0.396,3.194)	0.826
College or higher	230 (27.9)	1.417	(0.567,3.540)	0.455	1.291	(0.489,3.407)	0.606
Maternal age (years)							
<25	17 (27.4)	1.000			1.000		
25–29	128 (25.6)	0.911	(0.503,1.648)	0.758	0.891	(0.480,1.652)	0.713
30–34	92 (28.3)	1.045	(0.569,1.920)	0.887	0.997	(0.526,1.891)	0.993
≥35	24 (31.2)	1.199	(0.573,2.506)	0.630	1.156	(0.525,2.545)	0.718
Maternal prepregnancy BMI (kg/m^2)							
<18.5	42 (28.0)	1.000			1.000		
18.5–24.9	182 (26.2)	0.914	(0.616,1.356)	0.655	0.866	(0.572,1.310)	0.495
25–29.9	29 (31.5)	1.184	(0.672,2.085)	0.559	1.134	(0.622,2.065)	0.682
≥30	9 (34.6)	1.361	(0.563,3.292)	0.494	1.435	(0.550,3.746)	0.461
Household income							
<100K	74 (27.1)	1.000			1.000		
≥100K	146 (27.0)	0.997	(0.718,1.383)	0.983	0.922	(0.635,1.337)	0.667
Unknown	48 (27.3)	1.008	(0.659,1.544)	0.969	1.051	(0.659,1.675)	0.835

[a] *P*-values for binary logistic regression.
*$P \leq 0.05$.

levels ($P < 0.05$). Male gender and cesarean section were associated with higher CB-IgE levels.

Correlations between CB-IgE elevation and epidemiologic factors

As shown in Table 3, after adjusting for multiple newborn and maternal factors, newborn gender remained associated with CB-IgE elevation. Male was at a higher risk of elevated CB-IgE (OR = 1.642, $P = 0.001$).

Discussion

In this study, we found that CB-IgE levels were not normally distributed and that most CB-IgE levels were below 0.5 kU/L, as stated in previous reports.[9] A total of 268 (27.10%) infants had elevated CB-IgE (≥0.5 kU/L), which was similar to Ferguson et al.[13] (19.30%) and Chieh-An Liu et al.'s (23.70%) reports.[14] Most studies have shown that elevated CB-IgE levels have a role in the future development of allergic diseases.[4,5,15–18] For example, elevated CB-IgE has been a useful measure of subsequent risk of food allergy/urticaria at 12 months[19] and a cohort study showed that the risk of allergy development at the age of 4 (OR = 2.92) and 10 (OR = 1.73) was significantly correlated with increased IgE level in newborn umbilical cord blood.[20] Hence, CB-IgE level is believed to be correlated with allergic diseases. Then we evaluated the effect of variable factors on CB-IgE levels.

Our study showed that newborn gender was positively correlated with CB-IgE levels. Consistent with our findings, Petrovičová et al.,[21] De Amici et al.,[8] Iraj Mohammadzadeh et al.,[16] Scirica et al.,[22] and Chien-Han Chen et al.[23] also found that the CB-IgE level was higher in male newborns, possibly because of interaction between interleukin-13 (IL-13) and CB-IgE, which is modified by male sex.[24] And CB-IgE levels might reflect early differences in immune system development and function between boys and girls that contribute to the known predominance of asthma and related symptoms among boys rather than girls before puberty.[25] Based on the results of previous studies and our findings, it seems that gender is an important factor concerning the IgE level.

In this study, the univariate analysis indicated that cesarean section was associated with higher CB-IgE levels, which is consistent with current results.[7,21,26,27] The reason may be that cesarean section could induce neonatal stress and changes in intestinal flora.[22]

The present study has some limitations. Firstly, we did not collect blood samples from the mothers and could not measure maternal IgE levels; however, a strong positive association between maternal IgE level and CB-IgE level has been well proven.[11,16] Secondly, we did not measure IgA levels in the cord blood as a marker of maternal blood contamination, but previous studies using cord blood IgA levels as an indicator of maternal contamination have reported a very low rate of contamination.[28,29] Thirdly, subjects in this study should be followed up to reveal the link between CB-IgE elevation in boys and future allergy development. And the underlying mechanisms need to be explored in our future studies.

In conclusion, in this study, newborn gender was found to be a strong predictor of elevated CB-IgE. The delivery mode was a probable predictor.

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Conflicts of interest

The authors declare no conflicts of interest.

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