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Original Article

Interleukin-4 and immunoglobulin E levels in newborns at risk of atopic diseases

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Abstract

Background The clinical syndrome of atopy is associated with the production of immunoglobulin E (IgE) in response to antigenic stimulation as part of a type I hypersensitivity reaction. Since early prevention is regarded as an important cornerstone in the management of atopic diseases, the identification of reliable markers such as IgE and interleukin 4 (IL-4) in detecting individuals at risk are of major interest.

Objective To determine whether cord blood IgE and IL-4 levels can be used as an predictor of atopy in newborns with a family history of atopic diseases.

Methods We conducted a cross-sectional study on healthy-term newborns in the neonatal ward at R.D. Kandou Hospital from June to August 2010. A total of 50 healthy newborns in atopic and non-atopic groups were examined for cord blood IgE and IL-4 levels.

Result The mean cord blood IL-4 levels in the atopic and non-atopic groups were 0.1 μg/mL (SD 0.08) and 0.1 μg/mL (SD 0.16) (P=0.359), respectively. The mean cord blood IgE levels in the atopic and non-atopic groups were 2.2 IU/mL (SD 1.98) and 0.5 IU/mL (SD 0.29) (P<0.001), respectively. A point-biserial correlation coefficient analysis showed no significant correlation between IL-4 levels and family history of atopic disease (r_{pb} = 0.098), and a weak correlation between IgE levels and family history of atopic disease (r_{pb}= 0.54).

Conclusions Cord blood IgE and IL-4 levels should not be used to distinguish newborns with a family history of atopic diseases from those without. **[Paediatr Indones. 2011;51:12-6]**.

Keywords*: newborn, interleukin-4, immunoglobulin-E, atopic disease*

The clinical syndrome of atopy can be genetically transmitted, although environmental factors play a significant role in its development.[1] Studies have shown that the incidence of atopy in children is higher if one or both parents have similar atopic manifestations.[2] Atopy is associated with the type I hypersensitivity reaction, in which immunoglobulin E (IgE) is produced in response to antigenic stimulation. IgE is thought to be responsible for a wide range of allergic disorders.[1] Allergic disease development starts with allergen exposure and studies have shown that allergen sensitization may occur in the fetal stage, suggesting intrauterine sensitization.[3]

Since early prevention is regarded as an important cornerstone in the management of atopic diseases, the identification of reliable markers to detect individuals at risk are of major interest. Both IgE and interleukin 4 (IL-4) have been included in the search for predictive factors for atopy in human cord blood.[3] Results of studies on the association

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of neonatal IgE levels and a family history of atopic diseases were varied.[4-7] IL-4 is a key cytokine in the development of allergic inflammation. It is associated with the induction of isotype switching and secretion of IgE by B lymphocytes.[8,9] There is a lack of data on the association of cord blood IL-4 levels and family history of atopic diseases. The aim of this study was to determine if there is a relationship between family history of atopic diseases and cord blood IgE and IL-4 levels in newborns.

Methods

We performed a cross-sectional study carried out in the neonatal ward of R.D. Kandou Hospital from June to August 2010. Subjects were randomly selected and were limited to healthy, term newborns with spontaneous deliveries with a 5-minute APGAR score above 7. We excluded newborns from mothers who consumed alcohol, cigarettes or caffeine during pregnancy, and from mothers who suffered from fever and chorioamnitis during labor. Informed consent was obtained from parents.

All newborns underwent physical and laboratory examinations. Medical records, which were filled by the authors, included mother's name and age, gestational age of the newborn, sex, birth weight, family members with atopic diseases, and cord blood IgE and IL-4 levels. Birth weight was measured immediately after birth using an infant scale. Atopic disease manifestation in family members was determined using a standardized questionnaire for allergy by the International Study of Asthma and Allergies in Childhood (ISAAC).[10] Family history of atopic disease was considered positive if one or more family members had one or more of the following diseases: asthma, atopic dermatitis, rhinitis, urticaria, and food allergy. Cord blood-IgE levels were measured using an enzyme-linked fluorescent assay (ELFA) and IL-4 levels were measured using an enzyme-linked immunosorbent assay (ELISA), products of R&D Systems, Minneapolis, MN, USA. All data were recorded, tabulated, and analyzed using SPSS version 17.0. Data was analyzed by descriptive statistical test and point biserial correlation coefficient analysis with a P value < 0.05 considered statistically significant.

