ORIGINAL ARTICLE

Risk Factors of Respiratory Allergy in Children with Atopic Dermatitis

Sjawitri P. Siregar,Bambang Madiyono, Amar W. Adisasmito

(Department of Child Health, Medical School, University of Indonesia, Cipto Mangunkusumo Hospital, Jakarta)

ABSTRACT This paper described a case-control study among atopic dermatitis (AD) patients on the development of respiratoric allergy (RA) i.e., (asthma and/or allergic rhinitis), in Cipto Mangunkusumo Hospital, Jakarta. Secondary data were collected from January 1, 1995 to April 31, 1998. One hundred and one children with RA in AD patients (case group), and 101 children with AD (control group) aged <16 years were evaluated for exposure to possible risk factors for RA. The mean age of AD onset was 1 year and 5 weeks in the case group, and 2 years and 2 months in the control group (p = 0.000). Early AD onset <1 year was a significant risk factor (p = 0,0003; OR = 9.6, 95% confidence intervals 2.8 ; 33.3). History of inhalant allergy was associated with the excess risk for RA in children with AD (p = 0.0025; OR 2.9, 95%CI: 1.5 ; 5.7). Early onset of egg supplementation <6 months was statistically significant to increase that such risk (p = 0.05; OR 3.3, 95%CI: 1.0 ; 11.7). Our findings suggest that early onset of AD before the age of one year would increase the development of RA on AD patients. Besides, we conclude that postponing the administration of egg supplementation until the age of one year, and preventing the exposure of inhalant allergens would prevent RA, particularly in family history of atopy. **[Pediatr Indones 1999; 39:134-144]**

Introduction

There is a high prevalence of respiratory allergy (RA), i.. e., asthma and allergic rhinitis, in children with atopic dermatitis. Studies that have attempted to quantify the association have produced widely varying figures, ranging from 20% to 50%.[1-3] Parents of such patients, or patients themselves, with any respiratory symptoms during physical activity or in the case of upper respiratory tract infection, may have failed to

Author's address: Syawitri P Siregar, MD, Department of Child Health, Medical School, University of Indonesia, Jalan Salemba 6, Jakarta 10430. Tel. 62-21-3907742, Fax 390-7743.

recognize these symptoms as asthma symptoms.[1,4] Bronchial hyperreactivity has a strong association with decreasing function of the lung.[5] Such condition may also happen among allergic rhinitis patients,[6] which could prolong until adulthood, thus affecting growth-development and subsequently the quality of life.[5]

Preventing the exposure of food and inhalant allergens in infancy will decrease the occurrence of AD during the first year of life and RA in the future. Food allergy will develop in babies with early egg supplementation. Food allergens could be secreted from breast milk.[7-9] Respiratory allergy is more likely to develop in children with early onset of AD.[10] In normal children, although they can be sensitized by a certain allergens in the environment, they have already an epidermic barrier system, and no lesion will occur. While in AD children, that barrier system has been destroyed (by scratching), thus large allergen molecules can pass through.[11] In RA children, eosinophil cells cause the destruction of mucosal bronchial epithelium.[12] The hyperreactivity to histamine can develop on RA as well as AD patients.4 Viral infection could induce development of mucosal lesion, large molecule of allergen penetrations through mucosa, and bronchial hyperreactivity. Such infection could also depressed suppressor T-cell function, thus developing the IgE hypersecretion.[6,13] The aim of the present study was to investigate risk factors for the deleopment of RA among AD patients and the magnitude of them.

Methods

This was a case-control study on the association between AD patients and the development of RA, done in the Divisions of Allergy and Immunology and Pulmonology, Pediatric Department, and Dermatology and Venereal Disease Department, Cipto Mangunkusumo Hospital, Jakarta. Data were collected from January 1, 1995 to April 31, 1998. The inclusion criteria were: (1) subjects under the age 16 years, (2) the case group included outpatients with asthma and/or allergic rhinitis (RA) on AD patients, and the control group included outpatients with AD. The exclusion criteria were patients with severe disease, e.g. congenital heart disease, lung tuberculosis, hematological disorder. Cases and controls were collected at the same period between January 1, 1995 and April 31, 1998. Because of limited number of subjects, it was not possible to select the controls randomly. The total number of cases (AD patients with RA) was 104; 3 of which were excluded due to tuberculosis. The total number of controls (AD patients) was 102; one of them was excluded due to a ventricle septal defect.

