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Research Article

Cow's milk protein sensitization on the lymphocyte Th-1 and Th-2 activity in relation to wheezing in the first year of life

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Abstract. Background: Atopic diseases are common and represent a serious heatlh problem worldwide and the incidence was increased in last three decades. Allergic disease is developed by at least three things: the genetic background, exposure to allergens and amplified by environmental factors. Wheezing is known as a common symptom in infant. Objective: To find an overview of the role of cow's milk protein sensitization on the lymphocyte Th-1 and Th-2 activity in relation with wheezing in infants up to 1 year of age. Methods: This exploratory observational, cohort study included total 71 infants collected by consecutive sampling. Data were collected from questionnaires completed by the parents, medical records, blood samples and skin prick test examination. Results: A total of 64.8% from 71 subjects suffering from wheezing. Allergy risk factors (95% CI 1.184-2.177; p = 0.007), skin prick test > 3 mm (95% CI 2.073-5.910; p = 0.000), IFN-γ levels below 0.53 (95% CI 1.029-2.046; p = 0.033), IL-5 levels above 0.6 (95% CI 1.685-6.877; p = 0.000), and the father smoked (95% CI 1.168-2.542; p = 0.003) appear related to the occurrence of wheezing. Multivariate test shown, the level of IL-5 (p = 0.000; RR 20.69; 95% CI: 4.51 to 94.83) combined with the level of IFN-γ (p = 0.010; RR 10.28; 95% CI: 1.73 to 31.61) and exposed to tobacco smoke by dad in indoor (p = 0.020; RR 6.49; 95% CI: 1.33 to 31.61), are clinically the trigger factors of wheezing in infants in the first year of life. Conclusion: A significant sensitivity of cow's milk had happened on this research subject and was marked by the early allergic march baby wheezing friction. Allergy risk in parent and exposed to tobacco smoke by dad in indoor are contribute to the onset of wheezing, through the activity of Th-2 lymphocytes are increased so that the level of IL-5 to be higher in infants suffering from atopic wheeze.

Key Words: infant atopy, allergy risk factors, cow's milk sensitization, environmental factors, activity of Th-1 and Th-2.

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Introduction

Atopic diseases are common and represent a serious heatlh problem worldwide and the incidence was increased in last three decades (Bellanti et al 2005; Mohammadzadeh et al 2008; Patel et al 2008). Food allergy was found in 12-30% of all infants (Skripak et al 2007; Abraham and Ownby 2005).

There are more than 170 types of foods known to cause allergic reactions mediated by immunoglobulin E (IgE), but a number of prevalence studies only focused on the most common causes of food allergies, such as cow's milk, eggs, seafood and peanut (Sampson 1993). Cow's milk was given to infants were not given breast milk that has been causing cow's milk allergy sensitization (CMA). Cow's milk sensitization occurred frequently between 1 month and the age of 3 years and could be characterized as atopic dermatitis or wheezing (Abraham and Ownby 2005; Smith and Ownby 2009). Approximately 35% of atopic infants younger than 2 years will develop into CMA when cow's milk is not avoided (Skripak et al 2007; O'Brien 2002). Allergic disease is developed by at least three things: the genetic background, exposure to allergens and amplified by environmental factors (O'Brien 2002). Infants with a family history of allergic disease have two to three times higher risk to become an atopic person compared with infants without a history of allergic disease in the family (Bellanti et al 2005; Patel et al 2008). Wheezing is known as a common symptom in children. Previous studies showed about 15% of all children who experienced wheezing in infancy will be at risk of developing asthma in the future (Al-Essa 2003; Høst and Halken 2003).

Cow's milk protein caused increasing production of interleukin (IL)-4, IL-5 and IL-10 secreted by Th-2. Interferon (IFN) γ is a cytokine secreted by Th-1 that have the properties of inhibiting IgE production. Cytokines are key factors for the production of IgE. Besides of Th-1 and Th-2 cells, in the last decade,

it had been found new subsets of Th cell, which are known as T regulatory cell (Treg) and other cell type which produce IL-17 and is called Th 17 cell. Treg cells produce an anti-inflammatory cytokine such as TGF-β that has an important role in the inflammation control. Th-17 cell produces IL-17A, IL-17E, IL-21, dan IL-22 which are important in the defense of the infection and inflammation reaction on the autoimmune disease (Høst and Halken 2003; Rottem et al 2008).

