Paediatrica Indonesiana

VOLUME 47 November • 2007 NUMBER 6

Original Article

Relationship between atopic manifestations, family history of atopic disease and cord blood IgE levels in children

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Abstract

Background The incidence of atopic disease tends to increase over the past few decades and its morbidity interferes with the quality of life and health. Prediction of the disease is important for early prevention.

Objective To evaluate the relationship between atopic manifestations, family history (FH) of atopic disease and cord blood IgE (CB-IgE) levels.

Methods We conducted an analytic observational study with cohort retrospective design on children with an average age of 3 years whose CB-IgE had been measured at delivery in Kiaracondong Primary Health Care during October–December 2004. Manifestations of atopic disease were recorded using ISAAC questionaire for allergy. Chi-square, Mann-Whitney test, and logistic regression analysis were used for analysis.

Results Cord blood IgE was measured on 124 children after birth. Only 94 children (76%) fulfilled the inclusion criteria. Atopic disease was found in 17 children (18%), consisting of 8 children with atopic dermatitis, 4 with allergic rhinitis, and 5 suffered from both. There were significant differences in the mean value of CB-IgE ($Z_{M\text{-}W}=4.60$; $P<0.001$) and FH ($x^2=19.059$; $P<0.001$) between atopic and non atopic children. Cut off point of the CB-IgE concentration was 1.4 IU/mL (77.7%). The highest probability for atopic manifestations was found in children who had high CB-IgE and positive FH (P=45%). Relative risk of children with high CB-IgE level in positive FH group was 3.636 (95% CI 0.943;14.016).

Conclusion CB-IgE level and family history of atopic disease are risk factors for the development of atopic manifestation. **[Paediatr Indones 2007;47:278-282]**.

Keywords: *atopic disease, cord blood IgE, family history*

The incidence of atopic diseases has been increasing dramatically over the past few decades.[1,2] Although it doesn't cause significant mortality, its morbidity disturbs the quality of life[3] and increases health cost.[3,4] The prevalence of childhood atopic disease showed that atopic eczema is 20% in boys (12% in the year before study), and 19% in girls (11% in the year before 2000).[2] Allergic asthma varies between 8% and 12%, especially in industrialized world.[5] Seasonal allergic rhinitis (hay fever) is around 10-12%, as for perennial allergic rhinitis.[6] The prevalence reached a significant increase (6-14%) at the age of about 3 years old.[7]

Factors influencing the development of atopic manifestations might be internal[2,8] or external factors.[2,9] Atopy is a hereditary predisposition to produce IgE antibodies against common environmental allergens and manifests as one or more atopic diseases (i.e., allergic rhinitis, asthma, and atopic

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dermatitis).[10-12] Children with family history of atopic disease are at high risk to develop the disease.[4,13,14] Elevated serum IgE is the hallmark of atopic disease.[15] Initial exposure to allergen (which can occur with priming in utero) leads to sensitization[16] and production of IgE antibodies.[14] During subsequent allergen exposures, allergic inflammation is initiated by cross-linking the allergen with IgE antibodies, followed by mediator release which results in a cutaneous wheal-and-flare reaction, sneezing and runny nose, or wheezing within minutes.[17] For preventive measures, IgE levels are determined as soon as possible, i.e. by analyzing cord blood IgE (CB-IgE).

The role of CB-IgE as a risk factor or predictor of atopic disease has been widely discussed. Croner *et al*[18] who screened 1,701 newborns found atopic disease developed in 73% infants with high CB-IgE level and positive family history, compared to 3% of infants with low CB-IgE level and no FH. However, other studies couldn't find any association between elevated CB - IgE level and atopic manifestations.[19,20]

This study aimed to determine the relationship of atopic disease in children with cord blood IgE (CB-IgE) level and family history of atopic disease.

Methods

This was a retrospective cohort study performed from October-December 2004. The subjects were children of 3 years old, whose CB-IgE were already measured at delivery in Kiaracondong Primary Health Care. Data were obtained from a previous report.[21] The inclusion criteria were those whose parents/caregivers agreed to sign written informed consent. Subjects were excluded when they could not be found or moved from Bandung. The initial study consisted of 124 children with equal numbers of positive and negative FH of atopic disease. Total cord blood IgE was measured by Cobas Core Kit to detect the IgE by ELISA.

Determination of atopic disease

Manifestation of atopic disease was determined using the International Study of Asthma and Allergies in Childhood (ISAAC) standardized questionnaire for allergy.[22] Interview was done by the authors and assisted by trained medical staff to collect general data including children's weight and height.

Allergic asthma was diagnosed by recurrent wheezing and/or cough more than three nights in a series. Atopic dermatitis was defined as itchy rash occurring on typical distribution, such as face, neck, flexural and extensor area, and buttocks. Allergic rhinitis /rhino conjunctivitis defined as a nasal discharge, or attacks of sneezing and itching eyes without respiratory infection.

