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Cord and blood levels of newborn IgE: Correlation, role and influence of maternal IgE

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ABSTRACT

The role of cord blood immunoglobulin E (IgE) levels in predicting the development of atopy has been widely investigated. The aim of the study was to evaluate the correlation between serum and cord blood total IgE in newborns and the possible influence of the atopic status of the mother on them. It was also investigated the possible role of gestational age on neonatal total IgE levels. We considered 763 deliveries, 724 $\geq$ 37 weeks of gestation and 39 < 37 weeks of gestation. 14% of mothers (13.7% at term, 15.4% preterm) showed high total IgE levels. The results showed a significant correlation between serum and cord IgE levels both in preterm and term newborns. The data revealed also that mother's total IgE levels affect both neonatal serum and cord total IgE levels. For the latter we also found child gender as an additional independent predictor. On the contrary total IgE levels are not affected by gestational age. Clinical limitations of total IgE is known but their determination can be useful to define atopy and to suggest follow-up of the children.

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1. Introduction

In the last two decades the prevalence of atopic disorders in children has dramatically increased worldwide. The reasons are multifactorial: genetic inheritance, fetal sensitization, exposure to house dust mites and air pollutants (Asher and Weiland, 1998; ISAAC, 1998; Sly, 1999).

Sensitization to aeroallergens can occur as early as in utero, and the role of cord blood immunoglobulin E (IgE) levels in predicting the development of atopy has been widely investigated (Piccinni et al., 1993).

IgE evaluation in cord blood samples provides more information on the allergic status of the newborn as high IgE titers are discovered when maternal values are greater than 100kU/L (Shah and Bapat, 2006; Michel et al., 1980; Oryszczyn et al., 1999). Although the true relationship between serum total IgE levels at birth and total IgE of the mother is controversial, several studies have evaluated this issue (Shah and Bapat, 2006; Kjellman and Johansson,

1976; Businco et al., 1983; De Amici et al., 2008) to discern the true predictive value of total IgE in newborns for the development of asthma, allergic rhinitis or atopic dermatitis at the age of 12–18 months, or even at the age of 11 years or even in adulthood (Zetterstrom and Johansson, 1981; Edenharter et al., 1998; Hansen et al., 1992; Croner and Kjellman, 1990; Nissen et al., 2015).

The aim of the study was to detect the correlation between total IgE serum and cord blood levels and the possible influence of atopic mothers on neonatal total IgE levels and if there were differences based on gestational age.

2. Materials and methods

2.1. Studied population

During the period between April 2009 and April 2013, 763 healthy women with a physiologic pregnancy and normal delivery were enrolled in a tertiary referral center.

The IRB approved the study and all women gave written informed consent prior to enrolment. All pregnancy outcomes were obtained from the main delivery suite database and checked reviewing individual patient records.

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Term delivery was defined as ≥ 37 weeks of gestation (724 cases). Preterm delivery was defined as delivery < 37 weeks of gestation (39 cases). 14% resulted atopic (13.7% at term, 15.4% preterm).

Among term deliveries, maternal IgE and neonatal cord blood IgE were available in 680 cases (365 Male and 315 Female), maternal IgE and neonatal serum IgE were available in 722 cases (388 Male and 334 Female), while maternal IgE and both neonatal determinations were available in 95 cases (56 Male and 39 Female). For all the preterm deliveries (21 Male and 18 Female), maternal IgE and both neonatal determinations were available.

2.2. Sample methodology

Blood samples (5 ml) collected into a non-heparinized tube, were clotted and centrifuged. Maternal samples were routinely obtained at antenatal clinics; neonatal samples were obtained at two time points: at birth directly from the umbilical cord and one week later as a routine neonatal screening.

Total serum IgE were measured by a fluorescent immunoassay (ThermoFisher; Uppsala, Sweden) according to the manufacturer's instructions and for infants a low-range anti-IgE antibody was used. The IgE measurement range was $2 \div 200$ kU/L for mothers and $0.35 \div 100$ kU/L for infants. According to the age range in our sample (21–41 years) maternal IgE levels were considered normal when values were < 260 kU/L, otherwise they were considered positive. In neonates, cut-off values for IgE were fixed at 0.35 kU/L (De Amici et al., 2008; Zetterstrom and Johansson, 1981).

2.3. Statistical analysis

Since we had several cases with IgE values under the threshold (i.e. < 0.35 kU/L), which were not numerically quantified, we sampled, for each of them, a value between 0 and 0.349 from a uniform distribution. This allowed using statistical tests avoiding problems due to the presence of ties.

For the purposes of this study, statistical analysis was performed only in cases who fulfilled the following criteria: availability of Maternal IgE and neonatal IgE titer at birth (cord blood sampling) and/or within one week of gestational age (serum sampling).

