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Original Article

Association between immunization coverage and atopy in children with or without family history of atopic disease

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Abstract

Background Atopic diseases are determined by the interaction between genetic and environmental factors. The possible effects of immunization, as one of environmental factors, on atopy remain a matter of controversy.

Objective We conducted an observational clinical epidemiology to find out the protective effect of high vaccination coverage to atopy in children.

Methods During January through March 2006, 150 of 749 children at Garuda, Padasuka, and Babakan Sari Primary Health Care in Bandung were randomized from group with and without family history of atopic disease. Atopy derived from skin prick test and total serum IgE was evaluated. Atopy was defined as a positive skin test to any of the eight allergens tested. The immunizations were recorded from *Kartu Menuju Sehat* (KMS). Statistical analyses included Chi square to compare prevalence, independent T-test and Mann-Whitney to compare mean.

Results Atopy was found in 28.2% of 284 subjects, of which 32.4% with and 23.9% without a family history of atopic disease. The median of total serum IgE level was higher in children with family history of atopic disease and in atopy children. Children were grouped according to total dose of basic immunizations (0-17 and ≥18) based on *Program Pengembangan Imunisasi* (PPI). There was nonsignificant association between total doses of immunization and atopy. Even though no statistically significant, the cumulative immunization doses were inversely related to the median of total serum IgE level.

Conclusions The immunization coverage has not decreased atopy risk. **[Paediatr Indones. 2008;48:358-63]**.

Keywords: *atopy, immunization, total serum IgE, family history of atopic disease*

The atopic diseases like allergic rhino conjunctivitis, asthma and atopic dermatitis are the most common chronic diseases of childhood[1,2] and the prevalence is still increasing.[3] In developing countries, asthma was considered to be low but recent studies have shown that the prevalence is increasing especially in urban compared to rural areas.[4] Asthma and other atopic diseases were determined by the interaction between genetic and environmental factors. Family history is an important risk factor for atopy.[4-6] Many other risk factors for the development of atopic disease have been identified,[4,5] such as infection. Bacterial and viral infections induce a Th1 pattern of cytokine release, potentially suppressing the Th2 immune response involved in IgE mediated allergy and inhibited the development of atopy.[7,8]

In the first year of life, the children's immune system is relatively immature. This immaturity creates

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a 'window period' between birth and 24 months of age during which is an enhanced risk of allergic sensitization and subsequent atopic disease.[9] An issue of particular interest, which is becoming increasingly controversial, concerns interactions between the developing immune system in children genetically susceptible to atopy and microbial stimulation through normal environment contact or through deliberate exposure by vaccination.[10] This hypothesis known as 'hygiene hypothesis' argues that early childhood infections inhibit the tendency to develop allergic disease.[7,11]

Immunization as one of the factors that effect the immune system in early life, could have positive or negative effect on allergic disease.[12] This issue become an interest of the researchers but the possible effects of immunization on atopy remains a matter of controversy. A number of studies have found no association between immunization and atopy.[10,12-16] Some studies found the association between immunization and atopy, either a protective effect against atopy[17-20] or increased the risk for atopy.[21-24] Nevertheless, the question of an association between immunization and atopy remains. The aim of this study was to find out the protective effect of high vaccination coverage to atopy in children.

Methods

We conducted an observational clinical epidemiology on groups with and without family history of atopic disease as a part of "Prevalence of allergic and identification of risk factors in the first two years of life" study at Garuda, Padasuka, and Babakan Sari Primary Health Care in Bandung. The first phase study was a community survey that was done on May through August 2004. The second phase was on January through March 2006. If the parents agreed, a written informed consent was obtained. Inclusion criteria included that the child must had joined the first phase, was physically healthy, and had *Kartu Menuju Sehat* (KMS) or other legal letters. The exclusion criteria included that the child had change the address or was in the therapy of first generation antihistamine for three days, nonsedated antihistamine for seven days, and systemic or topical corticosteroid for three months before skin prick test.

From 800 children joining the first phase, only 749 were eligible for the next phase, of which 204 children had family history of atopic disease. The subjects for this study were randomized from two groups with and without history of atopic disease. Each group consisted of 150 children. Subjects who fulfilled the inclusion criteria were brought to Hasan Sadikin hospital Bandung for clinical evaluation, which included a medical history, physical examination, skin prick test, and blood draw for total serum IgE.

The skin prick test used the allergens *Dermatophagoides pteronyssinus, Blomia tropicalis,* cat hair, cow's milk, egg's white, soybeans, cockroach, and peanuts. Both positive (histamine) and negative controls (saline solution) were also used. Skin prick test was considered positive if the product of perpendicular wheal diameters was ≥3mm to any of the allergens tested when there was no reaction to saline solution. Atopy was defined as a positive skin test to any of the eight allergens tested.