The aim of this study is to find an overview of the role of cow's milk protein sensitization on the lymphocyte Th-1 and Th-2 activity in relation with wheezing in infants up to 1 year of age.

Materials and Methods

This observational cohort study was conducted in the Dr. Zainal Abidin General Hospital, Banda Aceh, the capital of Aceh Provence, from May to December 2013. The were 71 infants were collected by consecutive sampling and fulfilled the inclusion criteria: infants with low-moderate or high risk factor for allergy, infants feeded with breast milk, cow's milk or any other milk-base formula. Exclusion criteria were as follows: severe acquired or congenital diseases, gestational age of less than 37 weeks, birth weight of less than 2500 g, or incapability of the parents to comply with the study protocol.

Data were collected from questionnaires completed by the parents, medical records, blood samples and skin prick test examination. The study protocol was approved by the ethical committee of University of North Sumatra.

After explaining the purpose of the study, informed consent was obtained from each respondent. Infants were also requested for skin prick test examination as a diagnostic procedure and 5 ml of peripheral blood was taken for examination of the cytokines IL-5 and IFN-γ.

The risk of allergy in infants were obtained by asking the history of allergy in the family to the parents. Each answer was given the points that divide the subject into low-moderate or high risk factor for allergy (Munasir 2011).

Subject were monitored regularly every week by telephone to determine allergic complaints from prospective subjects and were confirmed by a pediatric allergist/immunologist, until the infant was 1 year of age. All infant who wheezed 0-12 months were compared to all infant who did not wheeze 0-12 months. Univariate analysis was carried out for all variables to describe their characteristics. In bivariate analysis, crude relative risk (RR) with 95% CI and Chi-square of Fisher's exact test (as appropriate) were calculated to identify associations between categorical variables. In multivariate analysis, a multiple logistic regression model was developed to identify the association between the dichotomous outcome variable: wheezing (yes/no) and potential predictors. Independent t test were used to assess the differences activity of Th-1 and Th-2 and the result of skin prick test in wheezing and non-wheezing group, and the differences value of skin prick test result in high allergy risk and low-moderate allergy risk. Significance level for p values for all analysis was set at 0.05 to control for multiple comparison. Analyses were performed using SPSS for Windows version 17.0.

Results

A total 71 infants could be followed up until first year of life. Subjects' characteristics are shown on Table 1.

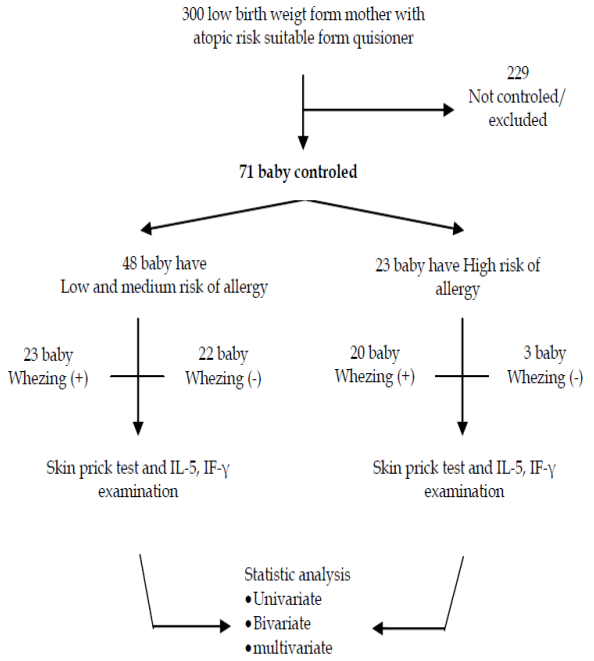

Figure 1. The plot of the study samples taking

Table 1. Subjects' characteristics (n=71)

Variable	Total subject (%)
Allergy Risk in Parent	
High	23 (32.4)
Low-Moderate	48 (67.6)
Skin prick test	
≥3 mm	36 (50.7)
<3 mm	35 (49.3)
IFN-γ Level	
Below 0.53	32 (45.1)
Above 0.54	39 (54.9)
IL-5 Level	
Above 0.6	47 (66.2)
Below 0.6	24 (33.8)
Smoker Dad (Indoor)	
Yes	37 (52.1)
No	34 (47.9)
History of Labor	
Caesarian	31 (43.7)
Vaginal Birth	40 (56.3)
Feeding History	
Non-exclusive/formula	66 (93)
Exclusive breastfed	5 (7)
Gender	
Male	35 (49.3)
Female	36 (50.7)