Data were put into the computer and processed by Epi-Info 6.0 version. In analyzing the influencing risk factors that might increase the development of RA, a logistic regression was used. The type I of error was 0.05 with the power of 80%. Odds ratio with 95% confidence intervals were analyzed with SPSS 6.0 version.

Results

I. Bivariate analyses

Among subjects who had their first visit at the age of <1 year, the percentage who had RA was 37.5%, whereas it was 53.3% among those who had such visit at the age of >5 years. The difference, however, was not statistically significant (Table 1). Among male subjects, there were 52.2% who had RA, while among female subjects the rate was slightly lower (47.1%). There was also no difference between those with family history of atopy and those without on the occurrence of RA, among those with history of inhalant allergy, and those who had history of having furred pets. Patients with AD onset <1 year, the percentage who had RA was higher than those with AD onset > 5 years.

Table 1. Distribution of AD patients according to their age at first visit to the hospital, sex, family history of atopy, inhalant allergy, and AD onset

	Total	Case group		Control group		OR
		n	%	n	%	(95% CI)
Age						
▪ < 1 year	24	9	37.5	15	62.5	0.53 (0.18 ; 1.49)
▪ > 1 - 4	103	52	50.5	51	49.5	0.89 (0.47 ; 1.70)
▪ 5 - 15	75	40	53.3	35	46.7	Reference
Sex						
▪ Male	115	60	52.2	55	47.8	0.82
▪ Female	87	41	47.1	46	52.9	(0.45 ; 1.49)
Family history of atopy						
▪ Yes	186	93	50.0	93	50.0	1.00
▪ None	16	8	50.0	8	50.0	(0.32; 3.11)
Inhalant allergy						
▪ Yes	123	73	59.3	50	40.7	2.45
▪ None	67	25	37.3	42	62.7	(1.27 ; 4.77)
AD onset (yr)						
▪ < 1	105	63	60.0	42	40.0	6.75 (1.94 ; 25.81)
▪ 1 - 4	75	34	45.3	41	54.7	3.73 (1.04 ; 14.67)
▪ 5 -16	22	4	18.2	18	81.8	Reference

Table 2 summarizes the association between several factors and the development of DA. It shows that there were no associations between DA and the duration of breastfeeding, age at cow's milk supplementation, age at egg introduction, and history of food allergy.

Table 2. Distribution of AD patients according to duration of breast feeding, onset of cow's milk supplementation, onset of egg supplementation, and history of food allergy

	Total	Case group		Control group		OR
		n	%	n	%	(95%CI)
Duration of breast feeding						
▪ None	10	5	50.0	5	50.0	0.92 (0.21 ; 4.03)
▪ < 4 mo	24	12	50.0	12	50.0	0.92 (0.34 ; 2.48)
▪ > 4 - <12 mo	70	33	47.1	37	52.9	0.82 (0.42 ; 1.60)
▪ > 12 - 48 mo	98	51	52.0	47	48.0	Reference
Onset of cow's milk suppl.						
▪ < 7 days	35	20	57.1	15	42.9	2.44 (0.82 ; 7.36)
▪ >7 hr-<4 mo	34	18	52.9	16	47.1	2,06 (0.69 ; 6.22)
▪ >4 mo-< 1 year	60	29	48.3	31	51.7	1,72 (0.66 ; 4.52)
▪ > 1 year	39	22	56.4	17	43.6	2.37 (0.80 ; 6.91)
▪ None	34	12	35.3	22	64.7	Reference
Onset of egg suppl						
▪ < 6 mo	35	20	57.1	15	42.9	3.56 (0.97 ; 13.49)
▪ > 6 -	79	44	55.7	35	44.3	3.35 (1.07 ; 10.93)
▪ > 12 - 48 mo	66	31	47.0	35	53.0	2.36 (0.74 ; 7.87)
▪ None	22	6	27.3	16	72.7	Reference
History of food allergy						
▪ Yes	92	44	47.8	48	52.2	0.85 (0.47 ; 1.55)
▪ No	110	57	51.8	53	48.2	

Table 3 depicts the comparisons of the means of continuous variables in tha case and in control groups. While the onset of AD was significantly difference between the 2 groups, other variables (duration of breastfeeding, age at cow's milk suppl.ementation, and at egg supplementation) did not show difference in the 2 groups. There was no linear correlation between AD onset and RA onset in the case group (data not shown).