Total serum IgE was analysed in Hasan Sadikin hospital laboratory using electrochemiluminescence immunoassay (ECLIA) method, with <60 IU/mL as a normal value from reagent package insert for children 1-5 years of age.

Immunizations records were obtained from KMS or other legal letters. According to *Program Pengembangan Imunisasi* (PPI), immunization for children through 24 months consists of BCG, Polio, hepatitis B, DPT, and measles.

Statistical analysis performed by using SPSS software version 11.5 for windows and EpiInfo version 6.0. Chi-square ($\chi 2$) test was applied to compare prevalence, Kolmogorov-Smirnov test for nominal data, independent T-test for means and Mann-Whitney for medians between groups.

This study was approved by the Health Study Ethics Committee at Medical School Padjadjaran University/Hasan Sadikin General Hospital Bandung.

Results

From 300 subjects, nine children had already moved from the address and the parents of seven children refused the study, therefore there were only 284 subjects in this study, with 142 children in each group.

The subject characteristics based on family history of atopic disease was seen in **Table 1**. There were no statistical differences between groups with or without history of atopic disease. Therefore, the subjects were homogen.

Table 1. Characteristic of children based on family history of atopic disease

Characteristic	Family history of atopic disease		P value
	(+)	(–)	
Sex			
Boys	64 (45.1%)	66 (46.5%)	0.812
Girls	78 (54.9%)	76 (53.5%)	
Age (mo)			
X (SB)	36.4 (1.8)	36.2 (1.8)	0.233
Range	32.1 – 40.5	32.5 – 40.2	
Nutritional status			
underweight	32 (22.5%)	39 (27.5%)	0.995
well nourished	107 (75.4%)	101 (71.1%)	
overweight	3 (2.1%)	2 (1.4%)	

Atopy was found in 80 (28.2%) children. Prevalence of atopy on group with history of atopic disease was 52% greater than the other group, but the difference was not statistically significant (OR: 1.52, 95% CI 0.87 to 2.65, P= 0.113). The atopy prevalence based on family history of atopic disease was described in **Table 2.**

Table 2. Prevalence of atopy based on family history of atopic disease

Family history of atopic disease	Atopy		Nonatopy		Total	
	n	%	n	%	n	%
(+)	46	32.4	96	67.6	142	100
(–)	34	23.9	108	76.1	142	100
Total	80	28.2	204	71.8	284	100

Note: $\chi 2$: 2.506; P= 0.113; OR : 1.52 (95%CI 0.87 to 2.65)

From 284 subjects, we had only been able to collect 271 (95.4%) sera for total serum IgE analysis. In this study, the median of total serum IgE was 120.05 IU/mL (5.22->2,500 IU/mL). The median of total serum IgE was 131.7 IU/mL (12.12->2,500 IU/mL) for group with family history of atopic disease, as compared to 105.9 IU/mL (5.22->2,500 IU/mL) for the other group. However, there was no statistical difference between the groups (P = 0.133).

The association between total serum IgE and the prevalence of atopy was indicated in **Table 3**. Generally for all subjects that had skin prick test and total serum IgE analysis, the median of IgE level was greater on atopy children and significantly different (P<0.05) except for group with family history of atopic disease (P=0.317).

Table 3. The association between total serum ige level and atopy

Total serum IgE on	Atopy	Nonatopy	P value
History of atopic disease (+)			
N	44	92	0.317
Median	162.8	125.8	
Range	18.28-1,517	12.12->2,500	
History of atopic disease (–)			
N	34	101	0.015*
Median	196.8	94.3	
Range	16.08->2,500	5.22-1,459	
All of Subjects			
N	78	193	0.011*
Median	181.8	106.5	
Range	16.08->2,500	5.22->2,500	

Note: *P<0.05

From immunization records, we found only 199 (69.8%) children had already completed basic immunization according to *Program Pengembangan Imunisasi* (PPI). Seven children (2.5%) had not any vaccination at all and the rest had not completely immunized. The subjects than were divided into two groups based on total dose of basic immunization. The children who did not immunize and not fully immunized (0-17) were on the first group and the children who had all the basic immunization and more (≥ 18) on the other group. Based on family history of atopic disease, there was no significant difference (P=0.358) in number of children between the two groups.

The association between atopy and immunization coverage was seen on **Table 4**. There was no association found between immunization coverage and atopy in children, whether in general or based on family history of atopic disease (P>0.05).

The median differences of total serum IgE based on groups of immunization coverage was seen on **Table 5**.