Based on the statistical tests, no significant relationship between infants who had consumed non-exclusive breastfeeding and exclusive breastfed suffered from wheezing (p = 0.232; relative

Table 2. Bivariate analysis between independent variables with the incidence of wheezing (n=71)

Independent Variables	Wheezing Complaints		p	Relative Risk (RR)	95% CI
	Yes	No			
	n (%)	n (%)			
Feeding History					
Non-exclusive/formula	44 (66.7)	22 (33.3)	0.232**	1.667	(0.562-4.942)
Exclusive breastfed	2 (40)	3 (60)			
Allergy Risk in Parent					
High	20 (86.9)	3 (13)	0.007*	1.605	(1.184-2.177)
Low-moderate	26 (54.2)	22 (45.8)			
Skin prick test					
≥3 mm	36 (100)	0 (0)	0.000*	3.5	(2.073-5.910)
<3 mm	10 (28.6)	25 (71.4)			
IFN-γ Level					
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 Level					
Above 0.6	40 (85.1)	7 (14.9)	0.000*	3.404	(1.685-6.877)
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					
Caesarian	22 (71)	9 (29)	0.337*	0.845	(0.603-1.186)
Vaginal birth	24 (60)	16 (40)			
Sex					
Male	23 (65.7)	12 (34.3)	0.872*	1.029	(0.730-1.449)
Female	23 (63.9)	13 (36.1)			

Table 3. Multivariate correlation between IFN-γ level combined IL-5 level and exposed to tobacco smoke by dad in indoor with the incidence of wheezing)

Variables	Coefficient	p	RR (95% CI)
IFN-γ level	2.33	0.01	10.28 (1.73-31.61)
IL-5 level	3.03	0	20.69 (4.51-94.83)
Smoker Dad (indoor)	1.872	0.02	6.49 (1.33-31.61)
Constant	-2.856	0.001	0.057

risk (RR) 1.667; 95% confidence interval (CI) 0.562-4.942). There were 93% of the subjects consumed non-exclusive breast-feeding (breastfed and other milk formula), whereas 7% of the subjects consumed exclusive breastfed.

Approximately 32.4% of the subjects were categorized into high risk of allergy in parent, and of these, 86.9% suffered from wheezing. Among the other 67.6% who had a low-moderate of allergy in parent, 54.2% of the subjects suffered from wheezing. Statistical tests showed significant relationship between groups (p = 0.007; RR 1.605; 95% CI 1.184-2.177).

Table 4. Bivariate correlation between the level of IFN-γ and IL5 with the skin prick test

Independent Variable	Skin prick test results		p	RR
	≥3 mm	<3 mm		95% CI
	n (%)	n (%)		
IFN-γ level				
Below 0.53	20 (55.6)	16 (44.4)	0.072*	2.396 (0.918-6.250)
Above 0.54	12 (34.3)	23 (65.7)		
IL-5 level				
Above 0.6	36 (100)	0 (0)	0.000*	3.182 (1.951-5.190)
Below 0.6	11 (31.4)	24 (68.6)		

All of the subjects who had a skin prick test result bigger than 3 mm, suffered from wheezing; from 49.3% of the subjects who had a skin prick test result smaller than 3 mm, 28.6% of the subjects suffered from wheezing. Based on the statistical test, there was difference found between groups (p = 0.000; RR 3.500; 95% CI 2.073-5.910).

No difference found between infants who had a sectio-caesarian labor and vaginal birth suffered from wheezing (p = 0.337; RR 0.845; 95% CI 0.603-1.186). From 47.3% subjects who had a sectio-caesarian labor, 71% of the subjects suffered from wheezing; and from 56.3% of the subjects who had a vaginal birth, 60% of the subjects suffered from wheezing.