Table 3. Tables of the mean continuous variables originating from the independent variables

	Case group		Control Group		p*
	Mean (SE)	Median	Mean (SE)	Median	
AD onset (year)	1.1 (0,18)	0.4	2.3 (0.27)	2.3	0.000
Duration of breastfeeding (mo)	13.4 (0,94)	12.0	12.8 (0.92)	11.0	0.642
Age at cow's milk suppl. (mo)	7.0 (0,85)	4.0	6.4 (0.74)	4.0	0.896
Age at egg suppl. (mo)	8.5 (0.42)	8.0	8.9 (0.40)	8.0	0.317

* Mann Whitney U test.

Multivariate analyses

Multivariate analyses were performed using SPSS version 6.0, with backward selection methods. The independent variables included in the multivariate analyses were those which had p <0.25 in bivariate analyses.[14] Subjects with AD onset <1 year compared to those >5 years had the biggest influence on the occurrence of RA (OR = 6.75, 95%CI: 1.94 ; 25.81). Further, the influences of other variables (history of inhalant allergy, onset of egg supplementation, and history of having furred pets) were analyzed towards the association between AD onset <1 year and the occurrence of RA (Table 4).

Table 4. Logistic regression of history of inhalant allergy, having furred pets, and onset of egg supplementation) towards the association between AD onset and the occurrence of RA

Independent variables	Crude OR (95%CI)	Adjusted OR (95%CI)
AD onset		
▪ < 1 year	6.75 (1.94 ; 25.81)	8.61 (2.52 ; 29.41)
▪ 1 - 5 year	3.73 (1.04 ; 14.67)	3.90 (1.15 ; 13.26)
▪ History of inhalant allergy	2.45 (1.27 ;4.77)	3.33 (1.73 ; 6.44)
AD onset		
▪ < 1 year	6.75 (1.94 ; 25.81)	6.97 (2.19 ; 22.22)
▪ 1 - 5 year	3.73 (1.04 ; 14.67)	3.84 (1.18 ; 12.52)
▪ History of having furred pets	1.48 (0.76 ; 2.87)	1.56 (0.82 ; 2.95)
AD onset		
▪ < 1 year	6.75 (1.94 ; 25.81)	8.19 (2.55 ; 26.32)
▪ 1 - 5 year	3.73 (1.04 ; 14.67)	4.33 (1.32 ; 14.18)
Onset of egg suppl (mo)		
▪ < 6	3.56 (0.97 ; 13.49)	4.31 (1.33 ; 14.01)
▪ 6 - 11	3.35 (1.07 ; 10.93)	4.49 (1.55 ; 13.02)
▪ 12 - 48	2.36 (0.74 ; 7.87)	3.37 (1.13 ; 10.04)

From the analyses above, variables of history of inhalant allergy and onset of egg supplementation had great influences in changing the AD onset crude OR (6.75). The adjusted ORs were 8.61 and 8.19 if history of inhalant allergy and onset of egg supplementation were included in model containing AD onset as the independent variables, consecutively.

Further, multivariate analyses were performed including AD onset, history of inhalant allergy, history of having furred pets, and onset of egg supplementation to see the influence of 3 covariates towards the association between AD onset and the occurrence of RA (Table 5).

Table 5. Final multivariate analysis of independent variables towards the occurrence of RA

Independent variables	β	*p* (Wald)	Adjusted OR (95% CI)
AD onset			
▪ < 1 year	2.6500	0.0003	9.6339 (2.78; 33.33)
▪ > 1 - 5 year		0.0193	4.3745 (1.27; 15.06)
▪ > 5 year			*Reference*
History of inhalant allergy			
▪ (+)	1.0561	0.0025	2.8752 (1.45; 5.69)
▪ (-)			*Reference*
History of having furred pets			
▪ (+)	0.3326	0.3611	1.3947 (0.68; 2.85)
▪ (-)			*Reference*
Onset of egg suppl			
▪ < 6 mo	1.2065	0.0585	3.3422 (0.96; 11.66)
▪ > 6 - 12 mo	1.1303	0.0478	3.0960 (1.01; 9.49)
▪ > 12 - 48 mo	0.8081	0.1721	2.2437 (0.70; 7.15)
▪ No egg			*Reference*
Constant	- 3.3669	0.0000	

