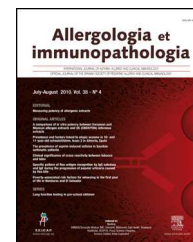


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ORIGINAL ARTICLE

Cord IgE and ECP levels of Malay neonates

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Abstract

Background: Cord IgE and ECP levels are major atopic markers implicated in early childhood allergy development. Most epidemiological studies to date have not utilised current technology to establish baseline cord IgE levels, further aggravated by lack of data in this region. This study also attempts to identify a relationship between cord IgE and ECP levels as a mean to improve sensitivity for early prediction of atopy.

Methods: A total of 3183 cord blood IgE including 44 cord ECP samples of term neonates from Malay parentage were recruited. Total IgE and ECP levels were determined by ImmunoCAP and fluoroimmunoassay, respectively.

Results: Cord IgE geometric mean was 0.15 kU/L. Males had higher IgE geometric mean than females (0.17 vs. 0.13). IgE values between 17 pair of twins was not significant ($p=0.169$). Frequency of males (29.9%) in >0.9 kU/L IgE category was higher than females (26.1%). In the <0.35 kU/L category, females had a higher frequency (44.8%) than males (39.1%). Males had significantly ($p=0.023$) higher IgE level than females. November and February had the highest mean and median cord IgE level whereas October and December were the lowest, respectively. IgE level across months was not significant ($p=0.234$). Cord ECP mean was 5.21 g/L and median was 3.75 μ g/L. There was no significant correlation ($p=0.513$; $r=-0.101$) between cord blood ECP and IgE levels.

Conclusion: Cord blood IgE level of Malay male neonates was significantly higher than females. These results do not support cord ECP as plausible adjunct parameter to IgE for early atopic detection.

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Introduction

The incidence of allergic conditions in developed nations has increased dramatically in recent decades. The social and economic burden of atopic diseases has called for early detection methods in anticipation of timely intervention and

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improved outcome. Serum IgE levels up to ages 9 months,¹ 18 months² and 11 years to 21 years^{3,4} correlated well with cord blood IgE level; an indication that influence on IgE levels occurs prior to birth. Ethnicity was another determining factor.^{5,6}

Elevated cord IgE level was associated with occurrence of atopy in early childhood.^{7,8} Currently no consensus on IgE cut-off level has been agreed upon, however values above 0.9 kU/L placed an increased risk for atopic manifestation by age seven years.^{9,10} Levels above 0.7 kU/L associated with development of atopic dermatitis by six months.¹¹ In infants, the cut-off value of 0.5 kU/L had significant association with atopic dermatitis at ages one, three and six months but only at three months for 0.9 kU/L.¹² Neonates with IgE above 0.5 kU/L had increased urticaria related to food allergy by 12 months,¹³ atopic dermatitis by two years,¹⁴ aeroallergen sensitisation by ages 4–10 years, wheezing by seven years and asthma by 10 years.^{4,9,15} An upper limit of 0.3 kU/L was a good predictor for development of atopic dermatitis by 18 months¹⁶ and on comparison to 0.5 kU/L, was found to be a better predictor for development of allergic conditions by age five years.² Cord serum IgE varies seasonally and the risk for atopic disease doubles by seven years of age in children with high cord IgE in May as compared to November.¹⁷

Cord IgE despite being a valuable marker for allergy development, still shows conflicting results.^{18,19} The predictive value of cord blood IgE exclusively as a measure for atopy currently remains too low to be recommended as a screening test. Eosinophilic Cationic Protein (ECP), a potent inflammatory marker during allergic reaction, positively correlated with atopic disease activity.²⁰ ECP was elevated in nasal washes of neonates with parental history of allergy²¹ and development of wheezing by six months.²² Serum ECP above 20 µg/L predicted an asthma outcome in wheezing infants.²³ When cord serum ECP exceeded 18 µU/L, newborns were at greater risk for atopic manifestation by three years.²⁴ Hence, ECP may prove to be a likely consideration in association with IgE for improved prediction of atopy.

The prevalence of asthma (10%), rhinitis (11%) and eczema (8.5%) are common among Malay urban children.²⁵ Malaysia being an advanced developing country may face new challenges of allergic diseases in its pursuit for industrialisation. Most epidemiological studies to date have used varying techniques with little data utilising current technology. We hope to establish baseline IgE level in Malay neonates for future reference and to determine the correlation between cord IgE and ECP levels.

Materials and methods

Cord blood

The study was approved by the ethical review board at University of Malaya and consent obtained from participants. A total of 3183 cord blood samples of term neonates of Malay parentage (including 17 twins) were randomly collected soon after delivery for total IgE analysis. Samples with elevated IgA levels believed to be contaminated were excluded. A consecutive series of 44 Malay cord blood samples for ECP levels was evaluated.