Statistical analysis

Data were analyzed with SPSS version 10.0. Descriptive statistics, including mean and range were calculated for subjects' characteristics. The differentiation of CB-IgE levels and FH between the atopic and non atopic children were analyzed by comparative statistics (Mann-Whitney and chi square test), and considered as significant if $P<0.05$. Prediction on the incidence of atopic disease was calculated by determining the cut off point of CB-IgE and logistic regression analysis.

Ethical approval

This study received approval from the Health Study Ethical Committee, at Faculty of Medicine University of Padjadjaran/Hasan Sadikin General Hospital Bandung.

Table 1. Characteristics of subjects

Characteristics of subjects	Subjects	Excluded	Significance
Sex			
Boys	52 (81%)	12 (19%)	$x^2 = 2.137$
Girls	42 (70%)	18 (30%)	P = 0.144
Family history of atopic disease			
Yes	49 (79%)	13 (21%)	$x^2 = 0.704$
No	45 (73%)	17 (27%)	P = 0.144
Cord blood IgE level (IU/mL)			
Mean (SD)	2.022 (2.333)	1.290 (1.674)	$Z_{M-W} = -1.654$
Median	0.850	1.150	P = 0.098
Range	0 – 7.6	0 – 13.4	
Age (months)			
Mean (SD)	39.7 (1.6)	39.9 (1.4)	t= – 0,649
Range	36 – 42	37 – 42	P = 0.518
Total subjects	94 (76%)	30 (24%)	

Note: Z_{M-W} = Mann-Whitney test; x^2 = chi-square test; t = t test

Results

Out of 124 subjects, 94 (76%) fulfilled the inclusion criteria. The characteristics of subjects who were included and excluded in this study are presented in **Table 1**. The characteristics include sex, family history of atopic disease and CB IgE level. There was no statistical difference between atopic and non atopic children incidence.

Manifestations of atopic disease occurred in 17/94 children, as seen in **Figure 1**. Atopic dermatitis was the most common symptom (8 children), followed by both atopic dermatitis and allergic rhinitis (5 children), and allergic rhinitis (4 children).

Comparative statistics were used to evaluate the association between family history and atopic manifestations (**Table 2**). Association between mean value of cord blood IgE levels in atopic and non atopic children is presented in **Table 3**.

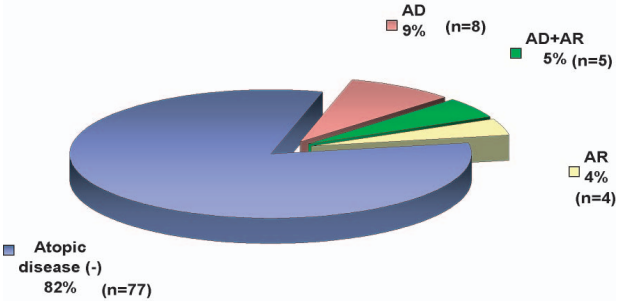

Figure 1. Atopic manifestation in children

Note: AD: Atopic Dermatitis; AR: Allergic Rhinitis

Table 2. Atopic manifestation in children based on family history of atopic disease

	Family History (+)	(-)	
Atopic Dermatitis			
(+)	13	0	x^2 = 13.855
(-)	36	45	P <0.001
Allergic Rhinitis			
(+)	9	0	x^2 = 9.140
(-)	40	45	P = 0.003
Atopic disease			
(+)	17	0	x^2 = 19.059
(-)	32	45	P <0.001

Children with family history of atopic disease showed higher incidence of atopic manifestations (P<0.001).

Mean value of cord blood IgE levels were also significantly higher in children with atopic manifestations than in non atopic children.

Determining the cut off point of cord blood IgE, the accuracy was highest at level 1.4 IU/mL (77.7%), with sensitivity of 88.2%, specificity of 75.3%. This cut off value pointed out the positive predictive value by 44.1% and negative predictive value by 96.7%. Based on this cut off value, CB-IgE were determined high (>1.4 IU/mL) in 34 children, and low (=1.4 IU/mL) in 60 children. The incidence of atopy was highest in children with high levels of cord blood IgE (15 out of 17 atopic children) compared to 19 out of 77 in non atopic children. Fifteen of 33 children with positive FH and high CB-IgE levels developed atopic disease. None of negative FH and low CB-IgE levels (n=44) developed atopic manifestations. (**Figure 2**).

By logistic regression analysis, the highest prediction of atopic disease was found with (+) FH and high CB-IgE (P=45%), **Table 4**.

Table 3. Mean value of cord blood IgE levels in several atopic manifestations

	Atopic manifestation (+)	(-)	
	Atopic Dermatitis		
X (SD)	3.738 (2.186)	1.747 (2.248)	Z_{M-W} = -3.895
Median	3.4	1.1	P <0.001
Range	1.4-8.5	0-13.4	
	Allergic Rhinitis		
X (SD)	4.556 (3.623)	1.754 (2.004)	Z_{M-W} = 4.60
Median	3.4	1.1	P <0.001
Range	1.3-13.4	0-9.6	
	Atopic disease		
X (SD)	4.171 (3.11)	1.548 (1.833)	Z_{M-W} = 4.60
Median	3.4	1.0	P <0.001
Range	1.3-13.4	0-9.6	

Table 4. Prediction of atopic disease based on family history and CB-IgE levels.