β = parameter estimate; OR = odds ratio; CI = confidence intervals

Three out of the 4 risk factors included in the multivariate analyses had substantial influence to the occurrence of RA. Odds ratio of AD onset <1 year compared to >5 years was almost 10. The risk of developing RA was 3 times due to any history of inhalant allergy compared to those without such history. Whereas such risk was 3.3 times among those who received egg supplementation at the age of <6 months compared to those who never received egg supplementation during their entire life.

Discussion

Our data demonstrated that early AD onset occurred more frequently in case group than in the control group (Table 1). When AD developed early (< 1 year), the risk of respiratory allergy (RA) was nearly 10 times more than when it developed later (Table 5). Pasternack reported that the prevalence of asthma in children with infantile AD was greater when it developed at age <3 months (45%), compared with those >6 months (30%).[15] This suggests that there is an increasing risk of RA in the early onset of AD. The same is reported by Braun-Falco and Rudzki, especially if there was family history of atopy.[10,16] Our data show that in the case group, there was no difference between the age of AD onset and RA onset. Early onset of AD (0-2 years) did not predict the age onset of RA (0-6 years).

In the case group, RA occurred around 21 months after the onset of AD. According to Guillet, allergic sensitization to aeroallergens with clinical RA symptoms appears 18 months after sensitization to food allergens in AD patients.[17] Fifteen patients in the control groups, who visited the hospital for the first time for their AD, was at the age of 1 year. Three of them visited the hospital in a period less then 1 year, nine of them between 1-2 years, and the remaining >2 years. Home visit or a follow up could be performed to ensure if their AD manifest as RA or not. A cohort study by Guillet showed that infants with early AD would develop RA at the age of 3 years.[17]

Gender had no correlation to RA on AD patients, similar to the study by Salob.[1] Two different intervention studies with clearly contrasting results by Zeiger and Horwood, found a significant relation ($p < 0.05$), in boys being at a disadvantage to be atopic than in girls. This might be caused by a higher IgE in boys with atopy,[18,19] and/or a higher airway mucosal sensitivity to aeroallergens.[20] fFrther studies are necessary to establish the final conclusion.

In this study, family history of atopy was not related with RA on AD patients (Table 2), which might be caused by recall bias. The case as well as the control group had the same chance to be at high risk of having atopy history in the family. In many studies, atopy disease has been found genetically inherited.[21] Family history of atopy would increase the incidence of asthma.[15,18,22]

A lot of difficulties were found to diagnose food allergy in this retrospective study, since the elimination and provocation test was not performed in all patients with food allergy histories. History of food allergy was not significantly associated with RA on AD (Table 5). Strong allergenic food e.g. seafood, contains allergen M (on fish muscles or crab/shrimp shells). Nuts, fruits, and certain vegetables are strong allergens, but usually they lost their allergenicity upon heating or freezing.[23]

In a cohort study of 250 patients with AD, Guillet reported that infants with food allergy and severe AD, the RA were estimated to develop at the age of 3 years.[17] Zeiger found that food and inhalant allergen avoidance during infancy will decrease RA risk in the future.[18] In conclusion, food and inhalant allergens appear to be in close relation with AD and RA.

In a case-control study by Lindfors, it was mentioned that aeroallergens sensitization during the first and second year of life would increase the risk of atopic diseases (OR= 2.1).[22] We found this to be a significantly greater risk.In two different investigations by Leung and Tan with inhalant and food double blind controlled test, it was concluded that both allergens caused an exacerbation of AD and RA.[3,7] Therefore both of these allergens were important risk factors of RA on AD patients. In this study, exposure to furred pets had no correlation with RA on AD patients, similar with the cross-sectional study by Cuijpers and Le-Roux.[20,24] Bener and Abdulrazzac pointed that exposure to furred pets favored the development of sensitization to furred pets twice in AD patients, compared with those without.[25,26]

Sensitization to furred pets in RA may be seen as a marker of exposure to these pets during the first year of life. This particularly happened in children sensitized to furred pets, and the dose of inhaled allergen may be increased with low indoor air exchange as allergenic particles were kept airborne for a longer period of time in a poorly ventilated dwelling.[22,27] We could not explain whether the furred pets were kept in or outdoor, the onset and duration of sensitization to fur coated pets.