Quantification of total IgE and ECP levels

Cord blood was centrifuged and the serum then used for the assays. Total IgE and ECP levels were determined via ImmunoCAP and fluoroimmunoassay method, respectively, (Pharmacia Upjohn, Sweden) as described by the manufacturer. The IgE levels were then stratified into three categories based on cut-off levels: <0.35 kU/L, 0.35–0.89 kU/L and >0.9 kU/L.

Statistical analysis

A scatter plot graph was used to observe the distribution pattern of IgE level in the study population and to assess any skewing tendency to determine the best parameter for central distribution of data. For calculation of the geometric mean, values below the detection level were assigned 0.01 kU/L. The chi-square test (χ^2) significance of results for cord blood total IgE risk group in relation to gender was calculated using the 2-tailed Fisher's test. ANOVA non-parametric test followed by a post hoc test was used to determine correlation of IgE level with month. Wilcoxon signed-rank test was used to determine IgE correlation between the pair of twins. Association of ECP with IgE level was calculated using Spearman's Correlation Coefficient. The level of significance used throughout the statistical analysis was $p < 0.05$ (5%). SPSS (version 18, Chicago, USA) was used for all calculations.

Results

A total of 3183 Malay newborns, consisting of 1664 males and 1519 females were investigated for cord blood IgE levels (Table 1). As the IgE level in the population was skewed based on scatter plot, central distribution of data was best represented by the geometric mean of 0.15 kU/L for Malays. When stratified by gender, males had a higher IgE geometric mean (0.17 vs. 0.13), mean (1.16 vs. 0.98) and median (0.47 vs. 0.41) compared to females. IgE values of the 17 twin pairs did not differ significantly between corresponding sets ($p = 0.169$; data not shown).

When compared to females, males displayed significant difference (Table 2) in the higher IgE category ($p = 0.023$). Frequency of males (29.9%) in the >0.9 kU/L category was higher than females (26.1%). Conversely in the lower IgE category of <0.35 kU/L, female newborns had a higher frequency (44.8%) than males (39.1%). Frequency in the 0.35–0.9 kU/L category for males and females was similar at 30.9% and 29.1%, respectively.

November and February had the highest cord IgE mean and median level, respectively; while mean and median was lowest in October and December, respectively (Table 3). However levels between the months of the year was not significant ($p = 0.234$).

Table 4 shows the mean and median value of cord ECP as 5.21 µg/L and 3.75 µg/L, respectively. ECP values in males were lower than females, both for the mean (3.96 vs. 6.47 µg/L) and median (3.09 vs 4.49 µg/L). Cord ECP median of 3.89 µg/L in the IgE >0.9 kU/L category was lower when compared to IgE level <0.35 kU/L category at 5.78 µg/L. There was no significant correlation (Spearman's correlation

Table 1 Cord Blood total IgE levels in Malay newborns.

Ethnic/Gender	Total Number of Newborns (n=3183)	Cord Blood IgE Level (kU/L)			
		Mean	Standard Deviation	Geometric Mean	Median
Malay	3183	1.04	3.64	0.15	0.44
Malay Male	1664	1.13	3.72	0.17	0.47
Malay Female	1519	0.94	3.55	0.13	0.41

Table 2 Cord Blood total IgE levels risk groups of Malay newborns.

Ethnic/Gender	Number of Newborns	Cord Blood Total IgE Level			P-value
		<0.35 kU/L	0.35–0.89 kU/L	0.9 kU/L	
Malay	3183	1331 (41.8%)	957 (30.1%)	895 (28.1%)	0.023
Malay Male (S)	1664 (52.2%)	651 (39.1%)	515 (30.9%)	498 (29.9%)	
Malay Female	1519 (47.7%)	680 (44.8%)	442 (29.1%)	397 (26.1%)	

Note: P-value was based on Fisher's 2-tailed test between Malay gender and total cord blood IgE level.

Table 3 Cord Serum IgE level of Malay newborns across the months of the year.

Months	N=3183	Mean	Median	P-value
January	258	1.03	0.47	0.234 (NS)
February	251	1.17	0.61	
March	240	0.92	0.54	
April	230	1.08	0.49	
May	352	1.05	0.44	
June	354	1.12	0.44	
July	245	0.92	0.40	
August	220	1.13	0.41	
September	262	0.78	0.40	
October	300	0.77	0.38	
November	239	1.72	0.45	
December	232	0.79	0.35	

coefficient, $p=0.513$; $r=-0.101$) between cord blood ECP and total IgE levels (Fig. 1).

Discussion

Elevated serum IgE is a hallmark of atopic disease. Hence, cord IgE offers a promising screening tool in high risk individuals as an early intervention for primary prevention of allergy. Cord IgE level has been shown to be genetically regulated,²⁶ suggesting IgE control begins early in utero. IgE level in an unselected twin study model was largely found to be heritable from birth till nine years of age.²⁷ Not surprisingly, IgE levels amongst twin pairs in our population carried a high degree of correlation.

