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Original Article

Prevalence and associated factors of airway hyper-responsiveness in children with recurrent chronic cough

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ABSTRACT

Background Airway hyper-responsiveness (AH) is a common characteristic of asthma. Patient who has recurrent chronic cough with AH is commonly referred as "cough variant asthma". Histamine provocation test should be performed to determine whether a patient has "cough variant asthma" or recurrent viral bronchitis.

Objective To determine AH prevalence in children with recurrent chronic cough and factors associated with it.

Methods A cross sectional study was conducted on 6-12 year-old children with recurrent chronic cough at the Pediatrics Outpatient Clinic, Sanglah Hospital Denpasar from September 2002 until June 2003

Results Twenty one out of 64 (33%) subjects suffering from recurrent chronic cough without wheezing had AH. Associated factors significantly associated with AH were age, allergic rhinitis, paternal and maternal history of atopy, passive smoking, use of mosquito-coil, positive skin prick test, and eosinophilia. Spearman correlation analysis between associated factors and AH showed that positive skin prick test and passive smoking were moderately correlated with AH ($r=0.56$, $p<0.0001$; $r=0.57$, $p<0.0001$, respectively), whereas multivariate regression logistic analysis on associated factors found true associated factors, such as positive skin prick test ($p=0.01$; OR=14.82), history of atopy in father ($p=0.02$; OR=22.75), and passive smoking ($p=0.03$; OR=11.97).

Conclusions The prevalence of airway hyper-responsiveness in children with recurrent chronic cough without history of wheezing was 33%. Independent associated factors of AH in recurrent chronic cough children are positive skin prick test, history of atopy in father, and passive smoking **[Paediatr Indones 2004;44:181-187].**

Keywords: *airway hyper-responsiveness, recurrent chronic cough, histamine provocation test, prick test, atopy, passive smoking, cough variant asthma*

Recurrent chronic cough is defined as the presence of cough lasting for at least 2 weeks and/or cough occurs at least 3 episodes in three consecutive months with or without other respiratory or non-respiratory symptoms (Consensus of KONIKA V 1981, Medan).[1] Asthma and recurrent viral bronchitis are two common causes of chronic cough in childhood.[2] History, physical, and supporting examinations are needed to differentiate asthma from recurrent viral bronchitis.[3] Histamine/methacholine provocation test is one of the supporting measures to establish airway hyper-responsiveness (AH). Airway hyper-responsiveness itself is a common characteristic of asthma.[4,5]

AH is the tendency of the airways to constrict more on physical or chemical stimuli.[5,6] AH can also be defined as a 20% fall in FEV_1 by a given dose or concentration of a challenging agent.[7] It is reported that around 40% of recurrent chronic cough patients have AH.[2] Some cross sectional studies on the general population and asthma patients found the association between AH and some factors such as age, gender, race, positive skin prick test, history of atopy in parents, atopic diseases (asthma, allergic rhinitis, atopic dermatitis, and urticaria), air pollutants (especially cigarette smoke), and eosino-

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philia.[8-10] So far, there has been no study about AH prevalence and its associated factors, such as age, gender, race, positive skin prick test, history of atopy in parents, atopic diseases, air pollutant, and eosinophilia, on recurrent chronic cough patients. The aim of this study was to determine AH prevalence in children with recurrent chronic cough and its associated factors.

Methods

This cross sectional study was conducted at the Pediatric Outpatient Clinic, Sanglah Hospital, Denpasar in September 2002 until June 2003. Subjects were selected by consecutive sampling until the minimal sample size required was met (64 subjects). Children aged 6-12 years old suffering from recurrent chronic cough without wheezing were included. Children were excluded if they had pneumonia, lung tuberculosis, asthma, pertussis, cystic fibrosis, heart diseases, neurological diseases, or congenital disorders, or if they did not agree to participate or were not cooperative. This study was approved by the Ethics Committee of Medical School, Udayana University/Sanglah Hospital, Denpasar.

Recurrent chronic cough children who met the inclusion criteria were requested to fill in a questionnaire. Physical and supporting examinations (complete blood count, chest x-ray, Mantoux test) were performed to complete the data. Information about this study was explained to the parents of each subject and an informed consent was signed if they had agreed to participate in this study. Skin prick test and histamine provocation test were performed if the subjects fulfilled the eligibility criteria.

History of atopy in one or both parents was considered present if they had at least one atopic disease such as asthma, allergic rhinitis, atopic dermatitis, or urticaria.[10] Passive smoking was involuntary inhalation of smoke produced by one or more family members in the house consuming at least six cigarettes a day.[11] Use of mosquito-coil was defined as usage of mosquito-coil at night for at least 8 hours a day. Eosinophilia was defined as the number of serum eosinophils of >275/ml[8] (Cell-dyn spectrophotometer).