Frequency (contingency) tables were used to analyze the data and Chi-Square tests were performed for unadjusted comparisons. The Fisher test was used when expected counts in the table cells were less than 5. The correlation between serum IgE and cord blood IgE was evaluated through Spearman correlation analysis. In addition, the non-parametric Kruskal Wallis test was used to compare samples of total serum IgE and cord blood IgE, according to gestational age. The non-parametric Wilcoxon's test for paired samples was used to compare values of serum IgE and cord blood IgE.

Multivariate analysis of dichotomous effects were carried out by multiple logistic regression to analyze which factors, if any, were independent predictors of neonatal serum IgE and cord blood IgE.

3. Results

Table 1(a and b) shows that the difference between the percentage of positive serum IgE in term and preterm infants is higher than in cord samples, even if, in both samples, this difference is not statistically significant (Table 1a: $X^2 = 0.549$, $p = 0.45$; Table 1b: $X^2 = 0.1$, $p = 0.70$).

Correlation between IgE serum and cord blood levels was strong both in term neonates (Fig. 1A) and preterm ones (Fig. 1B). This result is confirmed using dichotomized values: term newborns ($X^2 = 395.42$, $p < 0.000000001$) preterm ones ($X^2 = 24.74$, $p = 0.000000656$) (Table 2a, b).

When the difference between serum IgE and cord blood IgE was analyzed, the results were statistically significant only in the “term

Table 1

(a) Serum IgE levels in term and preterm infant. (b) Cord blood IgE levels in term and preterm infant.

(a)			
Serum IgE (n°) Infants	Term (n.)	Pre Term (n.)	Total (n.)
Negative	545 (75,5%)	32 (82%)	577
Positive	177 (24,5%)	7 (18%)	184

(b)			
Cord blood	Infants		Total (n.)
	Term (n.)	Pre Term (n.)	
Negative	480 (71%)	29 (74%)	509
Positive	200 (29%)	10 (26%)	210

Positive $> 0,35$ KU/L.

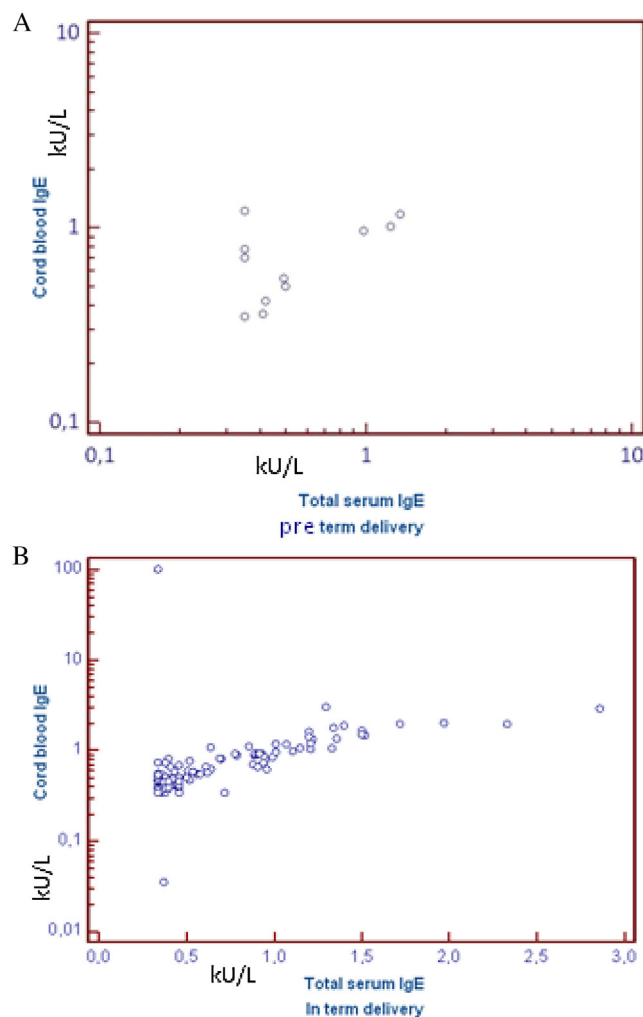


Fig. 1. Correlation between total serum IgE and cord blood IgE in term delivery (Fig. 1a) and in preterm delivery (Fig. 1b).

delivery” group ($p = 0.0001$), that showed higher cord blood IgE values. For the group “preterm delivery” no difference was found ($p > 0.05$). Group “term delivery”, with respect to preterm delivery, showed higher value of cord blood IgE (0.84 ± 4.95 KU/l vs 0.32 ± 0.31) and serum IgE (0.45 ± 1.41 KU/l vs 0.25 ± 0.3), but this difference was not significant ($p = 0.71$).

Multiple logistic regression analysis was carried out to examine which factors were important in determining positive values of neonatal serum IgE and cord blood IgE levels (Table 3).

Table 2

(a) Correlation between serum and cord blood IgE levels in term newborns. (b) Correlation between serum and cord blood IgE levels in preterm newborns.

