Immunoglobulin E levels in the 1st year of life

Mara De Amici, Ph.D.,* Cesare Belloni, M.D.,# Annalisa De Silvestri, Ph.D.,# Francesca Perotti, M.D.,§ Silvana Quaglini, Ph.D.,¶ Giorgio Ciprandi, M.D.,‖ and Gianluigi Marseglia, M.D.*

ABSTRACT

Asthma allergic rhinitis and atopic dermatitis are multifactorial disorders influenced by various familial and environmental factors. The correlation between maternal and fetal immunoglobulin E (IgE) seems to be caused by genetic factors rather than placental transfer. The purpose of this study was to evaluate and quantify the relationship of IgE levels between mothers and their offspring during the 1st year of life. Total serum IgE levels were assessed in 104 healthy pregnant women just before delivery, as well as in 104 newborns in the 1st days of life and then again at 3, 5, 6, 11 and 12 months of age. A serum IgE increase in infants during the 1st year of life is related to maternal serum IgE levels (and may be divided into three classes, according to IgE concentrations of <100, >100, and <260 kU/L), as shown by significant correlation coefficients and regression slopes. Our findings show that IgE levels in infants of mothers who presented serum IgE levels of >100 kU/L exceeded the norm during the 1st year of life, in the absence of overt atopic disease. It seems useful to consider different categories of infants, as a function of their mothers' IgE, to plan a particular follow-up for children in higher risk classes.

(Allergy Asthma Proc 29:74–77, 2008; doi: 10.2500/aap2008.29.3081)

Key words: Atopy, cohort, infancy, pregnancy, prevention, risk factors, risks of allergy, serial measurements, serum IgE

Total serum immunoglobulin E (IgE) levels are frequently, but not always, elevated in patients with atopic disease and may be increased in many other diseases.[1,2] However, when total IgE levels are elevated in cord blood (>0.9 kU/L), an increased risk for the development of atopic diseases has been evidenced,[3] and high cord blood IgE is significantly associated with the genetic polymorphism IL-4-590C7T, but not with the genotypes FcεRIβ, LT-α, and TNF-α.[4] Cord blood IgE evaluation is a simple, noninvasive and convenient test that can supplement the maternal history and provide more discriminative information on the allergic status of the newborn.[5]

Asthma, allergic rhinitis, and atopic dermatitis are multifactorial disorders influenced by various familial and environmental factors.[6] Distinct fetal and perinatal exposure may have an effect on cord blood lymphoproliferative responses. The implication of these findings on the future development of allergy or asthma are still unknown.[7]

The predictive relationship between serum IgE levels at birth and total IgE of the mother is controversial. It has been shown that there is no correlation between serum IgE in mothers and their newborns[8] or in the respective cord blood.[9] On the other hand, it has been indicated that cord blood IgE is significantly higher when maternal IgE is >100 kU/L.[10,11] Moreover, Lilja *et al.* have reported that paternal heredity has no significant influence on infant IgE, in contrast there is a strong maternal influence.[12]

In this study, total serum IgE levels were measured in 104 healthy pregnant women just before delivery as well as in their newborns in the 1st days of life and then again at 3, 5, 6, 11, and 12 months of age. The first aim of the study was to evaluate the relationship between maternal IgE levels and those of their offspring during the 1st year of life. The second was to investigate the possibility of using maternal IgE analysis to define atopy risk categories in the offspring.

MATERIALS AND METHODS

Subjects

One hundred four healthy, nonatopic, women with a normal-term pregnancy, who had been followed during pregnancy by our Obstetric Department and gave birth to normal infants, were enrolled in the study. Only mothers of children born by eutocic delivery and free from perinatal infection or congenital disease were enrolled. Four mothers were positive for total IgE, in the screening test, but without clinical signs. Parasitic infections were excluded, as well as other common causes of increased serum IgE levels.

