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The Role of Allergy Risk Factors and Environmental Factors Against Lymphocyte Th-1 and Th-2 Activity in Relation to Wheezing in Infants Age Up to 1 Year

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Infant atopy, allergy risk factors, environmental factors, activity of Th-1 and Th-2

A B S T R A C T

Allergic disease is an important issue because it occurs at all levels of society and increasing the number of accident in the last three decades. Risk factors and environmental factors play an important role in the mechanism of allergy. Wheezing is an early symptom of respiratory disorders that often occur as a result of allergic reactions in children. This study aims to find the role of allergy risk factors and environmental factors on the activity of Th-1 and Th-2 in association with wheezing in infants up to 1 year of age. This study is an exploratory of analytic observational with cohort design. Samples were taken with consecutive sampling technique has been obtained as many as 71 infants who had completed observed for 12-months-old. A total of 64.8% from 71 subjects suffering from wheezing. Allergy risk factors ($p = 0.007$), skin prick test $\geq$ 3 mm (0.000), IFN-γ levels below 0.53 ($p = 0.033$), IL-5 levels above 0.6 ($p = 0.000$), and the father smoked ($p = 0.003$) appear related to the occurrence of wheezing. Allergy risk factors contribute to the onset of wheezing, through the increased activity of Th-2 lymphocytes generate the levels of IL-5 to be higher in infants suffering from atopic wheeze.

Introduction

Allergic disease is an important issue because it all occurs at all levels of society and its incidence continues to rise in the last three decades.[1-3] Allergic incidences caused by food is estimated to occur between 12-30% of all infants.[4.5] More than 170 types of foods that cause allergic reactions, but a number of prevalence studies only focus on foods that most commonly cause allergy, namely cow's milk, peanut, *seafood*, and eggs.[6] Cow's milk fed to infants whose mothers did not have breast milk can cause cow's milk allergy sensitization (CMA). cow's milk allergy sensitization encountered since the first month of age 1 to age 3 years,

characterized by initial symptoms such as atopic dermatitis and changes in the respiratory tract, known as wheezing.[5.7]

Approximately 35-45% incidence of atopic dermatitis and respiratory allergy symptoms in babies aged less than 2 years due to CMA. When cow's milk is not inevitable that the clinical symptoms will appear in the upper respiratory tract such as wheezing, coughing and creacking.[4.8]

Development of allergic diseases is determined by at least three things: the genetic background, exposure to allergens and amplified by environmental factors.[8] Infants from families with a history of allergic disease at risk of allergy are two to three times higher compared with infants without a history of allergic disease in the family.[1-3]

Wheezing is a common symptom in children. Previous studies reported that about 5-15% of all children who experienced wheezing in infancy would be at risk of developing asthma in the future.[9-13] Children with family history of allergic diseases will suffer from allergies at risk two to three times higher than those without a history of allergy in the family.[1-3]

Cow's milk sensitization of food with cow's milk protein causes increased production of interleukin (IL)-4, IL-5 and IL-10 secreted by Th-2. Cytokines is a key cytokine for the production of IgE. Whereas *interferon* (IFN) γ is a cytokine secreted by Th-1 has the properties of inhibiting IgE. [13-15]

Experimental

Explorative study of analytic observational with cohort design was conducted at General Hospital dr. Abidin Abidin Banda Aceh from May to December 2013.

Sampling was done by *consecutive sampling* technique based on a single sample formula to estimate the proportion of the population using absolute precision in order to obtain 71 samples that fit the inclusion criteria. Samples were monitored regularly by telephone to determine allergic complaints from prospective subjects performed every week until the age of 1 year.

Sample criteria set out in this study is a baby suffering from atopic wheeze at age less than one year outpatient general hospital (RSU) Zainal Abidin, RSU Meuraxa, and Mother and Child Hospital and private hospitals and clinics in the city of Banda Aceh.

Infants with atopic parents were asked to fill out the consent of the sampled studies and also requested permission for examination of skin prick test as a diagnostic procedure as well as peripheral blood taken for examination by 5 ml of the cytokines IL-5 and IFN-γ.