Skin prick test was performed using some common allergen extracts (Extract Allergen Division, Sutomo Hospital, Surabaya), such as environmental allergen (mite, house dust mite), food allergen (peanut, chocolate, *tongkol* fish, shrimp, apple, soy, wheat), yeast allergen, and animal allergen (feather-duster, cat hair, dog hair), with normal saline solution as negative control and histamine 5% as positive control. Histamine and steroid were withheld for 3 days and 24 hours before the test day, respectively. Skin prick test was performed on the volar surface of the forearm. The skin of the volar surface of the forearms was cleaned with an alcohol and allowed to dry. A grid pattern for putting the allergen was then drawn on the forearm with a ballpoint pen. At each site, a drop of allergen extract solution was placed on the skin, and the skin was gently pricked by placing a 26 G needle at an angle of 45^{o} to the skin and lifting it so that a small amount of epidermis was abraded. After 15 minutes, an indurations of >2mm was considered positive and subjects with positive test results to at least one extract allergen were considered atopy.[12,13]

AH with inhaled histamine was measured by a method described by Cockcroft *et al.*[12-14] Histamine, steroid, and aminophylline were withheld for 24 hours before the test day, and b_2-agonist was withheld for 18 hours before the test day. Aerosols of the test solution were generated by a nebulizer (De Vilbiss PulmoAide, Chicago) operated to provide an output of 0.13-0.15 ml/min. Each aerosol was inhaled through the mouth (face mask) by tidal breathing for 2 minutes. The first aerosol was saline solution (0.9%), followed in 4-minute intervals by increased concentration of histamine (0.01; 0.1; 1; 2; 4; 8 mg/ml). The response was measured by FEV_1 (Vitalograph Spirometer, Inc., London, UK), before starting the procedure and 1 minute after each inhalation. Positive histamine provocation test was defined as a decline of 20% or more in FEV_1 from the post saline value after histamine provocation. Negative histamine provocation test was defined as no decline of 20% or more in FEV_1 until concentration of histamine provocation reached 8 mg/dl. The test was terminated when subjects showed a positive result. It was also terminated at the end of the dose when subjects showed no positive result. Salbutamol nebulization was given to subjects with positive test.

Data were tabulated and analyzed using SPSS ver. 10.0 for Windows program. Associations between dependent variable (AH) and independent variables were tested by chi-square test. Spearman correlation analysis was used to evaluate degree of correlation between associated factors and AH. After univariate analysis was done, multivariate logistic regression analysis was used to find independent associated factors. The level of significance was $p<0.05$ with 95% confidence interval.

Results

Subjects' characteristics

There were 71 children aged 6-12 years who had recurrent chronic cough without wheezing. From these children, 64 were included in this study and 7 were excluded (1 did not agree to participate, 3 had lung tuberculosis, 1 had pneumonia, 2 were not cooperative). Thirty-four of 64 subjects (53%) were boys and 30 (47%) were girls. The characteristics of the subjects can be seen in **Table 1**.

TABLE 1. CHARACTERISTICS OF THE SUBJECTS

	Total (n=64)	Percentage
Age, mean (SD), year	7.80 (1.89)	
Gender, male	34	53
Allergic rhinitis	9	14
Atopic dermatitis	12	19
Urticaria	19	30
History of atopy in father	18	28
History of atopy in mother	22	34
History of atopy in both parents	6	9
Passive smoking	19	30
Use of mosquito-coil	30	47
Positive skin prick test	24	38
Eosinophilia	29	53

Prevalence

AH prevalence in children with recurrent chronic cough without wheezing was 21 of 64 (33%). AH prevalence in 6-9 year-old subjects was 23%, and in 9-12 year-old was 10/17. Sixteen of 24 subjects with positive skin prick test had AH. AH prevalence in passive smokers was 14/19. Six of 9 subjects with allergic rhinitis had AH, whereas 5 of 6 subjects with history of atopy in both parents had AH. AH prevalence based on various characteristics can be seen in **Table 2**.

TABLE 2. PREVALENCE RATIO OF ASSOCIATED FACTORS OF AH

	AH n=21	Non AH n=43	PR	95%CI		p value
Sex						
Male	12	22	1.18	0.578;2.396		**0.65**
Female	9	21				
Age						
6-9 years	11	36	0.40	0.207;0.764		**0.01**
>9-12 years	10	7				
Allergic rhinitis						
Yes	6	3	2.44	1.299;4.600		**0.04**
No	15	40				
Atopic dermatitis						
Yes	6	6	1.73	0.853;3.521		**0.15**
No	15	37				
Urticaria						
Yes	9	10	1.78	0.902;3.498		**0.10**
No	12	33				
History of atopy in father						
Yes	10	8	2.32	1.200;4.498	1	**0.01**
No	11	35				
History of atopy in mother						
Yes	11	11	2.10	1.060;4.160	1	**0.03**
No	10	32				
History of atopy in both parents						
Yes	5	1	3.02	1.744;5.233		**0.01**
No	16	42				
Passive smoking						
Yes	14	5	4.74	2.278;9.848		**0.00**
No	7	38				
Use of mosquito -coil						
Yes	14	16	2.27	1.057;4.861		**0.02**
No	7	27				
Skin prick test						
Positive	16	8	5.33	2.240;12.696		**0.00**
Negative	5	35				
Eosinophilia						
Yes	14	15	2.41	1.126;5.173		**0.01**
No	7	28				