Approximately 52.1% of the subjects were exposed to tobacco smoke by dad in indoor, where 81.1% suffered from wheezing; and from the remaining 47.9% of the subjects were not exposed, 47.1% suffered from wheezing. The result is statistically significant relationship (p = 0.003; RR 1.723; 95% CI 1.168-2.542).

From total subject who had an IFN-γ level above 0.54 pg/mL (54.9%), only 53.8% suffered from wheezing; from 45.1% of the subjects who had an IFN-γ level below 0.53 pg/mL, 78.1% suffered from wheezing. There was significant difference found between groups (p = 0.033; RR 1.451; 95% CI 1.029-2.046).

Our study found 66.2% of the subjects that had an IL-5 level above 0.6 pg/mL, and of these, 85.1% suffered from wheezing. Among the other, 33.8% who had an IL-5 level below 0.6 pg/mL, only 25% of the subjects suffered from wheezing. Statistical tests showed significant relationship between groups (p = 0.000; RR 3.404; 95% CI 1.685-6.877). We've shown the analysis between the incidence of wheezing and independent variable in Table 2.

The multiple logistic regression test showed the factors that resulted in p < 0.25 is, smoker dad (indoor) (p = 0.003; RR 1.723; 95% CI 1.168-2.542), the level of IFN-γ (p = 0.033; RR 1.451; 95% CI 1.029-2.046), the level of IL-5 (p = 0.000; RR 3.404; 95% CI 1.685-6.877), the results of skin prick test (p = 0.000; RR 3.500; 95% CI 2.073-5.910), and allergy risk in parent (p = 0.007; RR 1.605; 95% CI 1.184-2.177). After the multivariate test, the level of IL-5 (p = 0.000; RR 20.69; 95% CI: 4.51 to 94.83) combined with the level of IFN-γ (p = 0.010; RR 10.28; 95% CI: 1.73 to 31.61) and exposed to tobacco smoke by dad in indoor (p = 0.020; RR 6.49; 95% CI: 1.33 to 31.61), are clinically the trigger factors of wheezing in infants in the first year of life (Table 3).

The bivariate correlation between the level of IFN-γ and IL5 with the skin prick test is shown in Table 4. Our study found that 54.9% of the subjects who had an IFN-γ level above 0.54 pg/mL, 34.3% had a skin prick test result bigger than 3 mm; from 45.1% of the subjects who had an IFN-γ level below 0.53 pg/mL, 55.6% had a skin prick test result bigger than 3 mm. Statistical tests showed no significant relationship between groups (p = 0.072; RR 2.396; 95% CI 0.918-6.250).

There were 66.2% of the subjects that had an IL-5 level above 0.6 pg/mL, and all of these subjects had a skin prick test result bigger than 3 mm. Among the other, 33.8% who had an IL-5 level below 0.6 pg/mL, only 31.4% of the subjects had a skin prick test result bigger than 3 mm. Statistical tests showed significant relationship between groups (p = 0.000; RR 3.182; 95% CI 1.951-5.190).

The difference between some variables with the incidence of wheezing is shown in Table 5. From 71 of the subjects who had a skin prick test result, were obtained a mean value of IFN-γ level in wheezing group was 1.67 ± 2.81 pg/mL, mean value of IFN-γ level in non-wheezing group was 2.77 ± 3.17 pg/mL. Statistical tests showed no significant relationship between groups (p = 0.192).

Mean value of IL-5 level in wheezing group was 0.95 ± 0.46 pg/mL, mean value of IL-5 level in non-wheezing group was 0.54 ± 0.13 pg/mL. Statistical tests showed significant relationship between groups (p = 0.000).

Mean value of the skin prick test result in wheezing group was 3.96 ± 1.93 mm, mean value of the skin prick test result in non-wheezing group was 0.40 ± not 0.81 mm. Statistical tests showed significant relationship between groups (p = 0.000).

Table 5. The difference between various variables with the incidence of wheezing

Independent Variable	Wheezing Complaint		p
	Yes	No	
	Mean ± SD	Mean ± SD	
IFN-γ level	1.67 ± 2.81	2.77 ± 3.17	0,192
IL-5 level	0.95 ± 0.46	0.54 ± 0.13	0.000
Skin prick test result	3.96 ± 1.93	0.40 ± 0.81	0.000

Mean value of the skin prick test result in a high risk of allergies group was 3.70 ± 2.05 mm, mean value of the skin prick test result in a low-moderate risk of allergies group was 0.40 ± not 0.81 mm. Statistical tests showed significant relationship between groups (p = 0.010) (Table 6).