The analysis used include univariate analysis to look at the distribution of each variable, bivariate analysis used to test the hypothesis with 2 variant and look for the point of intersection with the means of descriptive statistics (mean and median), and multivariate used to determine risk factors with multiple logistic regression. To determine the relationship between a history of atopy with a variety of risk factors suffer wheezing and allergies and an increase in levels of IL-5 and IFN-γ using Chi Square test and Fisher's exact test. To assess the differences in activity of Th-1, Th-2 and the results of skin prick test in wheezing and non-wheezing group used independent t test. The magnitude of the risk of wheezing in patients with atopic calculated using relative risk (RR). Statistical test of significance determined by $p < 0.05$.

Result and Discussion

Subject was conducted from May to December 2013, and obtained 71 subjects who met the study criteria and in accordance with the calculation of the amount of subjects. The subjects consisted of 64.8% patients with wheezing and 35.2% non-wheezing. Subjects with male gender consisting of 35 (49.3%) and 36 women (50.7%). A total of 48 (67.6%) subjects had a risk factor of allergic mild to moderate and only 23 (32.4%) had a high allergy risk factors. Subjects who are 71 samples came to the hospital with complaints of allergies by 36 (50.7%) subjects and 35 (49.3%) visit for immunization along with other complaints such as coughs and colds. Furthermore, as many as 66 (93%) subjects known to have a history of feeding dairy cows as well as additional food other than breast milk, only 5 (7%) who received only breast milk or cow's milk without any additional food. History of smoking parents *(indoor),* especially in the elderly man (father) was found in 37 (52.1%) study subjects.

Based on the analysis in Table 1, when the results of the bivariate test has a p-value <0.25, then the variables included in the multivariate analysis model. Variables entered into the multivariate is a smoking father (AM), the levels of IFN-γ (IFN), the levels of IL-5 (IL), the results of skin prick test (ST) and allergy risk factors (FR Having obtained the predictor variables important in the multiple logistic regression model, and then analyzes interactions together to examine the possibility of an interaction between the variables. equation best models consider the significance value of p <0.05. Results of multivariate analysis in this study shows that there are three variables that proved to be very effect on complaints of wheezing that levels of IFN-γ RR (95% CI) 10.28 (1.73 to 31.61), the levels of IL-5 RR (95% CI) 20.69 (4.51 to 94.83) and paternal smoking RR (95% CI) 6.49 (1.33 to 31.61). Results of detailed analysis as shown in Table 2.

t test

In Table 3 of the complaints of wheezing, obtained a mean value of IFN-γ levels in wheezing group was 1.67 ± 2.81 pg / ml, mean value of IFN-γ levels in the group do not wheeze is 2.77 ± 3.17 pg / ml . Results of statistical analysis using t-test p-value = 0.192 was obtained. Therefore, the value of p> 0.05 it can be concluded that there are no differences in levels of IFN-γ in children with symptoms of wheezing and non-wheezing.

Average value of the levels of IL-5 in the wheezing group was 0.95 ± 0.46 pg / ml, mean value of IL-5 levels in the group do not wheeze is 0.54 ± 0.13 pg / ml. Results of statistical analysis using t-test p-value = 0.000 was obtained. Therefore, p-value <0.05, it can be concluded that there are differences in the levels of IL-5 in children with symptoms of wheezing and non-wheezing.

Average value of the skin prick test results in wheezing group was 3.96 ± 1.93 mm, the mean value of the skin prick test results in wheezing group was 0.40 ± not 0.81 mm. Results of statistical analysis using t-test p-value = 0.000 was obtained. Therefore, p-value <0.05, it can be concluded that there are differences in skin prick test results between children with symptoms of wheezing and non-wheezing.

Based on Table 4 of allergy risk factors, the mean values obtained value of skin prick test in a high-risk group was 3.70 ± 2.05 mm, the mean value of the value of the skin

prick test in mild-moderate risk group was 2.23 ± 2.36 mm . Results of statistical analysis using t-test p-value = 0.010 was obtained. Therefore, p-value <0.05, it can be concluded that there are differences in the value of the skin prick test in children with high risk factors and risk factors for mild-moderate.