The study was formally approved by the San Matteo Hospital Ethical Committee. After obtaining informed consent from parents a small amount of peripheral

*From the Department of *Pediatrics, #Division of Neonatology and Neonatal Intensive Care, §Department of Obstetrics and Gynaecology, Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy, ¶Department of Computer Science and Systems, University of Pavia, Italy, and ‖Department of Internal Medicine, Azienda Ospedaliera Universitaria San Martino, Genoa, Italy*

Address correspondence and reprint requests to Giorgio Ciprandi, M.D., Semeiotica Medica I, Padiglione 3, A.O.U. San Martino, Largo R. Benzi 10, 16132 Genoa, Italy E-mail address: gio.cip@libero.it

Copyright © 2008, OceanSide Publications, Inc., U.S.A.

blood (50 μL) was drawn for IgE detection from the mothers before delivery and from all newborns during routine blood testing before discharge. Subsequently, 1 mL of peripheral blood was drawn from infants at 3, 5, 6, 11, and 12 months of age to determine total IgE and monitor their response to standard 1st year vaccinations. Sera were separated and frozen at −20°C until use. Total IgE was measured in the sera of mothers and their infants at each age time point in a single laboratory session.

IgE Analysis

Total serum IgE and IgE specific for the main respiratory allergens (screening test; Phadiatop; Phadia, AB., Uppsala, Sweden) was measured by a fluorescent immunoassay (Phadia) according to the manufacturer's instructions and for infants a low-range anti-IgE antibody was used.[13,14] The IgE standard was calibrated against the 2nd International Reference Preparation 75/502 of human serum IgE from the World Health Organization. The IgE measurement range was 2–2000 kU/L for mothers' and 0.35–100 kU/L for infants. The conversion of kilounit per liter versus nanogram per milliliter is the following: 1 kU/L = 2.6 ng/mL. The normality values used in our analysis have been described previously.[15]

Statistical Analysis

Median and 25th and 75th percentile values for serum IgE levels from both the mothers and their infants at all age time points were calculated. To evaluate the influence of maternal IgE levels at delivery on their infants at different time points, different univariate linear correlation analyses were performed at the 1st day of life and at 3, 5, 6, 11, and 12 months.

In addition, after subdividing the infants into three groups according to whether maternal serum IgE levels were either normal (≤100 kU/L), elevated (>100 kU/L, and ≤260 kU/L), or pathological (>260 kU/L), linear regression analysis was performed within each group of infants, relating serum IgE levels with the time of blood sampling. The differences between serum IgE levels in the groups of infants were compared using the nonparametric Mann-Whitney *U* test.

RESULTS

The mothers mean age was 29.8 ± 4.26 years (range, 17–37 years) and the 25th, 50th, and 75th percentile ages were, respectively, 27, 31, and 33 years. Four of 104 mothers (3.8%) had total serum IgE levels higher than normal reference values, but they did not show atopic clinical manifestations. Mean total IgE concentrations in the 100 mothers with IgE in the normal range were 54.8 kU/L (25th and 75th percentiles, 8.9 and 84.5 kU/L) compared with 470 kU/L (25th and 75th percentiles, 363–564 kU/L) in the four mothers with abnormally elevated serum IgE.

Table 1 **Median and quartiles of total IgE levels (kU/L*) from infants in the 1st days of life and during the 1st year of life**

Age (mo)	No. (%)	Median	25th	75th
1–5 days	104	0.3	0.3	0.4
3	48 (46%)	1.8	0.7	2.5
5	53 (51%	3.5	1.4	11.3
6	49 (47%)	7.2	3.3	16.5
11	50 (48%)	6.0	4.2	22.9
12	95 (91%)	25.6	10.3	54.6

**1 kU/L = 2.6 ng/mL.*

Table 2 **Median and quartiles of total IgE levels (kU/L*) in maternal serum after subdivision of mothers into four age groups**

Age (yr)	No.	Median	25th	75th
<25	9	23.9	14.1	135
26–30	42	25.5	6.83	93.6
31–35	45	22.8	8.87	82.7
>35	8	14.0	10.1	31.0
	104	24.1	9.45	91.8