Table 6. The difference between skin prick test result based on allergy risk in parent.

Independent Variable	Allergy risk in Parent		P
	High	Low-moderate	
	Mean ± SD	Mean ± SD	
Skin prick test result	3.70 ± 2.05	2.23 ± 2.36	0.01

Skin prick test is considered as the gold standard in allergy diagnostic procedures. Profile assessment of Th-1 and Th-2 can be a new diagnostic procedures to determine an atopy baby who were suffered from allergies. Because it does not capture the cut off point for IL-5 and IFN-γ, then classification is determined from calculation of receiver operating characteristic (ROC) (Table 7).

Table 7. Classification value of IL-5, IFN-γ and skin prick test result based ROC

Variable	AUC	CI 95%	Cut Off Point	Sensitivity	Spesificity
IL-5	86%	0.775-0.956	0.865	0.522	0.04
IFN-γ	34%	0.208-0.487	1.46	0.217	0.52
Skin prick test	92%	0.859-0.956	0.21	0.848	0.88

Discussion

From total subjects were followed up to 1 year of life were obtained the incidence of wheezing was 64.8%. In this study obtained a significant relationship between the allergy risk in parent and the occurence of wheezing, in which the infants that had a high risk of allergies in parent were more common suffered from wheezing. Previous study reported children with a history of atopy in parent have 2 times greater risk to suffer from asthma in the future (Balemans et al 2006).

Atopy symptoms were found in 39.8% of the children if their mother has a history of atopy and 30.2% if their father has the symptoms of allergy. Children with both parents without a history of atopy risk are only 10% (Johansson et al 2004).

Lymphocytes Th-1 and Th-2 imbalance in atopic infants are usually caused by cow's milk protein allergens. Cow's milk consumption before 6 months of age stimulates type I and IV hypersensitivity reactions and resulting early inflammation in the skin or mucosa (O'Brien 2002).

In this study there was significant difference level of IFY-γ found between wheezing and non-wheezing group, in which the wheezing group have lower level of IFY-γ than the non-wheezing group. Th-2 cytokines actually increases when the allergic process continues, followed by a decrease in Th-1 cytokine (Sicherer 2008). But because this study was conducted in infants who had experienced early symptoms of allergies so it is understood that we did not found the decreased level of IFN-γ. Although the level of IFN-γ decreased due to IgE synthesis, but in previous in vivo studies found the Th-1 shift toward lower showed only minimal asthma symptoms. IFN-γ level actually increased in patients with severe asthma symptoms who had experienced acute exacerbation or early wheezing symptom caused by pathogens such as viruses and Respiratory syncytial Human rhinovirus. So it is clear that asthma is not always said to be a Th-2 driven disease (van Rensel et al 2005; Jartti et al 2009). Another study found a decrease level of IFN-γ only happened in infants with recurrent wheezing at the first year of life (Guerra et al 2004). Another study reported an increase of the Th-1 and Th-2 activity only occured in infants with acute and chronic asthma (Cho et al 2005).

Individuals who tend to be allergic, exposure to antigen resulted in the activation of Th-2 cells and IgE production. Previous studies have reported an increase production of IL-4 and IFN-γ in individuals with atopic disease and their levels are correlated with an increased production of total serum IgE. When someone are exposed to the antigen, the T cell response is the activation of Th-2 cells (Borish and Rosenwasser 2009; Magnan et al 2000). In this study, we did not examinate the level of IL-4 because the storage time in the freezer at minus 20 degrees celsius should not exceed 24 hours, so that we examined the level of IL-5 which is have longer time of storage in the refrigerator (at a temperature of minus 20 degrees celsius) together with IFN-γ levels were reached 2 months. Based on the theory, 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 (Borish and Rosenwasser 2009).

Patients with asthma were associated with significantly increased level of IL-5 (Choi et al 2009). Increased IgE production was associated with increased production of Th-2 cytokines (IL-4 and IL-5) in the first 12 months of age. Increased level of Th-2 cytokines will predict the possibility of asthma up to the age of 5 years (Rothers et al 2011). In this study there was significant difference in the level of IL-5 between wheezing and non-wheezing group, in which the wheezing group have higher level of IL-5 than the non-wheezing group.