Data from cohort study on 71 subjects were followed for up to 12 months old and obtained the incidence of wheezing 64.8%, consisting of 56.5% low-moderate-risk subjects and 43.5% of high-risk subjects. In this study obtained a significant relationship between the risk factors of wheezing allergic to. Children who have parents with a history of atopy 2 times greater risk of suffering from asthma in the future.[16]

Atopy symptoms was found in 39.8% of children if they have mothers with a history of atopy and 30.2% if their fathers have atopic dermatitis. Children with both parents without a history of atopy risk is only 10%.[17]

Imbalance of Th-1 lymphocytes and Th-2 response in infants with atopic an immunologic due to cow's milk protein allergens. Given cow's milk before the age of 6 months stimulates type I hypersensitivity reactions and inflammation resulting IV early in the skin or mucosa.[18]

In this study there was no difference IFY-γ levels between wheezing and non-wheezing group. Th-2 cytokines actually increases when the allergic process continues, followed by a decrease in Th-1 cytokines.[19] But because this study was conducted in infants who had experienced early symptoms of allergies so it is understood that not found decreased levels of IFN-γ. Although in asthmatics levels of IFN-γ decreased due to IgE synthesis, but previous *in vivo* studies found the Th-1 shift toward lower asthma symptoms showed only minimal. IFN-γ levels actually increased in patients with *severe* asthma who experience acute exacerbations or wheezing symptoms early viral infection caused by pathogens such as *viruses* and *Respitarory syncytial Human rhinovirus* that asthma is not always said to be a Th-2 *driven disease*.[20,21] Another study found a decrease in levels of IFN-γ only in infants with recurrent wheezing at age less than one year.[22] Another study reported an increase in the activity of Th-1 and Th-2 only in patients with acute and chronic asthma.[23]

Individuals who tend to be allergic, exposure to antigen results in the activation of Th-2 cells and IgE production. Past studies have reported an increase in individuals with atopic production of IL-4 and IFN-γ production decrease is correlated with increased serum total IgE production. When individuals are exposed to the antigen, the T cell response is the formation of Th-2 cells.[14.24]

In this study, we did not calculate the levels of IL-4 as the storage time in the freezer at -20 degrees celsius should not exceed 24 hours, so that examined IL-5 is having the time of storage in the refrigerator (at a temperature of -20 degrees Celsius) together with IFN-γ levels were reached 2 months. Based on the theory of IL-5 is known to represent IL-4 on type 1 hypersensitivity mechanism that IL-5 is used as a surrogate measurement of IL-4.[14] In patients with asthma significantly increased levels of IL-5.[25] Increased IgE associated with increased production of Th-2 cytokines (IL-4 and IL-5) in the first 12 months of age will predict the possibility of asthma up to the age of 5 years.[26] In the study There are differences in the levels of IL-5 in wheezing and non-wheezing group.

Table.1 Bivariate analysis of independent variables on the occurrence of wheezing in 71 sample

Independent Variables	Wheezing Complaints		*P*	Relative Risk	CI 95%
	Yes	No			
	n (%)	n (%)			
Allergy Risk Factor					
a. High	20 (86,9)	3 (13)	0,007*	1,605	(1,184-2,177)
b. Mild-Moderate***	26 (54,2)	22 (45,8)			
Skin prick test					
c. ≥ 3 mm	36 (100)	0 (0)	0,000*	3,500	(2,073-5,910)
d. < 3 mm	10 (28,6)	25 (71,4)			
IFN-γ Levels					
- Below 0,53	25 (78,1)	7 (21,9)	0,033*	1,451	(1,029-2,046)
- Above 0,54	21 (53,8)	18 (46,2)			
IL-5 Levels					
e. Above 0,6	40 (85,1)	7 (14,9)	0,000*	3,404	(1,685-6,877)
f. Below 0,6	6 (25)	18 (75)			
Smoker Dad (*Indoor*)					
• Yes	30 (81,1)	7 (18,9)	0,003*	1,723	(1,168-2,542)
• No	16 (47,1)	18 (52,9)			
History of Labor					
1. *Caesarian*	22 (71)	9 (29)	0,337*	0,845	(0,603-1,186)
2. Vaginal Birth	24 (60)	16 (40)			
Feeding History					
• Not-Breastfed	44 (66,7)	22 (33,3)	0,232**	1,667	(0,562-4,942)
• Only Breast Milk	2 (40)	3 (60)			
Sex					
(1) Boy	23 (65,7)	12 (34,3)	0,872*	1,029	(0,730-1,449)
(2) Daughter	23 (63,9)	13 (36,1)			

Table.2 Variables in the equation results of multivariate analysis

Variables	Coefficient	*P*	RR (IK 95%)
IFN-γ levels	2,330	0,010	10,28 (1,73-31,61)
IL-5 levels	3,030	0,000	20,69 (4,51-94,83)
Smoker Dad (indoor)	1,872	0,020	6,49 (1,33-31,61)
Constant	-2,856	0,001	0,057