**1 kU/L = 2.6 ng/mL.*

Table 1 shows the median and 25th–75th percentile values for total IgE concentrations in the infants at the various sampling times and Table 2 shows the data from all 104 mothers, as well as the mothers' stratification into four age groups. As shown in Table 1, among the 104 infants who entered the study, 95 (91%) returned at 12 months of age, and ~50% returned for other intermediate visits, *e.g.*, compulsory vaccine administration and serologic evaluation of antibody titers after vaccination. The other infants were seen by their local pediatrician who did not report back to us because their clinical course was completely benign.

At 12 months, no infant had developed allergic disease, but some presented with wheezing episodes (12%). The analyses performed at different infant ages (Table 3) revealed a positive correlation between total serum IgE levels in the infants and total maternal serum IgE. All but one (at 3 months) of the correlations were statistically significant ($p < 0.05$). It is worth noting that the value of the correlation coefficient shows an increasing trend over time with notable increases in statistical significance.

After subdividing the infants into three groups according to whether maternal serum IgE was ≤100 kU/L ($n = 80$) or between 100 and 260 kU/L ($n = 20$) or >260 kU/L ($n = 4$), linear regression analysis of

Table 3 **Linear correlation coefficient of infants' IgE versus mothers' IgE at different infant ages**

Age (mo)	*r*	*p* value
0	0.22	0.03
3	0.23	0.13
5	0.37	0.01
6	0.47	0.001
11	0.44	0.002
12	0.36	0.0006

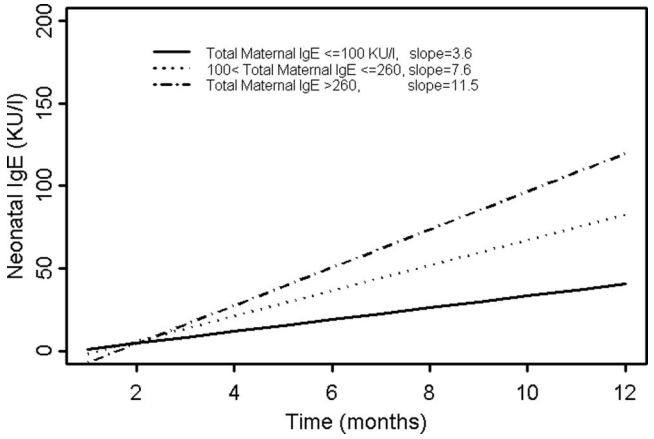

Figure 1. *The regression lines relating infant serum IgE and age, correlated with three maternal age groups, subdivided according to total IgE.*

total infants' IgE levels and sampling times revealed a slower increase in serum IgE during the 1st year of life in the infants of mothers with normal serum IgE than in infants of mothers with serum IgE between 100 and 260 kU/L or abnormally elevated (see slopes in Fig. 1).

Median neonatal IgE levels increased in relation to the three groups of mothers defined previously. Values were 3.24 (25th–75th percentiles, 0.54–88.4), 7.07 (25th–75th percentiles, 0.81–179), and 10.3 (25th–75th percentiles, 2.69–489); there was a considerable IgE increase ($p = 0.01$) in infants whose mothers' IgE was >100 kU/L, compared with infants whose mothers' IgE was ≤100 kU/L and an increasing trend ($p = 0.05$) also is present in the smaller sample of mothers ($n = 4$) with very high IgE values.