Skin prick test is the conventional diagnostic were used to help the diagnose accuracy after a physical examination and family history was obtained. Skin prick test were used 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. A mediator released produces a wheal and flare reaction, in which quickly type hypersensitivity reactions are mediated with allergen-specific IgE. The presence of specific IgE is used to predict the size of the wheal formed. Skin prick test is easy, fast and very sensitive in detecting specific IgE (Lasley and Shapiro 2000; Hahn and Bacharier 2005). In this study there were differences in the results of skin prick tests on a high risk and and low-moderate risk of allergies group. 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 (Sicherer 2008). Resulted of this study also analyzed the differences between the results of skin prick test in wheezing and non-wheezing group.

In this study we assess the profile of Th-1 and Th-2 as new diagnostic procedures to determine the possibility of an atopic infants suffering from allergies. Because it does not capture the cut off point for IL-5 and IFN-γ, then classification is determined from calculation of ROC with skin prick test result as a comparison as shown in Figure 5, 6 and 7. Study result shown increased level of IL-5 above 0,6 pg/mL has shown the area under the curve (AUC) amounting to 86% which illustrated as "good performance tools" to determined allergic disease. Environment plays an important role in the mechanism of allergy. Pollutants such as cigarette smoke is one of the allergens exposed at an early age (Bellanti et al 2005; Yadav and Yadav 2005; Subbarao et al 2009). Cigarette smoke exposures during prenatal and postnatal have 1.6 times greater risk occurrence of wheezing (Sheriff et al 2001). Infants with parental smokers are 68% more likely to have asthma (Berz et al 2007). 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 (Sangsupawanich et al 2007). In this study a history of smoking fathers appear to be associated with the incidence of wheezing.

In this study there were no significant relationship between the sexes and wheezing symptom. This may be caused at an early age the majority of subjects spending more time at home. Previous studies reported the risk of allergy in boys is 1.5 times greater than girls. Boys have higher production capacity of IL-5 level than girls so that boys are more prone to experience early wheezing than girls (Sheriff et al 2001; Keski-Nisula et al 2010). Infants who consume non-exclusive breast milk formula are more prone to suffer wheezing. The incidence of allergies caused by food was found in 12-30% of all infants with cow's milk formula is known to be the most common cause of food allergy is in infants. CMA was found in 2-3% of the entire population of children in the world at the first year of life (Sheriff et al 2001; Boyce et al 2010; Lopez et al 2002). In this study 93% subjects

were given food containing cow's milk protein and other food addition (non-exclusive breastfeeding), 66.7 % of them suffer from wheezing. The domination of Th-2 or the increase of IL-5 level which is proven by the skin prick test of this positive cow milk is a door for the other food allergic such as egg, peanut, sea fish and another hyper allergenic food and if there isn't any prevention will cause the continuation of allergic march.

History of sectio-caesarian (SC) childbirth has 1.3 times greater risk for asthma in the future. SC labor may actually increase the risk of allergies for infants because unexposed vaginal flora (Abraham and Ownby 2005; Hakansson and Kallen 2003). However, in this study the history of labor has insignificant relation to the incidence of wheezing. This is because the age of the subjects was too young to show the differences of early wheezing symptoms suffered by research subjects. But if these factors are not avoided then the possibility of a baby suffering from atopic wheezing are greater in accordance with the above study. Study in Jakarta obtained that atopic dermatitis is appear earlier than other symptoms as an allergic march picture (Munasir et al 2011). This is consistent with the description of a previously reported allergic march (Liu 2006). However, in this study wheezing is a sign of illness that emerged early in the picture of allergic march in Aceh. There is a shift of allergic march picture in Aceh today.

In conclusion, A significant sensitivity of cow's milk had happened on this research subject and was marked by the early allergic march baby wheezing friction. This study also showed that allergy risk in parent and exposed to tobacco smoke by dad in indoor are contribute to the onset of wheezing, through the activity of Th-2 lymphocytes are increased so that the level of IL-5 to be higher in infants suffering from atopic wheeze.

Study limitations

The possibility of the subject under study has been recommended by doctors for a healthy lifestyle (no smoking, delaying solid foods) in women who are breastfeeding can result in bias.

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