Table.3 The relationship of various variables against wheezing

No	Independent Variables	Wheezing Complaint		*P*
		Yes Mean ± SD	No Mean ± SD	
1.	IFN-γ levels	1,67 ± 2,81	2,77 ± 3,17	0,192
2.	IL-5 levels	0,95 ± 0,46	0,54 ± 0,13	0,000
3	Skin prick test results	3,96 ± 1,93	0,40 ± 0,81	0,000

Table.4 The difference in the results of skin prick test of high and mild-moderate risk factors group

Independent Variable	Risk Factors		*P*
	High Mean ± SD	Mild-Moderate Mean ± SD	
Skin prick test results	3,70 ± 2,05	2,23 ± 2,36	0,010

Skin prick test is the conventional diagnostic methods to assess allergen-specific IgE bound to mast cells in the skin. When skin is punctured, the allergen triggers cell activation and release of inflammatory mediators. Mediators released produces a wheal and flare reaction, which quickly type hypersensitivity reactions are mediated allergen-specific IgE. The test will produce a maximum wheal size after 15 to 20 minutes. Wheal size with a diameter of 3 mm or more of control showed positive results. The presence of specific IgE to predict the size of the wheal size formed. Skin prick test is easy, fast and very sensitive in detecting specific IgE.[27-28]

Skin prick test is useful to help the accuracy of the diagnosis after a physical examination and family history was obtained. In this study there were differences in the results of skin prick tests on a group of high risk factors and mild-moderate. This test is recommended to support the effectiveness of the treatment will be given. There is no age limit for this examination but have appeared on the skin reaction in infants and young children. Determination of positive test results when lesions ≥ 3 mm of control. Past studies reported lesion with size ≥ 3 mm clinical relate more closely to the reaction of allergens although lesion size 3mm or 6mm equally showed positive results.[19] Results of this study also analyzes the differences between the results of skin prick test wheezing and non-wheezing group.

Environment plays an important role in the mechanism of allergy. Factors pollutants such as cigarette smoke is one of the allergens at an early age.[1,8,29] cigarette smoke exposure during *prenatal* and *postnatal* 1.6 times greater risk of wheezing occurred.[30] Infants with parental smokers 68% more likely to have asthma.[11] cohort study in Thailand also gained exposure to cigarette smoke are 1.5 times more likely to occur wheezing in infants aged 0-6 months and 1.4 times greater in infants 7-12 months.[31] In this study a history of smoking fathers appear to be associated with the incidence of wheezing. Can an increase in levels of IL-4, IL-5 and IFN-γ which can cause symptoms early wheezing in infants whose mothers smoked during pregnancy although the study was not found to mothers with a history of smoking.[32]

In this study there was no correlation to the sex of wheezing. This may be caused at an early age the majority of subjects spending more time at home indoors or while the larger age, boys are more outside the home were more likely exposed to inhaled allergens. Previous studies reported risk men 1.5 times more likely to suffer from allergies than women. Baby boy has a production capacity of IL-5 levels higher than women so that male infants are more prone to experience wheezing early (pre asthma) than women.[30.33]

Infants who consume non-breast milk foods are more prone to suffer wheezing. The incidence of allergies caused by food is estimated to occur approximately 12-30% with cow's milk is the most allergen triggers in infants and children. ASS occurs in approximately 2-3% of the entire population of children in the world at the age of 1 year the first.[30.34-35] In this study 93% of subjects were given food containing cow's milk protein and other food additives (non-breastfeeding), 66.7 % of them suffer from wheezing.

History childbirth SC 1.3 times greater risk for asthma occur in the future. SC labor may actually increase the risk of allergies for infants born to unexposed vaginal flora.[5.36] However, in the study of labor history seem unrelated to the incidence of wheezing. This is because of the age of the subjects who were too young to not appear to be differences early wheezing symptoms suffered by research subjects with a history of vaginal delivery and SC. But if these factors are not avoided the possibility of a baby suffering from atopic wheezing greater in accordance with the above study.

Studies in Jakarta obtained as atopic dermatitis *allergic march* picture that appears earlier than other symptoms.[37] This is consistent with the description of a previously reported *allergic march.*[38] However, in this study actually *allergic march* in Aceh picture that emerged early is a sign of wheezing illness asthma. So the

picture is said to have been a shift in *allergic march* in Aceh today.

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