Results

There were 21 newborns in the atopic group (8 male and 13 female) and 29 newborns in the non-atopic group (15 male and 14 female). Seven newborns in the atopic group had two family members with atopic diseases, while the remaining 14 had only one each. The mean cord blood IL-4 and IgE levels in newborns from both groups are shown in **Table 1**. Cord blood IgE levels in newborns using a cut-off point of 1.0 IU/ml are shown in **Table 2**.

We found no correlation between IL-4 levels and family history of atopic disease. However, IgE levels and family history of atopic disease were weakly correlated. **Table 2** shows a significant distribution difference in the number of newborns when comparing IgE levels with a cut-off point of 1.0 IU/ml and family history of atopic diseases ($P< 0.001$). In addition, there was no significant correlation between cord blood IL-4 and IgE levels by Pearson's correlation coefficient analysis, as shown in **Figure 1**.

Table 1. Mean cord blood IL-4 and IgE levels in newborns

Groups	Atopic	95% CI	Non Atopic	95% CI	r_{pb}	P
IL-4, mean (SD) (µg/mL)	0.1 (0.08)	0.04-0,12	0.1 (0.16)	0.05-0.17	0.098	0.359
IgE, mean (SD) (IU/mL)	2.2 (1.98)	1.33-3.14	0.5 (0.29)	0.46-0.69	0.54	<0.001

Table 2. Mean cord blood IgE levels in newborns with cut-off point of 1.0 IU/ml

IgE (IU/ml)	Atopic (n) n=21	Non Atopic (n) n=29	n	X^2
≥ 1.0	18	2	20	P < 0.001
< 1.0	3	27	30	

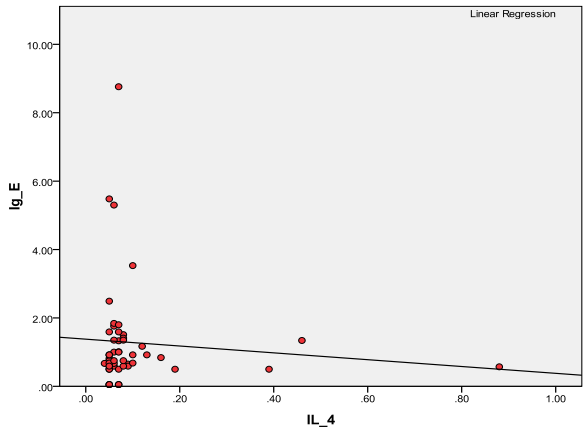

Figure 1. Correlation between cord blood IL-4 and IgE.

Discussion

The prevalence of atopic disorders in children has dramatically increased globally in the past two decades. This increase in atopic prevalence may be due to several factors, such as genetic-environmental interaction, fetoplacental interaction, indoor allergens, and air pollutants.[11,12] In our sample of newborns with family history of atopy, we found 14 (67%) had one family member with atopic disease, and 7 (33%) had two family members with atopic diseases. A study in Bandung reported 50% of newborn subjects had one family member with atopic diseases, 34% had two parents with atopic diseases, and 16% had three family members with atopic diseases.[4]

A characteristic feature of atopy is a T helper (Th) 2 immune response involving the cytokines IL-4, IL-5 and IL-13. IL-4 is critical to the development of allergic inflammation.[8,13] Bottom of FormData has been limited on the relationship of cord blood IL-4 concentrations and family history of atopic diseases. Our study showed the lowest level of cord blood IL-4 was 0.04 pg/mL in male newborn without history of atopic disease, and the highest level of cord blood IL-4 was 0.88 pg/mL in male newborn without history of atopic disease. There was a great deal of overlap of IL-4 levels in the 2 groups. We also found no significant difference in cord blood IL-4 levels between male and female newborns.