DISCUSSION

From the literature it is known that significant correlations between maternal–fetal, paternal–fetal, and maternal–paternal IgE levels exist and may be explained by the influence of the circulatory milieu of the entire family including the fetus.[16] Besides genetic factors, the preferential maternal versus paternal role in causing allergy also is present and associations with large head circumference and placental calcifications support the hypothesis and the role of environmental factors during pregnancy on the levels of cord blood IgE.[6,11,17] Moreover, it has been shown that the maintenance of a healthy lifestyle may be a more important strategy for the reduction of cord blood IgE levels.[18]

To date, numerous IgE^+ cells in the human placenta suggest an unknown role for IgE in a successful pregnancy, irrespective of whether or not the mother is atopic.[19] Maternal IgE, IgG, and the fetomaternal environment are all possible factors involved in the outcome of infant Th1/Th2 responses to common environmental antigens.[20] Maternal sensitization to allergens is associated with reduced maternal production of the Th2 antagonist IFN-γ and elevated production of the Th2 cytokine, IL-13 in their offspring.[21]

In our study we observed, as expected, an increase in mean total serum IgE from the 1st days of life to 12 months of age. However, higher increases of serum IgE levels were observed in infants whose mothers had higher IgE. Furthermore, infants' total IgE increased more slowly over the 1st year of life in infants whose mothers had a total serum IgE of ≤100 kU/L than in infants whose mothers had a total serum IgE of >100 kU/L. Considering these data we concluded that maternal IgE drives a risk category differentiation, *i.e.*, children requiring particular attention for prevention of allergy development[22,23] and it has been described that maternal vitamin supplement intake is negatively associated with the presence of total IgE at birth.[24]

We only observed children up to 12 months during the follow-up. Those with higher IgE still have not presented with allergic disease, but their high IgE production may suggest a possible predisposition for atopy. The presence of lower respiratory disease in this small group in the 1st year of life, however, does not necessarily indicate a predisposition for allergic manifestation.[25] Additional studies are needed to establish whether higher total IgE or normal underlyng causes lead to asthma development so that preventive and curative modalities may be developed rationally.[26] Moreover, it is important to identify an early marker of atopy to single out preventative measures, because allergy is now considered epidemic.[27,28] Only a long-term follow-up could confirm or negate this hypothesis considering that many factors including the frequency and severity of infection and timing and intensity of allergen and animal exposure continue to influence immune development.

ACKNOWLEDGMENTS

The authors thank Cristina Torre for technical support.

REFERENCES

1. Johansson SG, and Yman L. In vitro assays for immunoglobulin E. Methodology, indications and interpretation. Clin Rev Allergy Summer 6:93–139, 1988.