Table 4. The association between immunization coverage and atopy

Immunization Coverage	Family history of atopic disease				Total	Statistic
	(+)		(–)			
	Atopy	Nonatopy	Atopy	Nonatopy		
0-17	14	30	8	29	81	$\chi 2$: 0.996
≥ 18	32	66	26	79	203	P= 0.802
Total	46	96	34	108	284	df = 3

Table 5. Total serum ige level on immunization coverage

Total serum IgE on	Immunization Coverage		P value
	0-17	≥ 18	
History of atopic disease (+)			
N	42	94	0.320
Median	150.35	123.30	
Range	15.83->2,500	12.12-2,482	

In this study, we found that the higher the cumulative doses of immunization, the lower the median of total serum IgE, but statistically no significant (P>0.05).

Discussion

Family history is an important risk factor for atopic disease. Subjects with a family history of atopic disease have a two- to threefold higher risk to develop atopic disease than those with no such history.[4-6]

In this study, the prevalence of atopy on group with family history of atopic disease was 32.4% compared to 23.9% on group without. Björkstén (cited by Koning),[25] found that if a child has one atopic parent, the risk to become allergic is approximately 20%, increasing to 60% with two atopic parents, whereas without atopic parents the risk is around 10%.[25] Alford[6] found 39.8% atopy children if they had an atopic mother and 30.2% atopy children if their father had atopic disease, whereas without atopic parents, the prevalence of atopy was 29%.[6] In this study, the family history of atopic disease based only on anamnesis without other examinations such as skin prick test or serum allergen-specific IgE, might cause a nonsignificant different of atopy between children with or without family history of atopic disease.

The median of total serum IgE was higher than normal value from package insert reagent (120.05 IU/mL: <60 IU/mL). In addition to age and genetic factors, the total serum IgE was influenced by racial factor. Orgal who studied 27 Filipino and 24 white children born and raised in the United States found that in Filipino children the mean IgE level were significantly higher than in white children.[26] The IgE level was higher on group with as compared to group without family history of atopic disease but the difference was not statistically significant. It was likely because children with family history of atopic disease had a familial tendency to produce IgE antibodies that even often appear before any clinical symptoms have developed.[27,28]

The median of IgE level was also higher on atopy than nonatopy children and the difference was statistically significance except on group with family history of atopic disease. A child with atopy indicates a Th2 predominance that produces IgE antibodies in response to ordinary exposures to allergens[1,2,29] and the term atopy can not be used until IgE sensitization has been documented by a positive skin prick test.[28] The different kinetic in the development of IgE antibodies in atopic and nonatopic children is well known because excessive IgE antibody formation is a hallmark of the atopic individual.[27]

The immunization records showed only 69.8% children had completed basic immunization. There was no difference of atopy between groups that had completed and uncompleted basic immunization (OR: 0.93, 95%CI: 0.50;1.72, P=0.811). Anderson who used ecologic analysis to find the relation between the prevalence of symptoms of atopic diseases in children and immunization records at the national and local ISAAC centre levels for DPT, BCG, and measles, found no association with national immunization rates to atopic disease in children.[12] On the other side, Gruber who analysed the prevalence of atopic disease in relation to immunization coverage, found the cumulative vaccine dose was inversely related to atopic dermatitis and asthma prevalences.[18]

Our study showed no association between immunization and atopy as atopy could be caused by multifactor and immunization is only one of the environmental factors. The limited information regarding life style factors could lead to confounding bias. A conscious choice of parents not to have their child immunized might go with other lifestyle factors that effect the development of atopy.[30]

The mechanism contributing to microbial protection against atopy relates to dendritic cells, an efficient APC that can stimulate naive T cells and drive them to Th1 or Th2. When stimulated, dendritic cells can produce cytokines that may down-regulated allergic responses. The limited induction of Th1 responses after immunization early in life appears to result from suboptimal interactions between APC and T cells in infancy. The induction of adult-like Th1 responses early in life requires optimal activation of neonatal dendritic cells.

Since modern subunit vaccines were mostly lack of microbial antigens, they may not activate dendritic cells efficiently. As a result, the absence of microbial antigens from vaccines may impair regulation of the adaptive immune response. Recent advances in understanding how cell-mediated immunity is regulated have indicated substantial differences between responses after natural infection and immunization that may contribute to the limited induction of Th1 responses after immunization.[30]

An interesting issue we found in this study was the higher the immunization coverage, the lower the total serum IgE, but the difference was not statistically significant. Gruber found the similar result that the median of total serum IgE was inversely related to immunization coverage.[18] IgE was produced as a response to certain antigen like allergen and parasite. Low dose antigen will induce Th2 cells to produce IL-4 and IL-13 that stimulates the production of IgE.[1] Immunization could directly stimulate Th1 immunity. Th1 cells response was down modulating the effects of Th2 cells that would influence IgE production.[31]

We conclude that the immunization coverage has not decreased atopy risk in children. The higher the immunization coverage, the lower the total serum IgE.

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