Herbert et al found that a high percentage of IL-4-producing T cells in cord blood in German children were associated with an increased risk for atopic dermatitis during the first 2 years of life.[3] In addition, Borres et al found that low levels of IL-4 were detected in 10 of 63 cord blood samples (median 0.14 and range 0.32 μg/l). After monitoring these children for 18 months, they found that the levels increased in both healthy and atopic infants, reaching a peak at either 6 or 9 months, then decreased up to 18 months of age.[13] Furthermore, Ohshima et al found that children who developed atopic disease during the first 18 months of life had significantly higher IL-4 median levels than those who did not.[14]

Although we did not find a correlation between cord blood IL-4 levels and family history of atopic diseases, other studies suggest the release of IL-4 may be influenced by other factors such as the combination of calcium ionophore and pahrbol esther can induce a higher level of IL-4.[15] Several studies also suggest a significant correlation of cord blood IL-4 with genetic polymorphism.[16]

In our study, we found a weak correlation between increased cord blood-IgE levels in newborns and a family history of atopic diseases, consistent with the findings of Croner et al.[5] Also, we found no significant differences between the cord blood IgE levels in male and female newborns, similar to previous reports.[17,18] Although different cord blood-IgE cut-off points have been proposed, we used a cut-off point of 1.0 IU/ml, based on a study by Kobayashi et al.[19] **Table 2** shows 18/21 (86%) newborns with a family history of atopic diseases had cord blood IgE levels $\geq$1.0 IU/ml.

In our study, there was no significant correlation between the cord blood IL-4 and IgE levels, consistent with the findings of Borres et al. who observed no significant relationship between IL-4 levels and clinical outcome, nor with serum IgE levels.[13] Another similar finding stated that in spite of the common features in atopic patients, such as raised serum IgE and eosinophilia, the underlying aberrations in their cytokine network are different.[15]

IL-4 is the essential factor for induction of human IgE synthesis, since no substantial in vitro IgE production can be obtained in the absence of this lymphokine. Another T cell-derived lymphokine, IFN-gamma, negatively regulates the IgE synthesis induced by IL-4. These two lymphokines can be produced by different T helper cells, but they can also represent

the product of the same T cell clone (TCC). In this case, the possibility that a given TCC provides helper function for IgE seems to be dependent upon the balance between the amounts of the two lymphokines produced. Additional cellular and/or molecular signals are involved in IL-4-dependent IgE synthesis, possibly explaining why there was no significant relationship between IL-4 and IgE levels.[20]

Our study showed a weak correlation between cord blood IgE levels in newborns with a family history of atopic diseases. These results support the notion of primary prevention. Families with a history of atopic diseases can be advised that their newborns may have a predisposition to atopy. Both pregnant and breastfeeding mothers with family history of atopy, may be advised to avoid foods that are often hypoallergenic.

A limitation of this study was the determination of allergic status in family members by taking family history only, without performing the more objective skin prick test to diagnose allergic disease. Also, we examined only the IL-4 cytokine levels. Further investigation is needed on other Th2 cell cytokines that affect the production of IgE, such as IL-13 and interferon γ. Additional genetic studies will offer a better understanding on the influence of genetic polymorphism on IL-4 release and IgE synthesis.

In conclusion, cord blood IgE levels had a weak correlation with family history of atopic diseases. There was no significant correlation between the cord blood IL-4 and family history of atopic diseases.