2. Saini SS, Klion AD, Holland SM, et al. The relationship between serum IgE and surface levels of FcepsilonR on human leukocytes in various diseases; correlation of expression with FcepsilonRI on basophils but not or monocytes or eosinophils. J Allergy Clin Immunol 106:514–520, 2000.
3. Edenharter G, Bergmann RL, Bergmann KE, et al. Cord blood IgE as risk factor and predictor for atopic diseases. Clin Exp Allergy 28:671–678, 1988.
4. Wen HJ, Lin YC, Lee YL, and Gou YL. Association between cord blood IgE and genetic polymorphisms of interleukin-4, the beta-subunit of the high-affinity receptor for IgE, Lymphotoxin-alpha and tumor necrosis factor-alpha. Pediatr Allergy Immunol 17:489–494, 2006.
5. Shah S, and Bapat MM. Parental history of allergy, maternal serum IgE and cord serum IgE. Indian J Med Sci 60:13–18, 2006.
6. Dold S, Wjst M, von Mutius E, et al. Genetic risk for asthma, allergic rhinitis, and atopic dermatitis. Arch Dis Child 67:1018–1022, 1992.
7. Willweth BM, Schaub B, Tantisira KG, et al. Prenatal, perinatal, and heritable influences on cord blood immune responses. Ann Allergy Asthma Immunol 96:445–453, 2006.
8. Kjellman NI, and Johansson SG. IgE and atopic allergy in newborns and infants with a family history of atopic disease. Acta Paediatrica Scand 85:601–607, 1976.
9. Businco L, Marchetti F, Pellegrini G. and Perlini R. Predicative value of cord blood IgE levels in "at risk "newborn babies and influence of type of feeding. Clin Allergy 13:503–508, 1983.
10. Michel FB, Bousquet J, Greillier P, et al. Comparison of cord blood immunoglobulin E concentrations and maternal allergy for the prediction of atopic diseases in infancy. J Allergy Clin Immunol 65:422–430, 1980.
11. Oryszczyn MP, Annesi Maesano I, Campagna D, et al. Head circumference at birth and maternal factors related to cord blood total IgE. Clin Exp Allergy 29:334–341, 1999.
12. Lilja G, Magnusson CG, Kuaoffsky E., et al. Neonatal IgA and IgE levels among infants with paternal heredity for atopic disease. Allergy 50:723–728, 1995.
13. Kjellman NI, Johansson SG, and Roth A. Serum IgE levels in healthy children quantified by a sandwich technique (PRIST). Clin Allergy 6:51–59, 1976.
14. Vidal C, Gude F, Boquete O, et al. Evaluation of the phadiatop test in the diagnosis of allergic sensitization in a general adult population. Investig Allergol Clin Immunol 15:124–130, 2005.
15. Zetterstrom O, and Johansson SG. IgE concentrations measured by PRIST in serum of healthy adults and in patients with respiratory allergy. A diagnostic approach. Allergy 36:537–547, 1981.
16. Avrech OM, Samra Z, and Lazarovich Z. Efficacy of the placental barrier for immunoglobulins: Correlations between maternal, paternal and fetal immunoglobulin levels. Int Arch Allergy Immunol 103:160–165, 1994.
17. Lopez N, de Barros Mazon S, et al. Genetic and environmental influences on atopic immune response in early life. J Investig Allergol Clin Immunol 9:392–398, 1999.
18. Shirakawa T, Morimoto K, Sasaki S, et al. Effect of maternal lifestyle on cord blood IgE factor. Eur J Epidemiol 13:395–402, 1997.
19. Sverremark-Ekstrom E, Nilsson C, Holmlund U, et al. IgE is expressed on, but not produced by, fetal cells in the human placenta irrespective of maternal atopy. Clin Exp Immunol 127:274–282, 2002.
20. Warner JA, and Warner JO. Early life events in allergic sensitisation. Br Med Bull 56:883–893, 2000.
21. Kopp MV, Zehle C, Pichler J, et al. Allergen specific T cell reactivity in cord blood: The influence of maternal cytokine production. Clin Exp Allergy 31:1536–1543, 2001.
22. Muraro A, Dreborg S, Halken S, et al. Dietary prevention of allergic diseases in infants and small children. Part I: Immunologic background and criteria for hypoallergenicity. Pediatr Allergy Immunol 15:103–111, 2004.
23. Muraro A, Dreborg S, Halken S, et al. Dietary prevention of allergic diseases in infants and small children. Part II: Evaluation of methods in allergy prevention studies and sensitization markers. Definitions and diagnostic criteria of allergy disease. Immunol 15:193–205, 2004.
24. Kuiper S, Muris JW, Dompelling E, et al. Association between first-degree familiar predisposition of asthma and atopy (total IgE) in newborns. Clin Exp Allergy 36:594–601, 2006.
25. Halonen M, Stern D, Taussig LM, et al. The predictive relationship between serum IgE levels at birth and subsequent incidences of lower respiratory illnesses and eczema in infants. Am Rev Respir Dis 146:866–870, 1992.
26. Halonen M, and Stern DA. Predicting the course of asthma. Allergy Asthma Proc 27:328–331, 2006.
27. Karaman O, Turgut CS, Uzuner N, et al. The determination of asthma, rhinitis, eczema, and atopy prevalence in 9- to 11-year-old children in the city of Izmir. Allergy Asthma Proc 27:319–324, 2006.
28. Thomsen SF, Ulrik CS, Porsbjerg C, and Backer V. Early life exposures and risk of atopy among Danish children. Allergy Asthma Proc 27:110–114, 2006. □

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.