Family History of Atopic Disease	Cord Blood IgE Level	Prediction of Atopic Disease
Yes	High	0.45
Yes	Low	0.12
No	High	0.00007
No	Low	0.00001

Note: Yes/High=1; No /Low=0

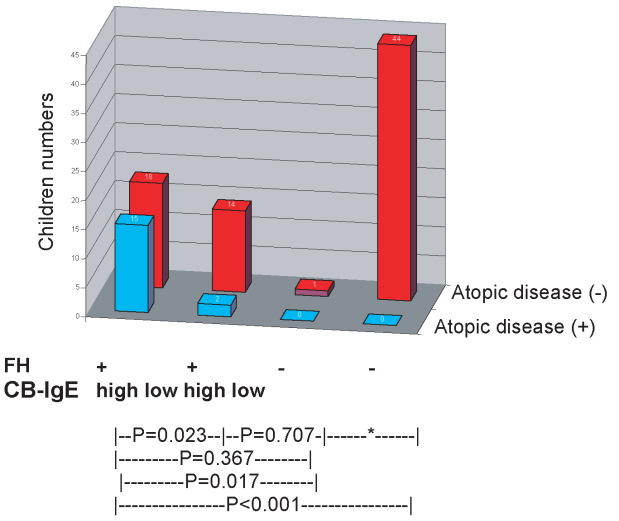

Figure 2. Developed atopic manifestations

Note: * = can not be analyzed
FH = family history of atopic disease
CB-IgE = cord blood IgE

The relative risk of children with high CB-IgE level exclusively in positive family history of atopic disease group (n=49) was 3.636 (95% CI 0.943;14.016).

Discussion

Of the 94 children recruited, atopic disease was found in 18%, with atopic dermatitis as the most common manifestation. This was quite high since this study was done on three year old children, when almost all atopic manifestation arise in the natural history of atopic march.[7] If the data was collected when they were younger (i.e at 18 months), atopic manifestation might be less. In fact our study found that some manifested after the age of two. Other studies showed different finding. Croner[18] found 8% children developed obvious or probable atopic disease, predominantly atopic dermatitis and bronchial asthma during the first 18 months of life, while other investigators found incidence of 12.9% and 36.6%.[19,20] Great variations of the definition of atopy between the different studies could interfere with the results. Our study used ISAAC standardized questionnaire for allergy which had been validated to determine the incidence of atopic manifestation. However, other tests are also useful in confirming the precise diagnosis, such as the skin prick test.

Genetic factors play an important role in the development of atopic disease. Atopic manifestations in children with family history of atopic disease was highly significant in our study (P<0.001).

In children with atopy, there is no doubt that elevated total IgE level has positive association with disease manifestation. An increase in IgE level points out evidence of sensitization which could occur with priming in utero.[8,14,16] Cord blood IgE measurements in several studies showed different results.[18-20] IgE screening in 1,701 newborn infants noted that 70% infants with high cord blood IgE concentration developed obvious or probable atopic disease during the observation period,[18] while others reported otherwise.[19,20] Many factors might influence the outcome, such as laboratory methods, blood sampling techniques, cut off values and also precise criteria of atopic diagnosis. By using a level of 1.4 IU/ml CB-IgE concentration as cut off value in our study (which was different from other reports), significant differences were noticed. The predictive value was quite poor (44.1%), however measuring CB-IgE at delivery should have significant meaning for identifying risk factor in infants.

Children with positive FH and high CB-IgE levels developed atopic disease more often[18] as found in our study (P=45%).

Expression of Th2-skewed immunity to ubiquitous environmental allergen is the hallmark of the atopic phenotype, in contrasts with the balanced Th1/Th2 pattern in normal individuals. Synthesis of IgE and clinical manifestations depend on the interaction of multiple gene products with environmental allergens.[2] The fetus is known to synthesize IgE from the 11th gestational week. The study by Croner *et al*[18] did not suggest that IgE could be transmitted across the placental barier. Assuming that sensitization can occur in fetal life, the relative risk for atopic manifestation in children with (+) FH and increased CB-IgE level should be higher than those without. In our study the relative risk was 3.636 (95% CI 0.943;14.016). However, the evidence of fetal specific sensitization to certain allergens was unproven, since the cord blood specific IgE were not measured in this study. Overall, our findings may be useful to plan early prevention[22,23]

in children who might have atopic disease later. The cut off value of cord blood IgE in this study should be determined further. For appropriate recommendations, further investigation with larger population is necessary.

In conclusion CB-IgE level and family history of atopic disease are risk fators for the development of atopic manifestation.

Acknowledgments

We would like extend our gratitude to the headmaster and staffs of Kiaracondong Primary Health Care for being helpful and supporting during this study.

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