The geometric mean of cord IgE in Malays was comparable to previous reports ranging 0.11–0.17 kU/L,^{19,28,29} however lower than other Asian populations including Chinese (0.27 kU/L)³⁰ and Arabs (0.28 kU/L)³¹ of smaller study size using varying test methods. Boys had higher cord IgE mean than girls which was significant for the IgE category, as noted

Table 4 Cord serum ECP levels in relation to cord serum IgE level of Malay newborns.

	Number of Newborns	Cord Blood ECP Levels	
		Mean ($\mu\text{g/L}$)	Median ($\mu\text{g/L}$)
Gender			
Male	22 (50.0%)	3.96 \pm 4.66	3.09
Female	22 (50.0%)	6.47 \pm 5.81	4.49
Cord Serum IgE Level			
IgE <0.35 kU/L	8 (18.2%)	7.23 \pm 5.25	5.78
IgE 0.35–0.89 kU/L	13 (29.5%)	5.78 \pm 6.64	2.97
IgE >0.9 kU/L	23 (52.3%)	4.19 \pm 4.53	3.89
Total	44 (100%)	5.21 \pm 5.36	3.75

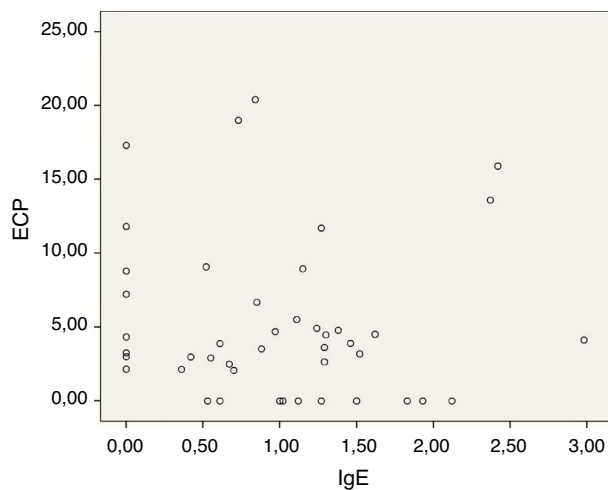


Figure 1 Scatter plot of cord blood ECP vs. IgE level in Malay neonates. There was no significance on Spearman's correlation coefficient ($p=0.513$; $r=-0.101$).

in other studies.^{6,29,32} Young boys tend to have higher IgE level than girls.³³ The reason for gender discrepancy remains uncertain and yet to be determined if boys are indeed at increased risk for allergy or a separate cut-off level is warranted for each gender. Interestingly, Malaysian school going boys were reported to have higher asthma rates than girls.³⁴

A significant cyclic distribution of cord blood IgE values peaking in spring²⁷ and with a trough in autumn has been reported.^{1,29,35} However a multicentre study reported the highest and lowest values to be inconsistent at each centre.²⁸ No significant seasonal variability was noted between month of birth and IgE level in our population, perhaps due to constant equatorial weather throughout the year, contrasting with cyclical trends of other populations in a temperate climate.³⁶ To the best of our knowledge this is the first report from the tropics.

Serum ECP is an important biomarker of eosinophil activation and degranulation. Neonates carried a 16-fold increased risk of atopy when cord ECP $>18 \mu\text{U/L}$ and positive family history of atopy but only 1.4 in the absence of family history.²⁴ This indicates that elevated ECP solely may not be a highly sensitive predictor for atopy and therefore should be evaluated in association with other biomarkers. Gender discrepancy of ECP remains uncertain as levels have not been clearly defined. In this study, no correlation between cord IgE and ECP levels was found. Whilst significant elevated IgE was detected in allergic rhinitis children, no concurrent ECP difference was noted between atopic and asymptomatic children.³⁷ Cord ECP level was not significantly different irrespective of family history of allergy.³⁸ Furthermore, no correlation between serum IgE and ECP levels in atopic dermatitis, asthmatic children³⁹ and drug eruption or urticaria⁴⁰ has been demonstrated.

In summary, we conclude that cord blood IgE level of Malay male neonates was significantly higher than females. Due to lack of correlation between cord ECP and IgE levels, our results do not support the plausible role of ECP as an adjunct parameter for the purpose of early atopic detection.

Ethical disclosures

Protection of human subjects and animals in research.

The authors declare that the procedures followed were in accordance with the regulations of the responsible Clinical Research Ethics Committee and in accordance with those of the World Medical Association and the Helsinki Declaration.

Patients' data protection. Confidentiality of data. The authors declare that no patient data appears in this article.

Right to privacy and informed consent. The authors declare that no patient data appears in this article.

Conflict of interest

The authors have no conflict of interest to declare.

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