References

1. Ring J. Genetics and environment in the development of allergy. In: Ring J, editor. Allergy in practice. Berlin: Springer, 2005; p. 31-5.
2. Shah S, Bapat MM. Parental history of allergy, maternal serum IgE and cord serum IgE. Indian J Med Sci. 2006;60:13-8.
3. Herbert G, Heinrich J, Roder S. Reduced IFN-δ and enhanced IL-4 producing CD4 cord blood t cell are associated with a higher risk for atopic dermatitis during the first 2 years of life. Pediatr Allergy Immunol. 2010;21:5-13.
4. Hutapea AT, Setiabudiawan B, Soepriadi M, Rustama DS. Association between cord blood IgE levels in newborns and family history of atopic disease. Pediatr Indones. 2006;46:199-203.
5. Croner S, Kjellman NAM, Eriksson B, Roth A. IgE screening in 1701 newborn infants and the development of atopic disease during infancy. Arch Dis Child. 1982;57:364-8.
6. Edenharter G, Bergmann RL, Bergmann KE, Forster VW, Zepp F, Wahn U. Cord blood-IgE as risk factor and predictor for atopic diseases. Clin Exp Allergy. 1998;28:671–8.
7. Eiriksson TH, Sigurgeirsson B, Ardal B, Sigfusson A, Valdimarsson H. Cord blood IgE levels are influenced by gestational age but do not predict allergic manifestations in infants. Pediatr Allergy Imunol. 1994;5:5-10.
8. Steinke JW, Borish L. Th2 cytokines and asthma - Interleukin-4: its role in the pathogenesis of asthma, and targeting it for asthma treatment with interleukin-4 receptor antagonists. Respir Res. 2001;2:66-70.
9. Moser R, Feehr J, Bruijn PL. IL-4 controls the selective endothelium-driven transmigration of eosinophils from allergic individuals. J Immunol. 1992;149:1432-8.
10. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International study of asthma and allergies in childhood (ISAAC): rationale and methods. Eur Respir J. 1995;8:483-91.
11. Holt PG, Yabuhara A, Presscot S, Venaille T, Macaubas C, Holt BJ, et al. Allergen recognition in the origin of asthma. Ciba Found Symp. 1997;206:35-49.
12. Harsono A. Pencegahan primer penyakit alergi. Presented on 35th Pediatric Continuing Education. Surabaya: Department of Child Heath, Medical School, Airlangga University, 2005; p. 79-85.
13. Borres MP, Einarsson R, Björkstén B. Serum levels of interleukin-4, soluble CD23 and IFN gamma in relation to the development of allergic disease during the first 18 months of life. Clin Exp Allergy. 1995;25:543-8.
14. Ohshima Y, Katamura K, Miura M., Mikawa H, Mayumi M. Serum levels of interleukin 4 and soluble CD23 in children with allergic disorders. Eur J Pediatr. 1995;154:723-8.
15. Paulsen LK, Bindslev JC, Diamant M, Hansen MB, Jepsen KF, Reimert CM. Biomolecular regulation of the IgE immune response III. Cytokine profiles in atopic dermatitis, inhalant allergy and non-allergic donors. Cytokine. 1996;8:651-7.
16. Wen HJ, Lin YC, Lee YL, Guo YL. Association between cord blood IgE and genetic polymorphisms of interleukin-4, the β subunit of the high-affinity receptor for IgE, lymphotoxin-α and tumor necrosis factor-α. Pediatr Allergy Immunol. 2006;17:489-94.
17. Velazquez PSV, Angeles MB. Concentraciones de IgE en sangre de cordon umbilical y su asociacion con factores de riesgo atopico. Educ Invest Clin. 2000;1:172-6.
18. Alawar B, El Kalla S, BjorkstCn B. Cord blood IgE levels in the United Arab Emirates. Pediatr Allergy Immunol.

1994;5:59-61.

19. Kobayashi Y, Kondo N, Shinoda S, Agata H, Fukutomi O, Orii T. Predictive values of cord blood IgE and cord blood lymphocyte responses to food antigens in allergic disorders during infancy. J Allergy Clin Immunol. 1994;94:907–16.
20. Romagnani S, Del Prete G, Maggi E, Parronchi P, Ricci M. New insights into the mechanisms which regulate IgE synthesis in man. Haematologica. 1992;74:317-23.