Data of environmental tobacco smoke (ETS) history in the control group could not be analyzed. History of ETS during the first year of life is related with development of RA in children. RA risk is 4 times greater if there was ETS history during the patients' entire life or 3 times if family members smoked 11-20 cigarettes per day.[20] The risk of RA became twice greater if there was ETS history in the family, especially for patients <30 months. This was similar with cross-sectional study[24] which was 1.79 times.[22]

Physiological immaturity of gastro-intestinal tract in infants with secretory IgA insufficiency increases mucosal permeability, and subsequently IgE over-production.[17] Secretory IgA has a protective role during breast feeding by binding allergens.[21] Patients with a breast feeding duration until 1 year, have less RA symptoms, although statistically not significant. Lindfors et al reported that duration of breast feeding in high risk infants could not prevent the occurrence of asthma.[22]

Patients with a breast feeding duration of more than 1 year, indicated higher percentage with RA symptoms. If this is true, their mother might have given allergenic food supplement before the age of 1 year. Cow's milk protein consumed by mother may cause early sensitization in their child.[23,28,29]

Cow's milk formula contains minimally 20 kinds of proteins. -lactoglobulin is the most important cow's milk protein.[23] In case-control study by Lindfors et al, if the child consumed cow's milk before the age of 3 years, there was a higher percentage of RA (44%) compared with the ones without (38%).[22] Early exposure with allergens in infancy enhances sensitization, influenced by immaturity of gastro-intestinal immunology.[23] This study failed to prove an association between early cow's milk consumption and RA on AD patients, similar to others.[19,30]

Patients with cow's milk supplementation starting on the age of more than 1 year, indicated a higher percentage of RA on AD patients. If this is true, their mother might have given allergenic food supplementation to their child before the age of 1 year. Or their mother had been lactating their babies without avoiding allergenic foods, thus their breast feeding contained allergenic protein. Over the age of 1 year, sensitization to aeroallergens secondarily occurred after food sensitization, as reported by Guillet et al.[17] In this group, the possibility of a former aeroallergen sensitization could not be neglected, thus their AD became RA.

This study stressed that early egg supplementation before the age of 1 year on AD patients, would have an effect of a three times larger RA risk. In two different intervention studies by Zeiger and Arshad, avoidance to egg supplementation before the age of

1 year would lessen the RA risk.[8,18] The explanation is, early egg supplementation is one of the risk factor. It is suggested to postpone egg supplementation until the age of 1 year. The most allergenic part of the egg is ovomucoid protein in the egg white.[23] This protein implies IgE overproduction on AD or RA patients. In the cohort study by Nickel et al, an egg-specific IgE antibodies increase, observed at the age of 12 months, could predict aeroallergen sensitization at the age of 3 years.[31]

Inhalant allergy and onset of egg supplementation variables act as confounding or have substantial influence towards the association between the onset of AD and the incidence of RA. While sensitization to furred pets variable has no correlation (Table 7). Each of the variables above mask the effect of onset of AD on the occurrence of RA.

There is substantial difference between the crude and adjusted odds ratios of AD onset <1 year of having RA (6.75 vs 9.63, consecutively), suggesting that there is a material effect on the occurrence of RA. Without the presence of other variables, the risk of having RA was nearly 7 times. However, in the presence of other variables (inhalant allergy, history of having furred pets, and early onset of egg supplementation), the effect of AD onset < 1 year was slightly less then 10 (Table 5). This is due to confounding effect of the other variables towards the association between AD onset and the occurrence of RA. Analyses of modification effects were not done in this study.

To sum up, our data indicate that early onset of AD before the age of 1 year, the presence of inhalant allergy, and the early egg supplementation before the age of 1 year, increase the RA risk on AD patients. The mean age onset of AD was earlier in the AD patients which develop RA, compared to patients with isolated AD. The mean of RA symptoms develop around 21 months after the onset of AD. This study can be used as a based data for further investigation with cohort design study and greater number of samples. This data can also be utilized for parents' counseling for the benefit of allergen avoidance. Child management with these atopic diseases could give high burden to the family.

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