(a)	IgE Cord blood (n°-%)		Total (n°)
	negative	positive	
Serum IgE (n°)			
Negative	462 (97%)	49 (24.5%)	511
Positive	16 (3%)	151 (75.5%)	167

(b)	IgE Cord blood (n°-%)		Total (n°)
	negative	positive	
Serum IgE (n°)			
Negative	29 (100%)	3 (30%)	32
Positive	0	7 (70%)	7

positive > = 0,35 KU/l.

Table 3

Multiple logistic regression analysis to examine which factors were important in determining the positivity of neonatal serum IgE and cord blood IgE.

Neonatal Serum Samples			
Variable	Odds Ratio	95% CI for Odds Ratio	p-value
Gender	0.9312	0.6649–1.3042	0.6784
Maternal IgE	2.2289	1.4399–3.4503	0.0003
Neonatal Cord Samples			
Gender	0.6893	0.4931–0.9635	0.0295
Maternal IgE	3.6336	2.3327–5.6600	<0.0001

Positive maternal IgE contributed significantly to the positivity of neonatal serum IgE ($p = 0.0003$) and cord blood IgE ($p < 0.0001$). No other variables did reach statistical significance except from gender which had a significant contribution on cord blood IgE ($p = 0.0295$).

Analysis of neonatal IgE serum and cord blood levels by week of gestation has not shown any significant time trend (Table 4).

4. Discussion

Most studies in the literature focus on the value of fetal IgE levels in umbilical cord, and on its correlation with maternal/parental atopic disease and the environment (Liu et al., 2003; Scirica et al., 2007; Shirakawa et al., 1997).

To date, to the best of our knowledge, this is the first study that correlates maternal gestational age and serum IgE within the first seven days of life (Meulenbroek and Knippels, 2015).

Despite recent advances in understanding the pathophysiology of atopic diseases, the precise developmental and immunological pathways remain poorly understood.

Little is known about factors that influence cord blood IgE levels in newborns at risk for atopy, and to date two theories have been suggested: a direct allergen exposure in utero or a direct effect of maternal allergic response. Previous studies have found that maintenance of a healthy lifestyle, especially proper exercise and sleep habits may be a more important strategy for reducing cord blood IgE levels (Shirakawa et al., 1997; Yu et al., 2015a).

Table 4

Neonatal IgE serum and cord blood levels by week of gestation.

Gestational Age (weeks)		30	34	35	36	37	38	39	40	41	42
n.positive/total (% positive)	serum	5/23 (21,7%)	1/3 (33,3%)	1/6 (16,7%)	0/7 (0,0%)	5/36 (13,9%)	24/109 (22,0%)	49/183 (26,8%)	52/213 (24,4%)	41/160 (25,6%)	6/23 (26,1%)
	Cord	8/23 (34,8%)	1/3 (33,3%)	1/6 (16,7%)	0/7 (0,0%)	8/36 (22,2%)	27/109 (24,8%)	54/183 (29,5%)	61/213 (28,6%)	42/160 (26,3%)	8/23 (34,8%)
	Blood										

In another study, an association of cigarette smoke with elevated cord serum IgE was found only in non-atopic mothers (Herr et al., 2011).

In the first case, it is believed that several allergens may be transferred through the placenta or amniotic fluid, thus gaining access to the gut-associated lymphoid tissue (Holloway et al., 2000; Loibichler et al., 2002; Schaub et al., 2005); (in the latter), IgE in the amniotic fluid might bind to IgE receptors in the fetal gastrointestinal tract or alternately and more reasonably, an overproduction of maternal IgE may be associated with an increased production of cytokines and chemokines, which are known to cross the placental barrier and may, in turn, influence the fetal immune system (Jones et al., 1998; Thornton et al., 2003; Dammann and Leviton, 1997; Dahlgren et al., 2006; Lombard et al., 2015).

Our results suggest a strong correlation between maternal IgE and neonatal IgE although other studies showed that maternal IgE cannot be transferred to the child in utero and maternal atopic status has no significant effect on neonatal immune responses (Yu et al., 2015b). No differences according to weeks of gestation were documented probably due to the low number of mothers enrolled. Moreover other studies revealed no correlation when delivery occurred prematurely before 37 weeks gestational age.

As a matter of fact, when delivery occurred after 37 weeks of gestation, mothers with high IgE values for their age gave birth to neonates showing increased levels of IgE, either at birth, in cord blood sampling, or within one week of age, in serum sampling, result also achieved by previous studies (De Amici et al., 2008).

Previous studies showed higher serum IgE level in term newborns compared to preterm ones. (Mirjani et al., 2001).

Early identification of children at risk for allergies would be helpful in preventing the development of allergic disease (De Amici et al., 2006). Despite clinical limitations are known for total IgE, their determination can be useful to define atopy and, in the future life, possible presence or absence of sensitization to common allergens (De Amici et al., 2015). Thus, these neonates require a more accurate follow-up as they are at increased risk of developing asthma and allergies at an earlier age.

Conflict of interest

None.

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