PR= prevalence ratio; 95%CI = 95% confidence interval

Prevalence ratio of factors associated with AH

Factors associated with AH in children with recurrent chronic cough were age, allergic rhinitis, history of atopy in father, mother, and both parents, passive smoking, use of mosquito-coil, positive skin prick test, and eosinophilia. All of these had significant PR; the PR and their 95% confidence interval are depicted in **Table 2**. Positive skin prick test had the highest prevalence ratio (PR=5.33; 95%CI 2.24;12.69). In this study, one protective factor was age of 6-9 years. The prevalence ratio of this protective factor was less than 1 i.e., 0.40 with 95%CI of 0.21; 0.76.

Correlation between associated factors and AH

There were significant correlations between some associated factors and AH. **Table 3** shows correlation coefficients and p values of some variables by Spearman correlation test. There was a negative correlation between AH and age of 6-9 years (r=-0.33). The strongest correlation was found between passive smoking and AH (r=0.57), followed by that between positive skin prick test and AH (r=0.56).

Correlation coefficients of more than 0.5 were found between both passive smoking and positive skin prick test and AH, which meant that these factors were moderately correlated with AH.

Multivariate logistic regression analysis on factors associated with AH

By multivariate logistic regression analysis on some factors associated with AH, we found only three independent associated factors i.e., positive skin prick test (OR=14.82, 95%CI 1.96;111.95, p=0.01), history of atopy in father (OR=22.75, 95%CI 1.76; 294.68, p=0.02), and passive smoking (OR=11.97, 95%CI 1.23;116.46, p=0.03) (**Table 4**).

Discussion

The prevalence of AH by histamine provocation test on recurrent chronic cough patients depends on risk factors and conditions at the time the test is performed. Some risk factors which can influence AH are atopy status, smoke, and air pollutants.[15,16]

Sovijarvi *et al*[17] found that the prevalence of AH (by a rapid dosimetric method) in chronic cough patients was 20%, whereas Cockcroft *et al*[18] found that the prevalence of AH in patients with cough without other chest symptom was 47%. In this study, we found that the prevalence of AH as determined by histamine provocation test in patients with recurrent chronic cough without wheezing was 33%. This result was higher than that of Sovijarvi's study, possibly due to the difference in provocation test method.

Sparrow *et al*[19] in their study on asthma patients show that nonspecific airway responsiveness will increase along with the increase of age. In our study, AH prevalence in 6-9 year-old group (23%) was lower than that in 9-12 year-old group (10/17). This difference was significant statistically, but on multivariate logistic regression analysis if was found that age was not associated with AH. The prevalence of AH in older children was higher because the increase of age will cause longer child induction by irritant agent (cigarette smoke, mosquito-coil) and allergen, so that inflammation process will be more serious.

Sears *et al*[20] reported that male sex was a predicting factor for AH. In our study, we found that AH prevalence in male subjects was higher than that in female subjects, but this difference was not significant statistically. This result was similar to the study of Peat *et al* in Australia.[9]

Table 3. Spearman correlation matrix between associated factors and AH

		AH	Age	Allergic rhinitis	History of atopy in father	History of atopy in mother	History of atopy in both parents	Passive smoking	Use of mosquito -coil	Passive skin prick test	Eosi nophilia
AH	r	1.000	**-0.333**	0.292	0.303	0.265	0.346	**0.566**	0.277	**0.559**	0.300
	p		0.007	0.019	0.015	0.034	0.005	0.000	0.027	0.000	0.016

r = correlation coefficient

Table 4. Multivariate logistic regression analysis on associated factors of AH

	B	*P* value	RO	95%CI
Age	-1.54	0.14	0.21	0.027;1.686
Allergic rhinitis	0.23	0.85	1.26	0.106;4.950
History of atopy in father	3.12	**0.02**	22.75	1.757;294.683
History of atopy in mother	0.51	0.68	1.66	0.143;19.253
History of atopy in both parents	-2.62	0.26	0.07	0.001;7.055
Passive smoking	2.48	**0.03**	11.97	1.231;116.458
Use of mosquito-coil	0.73	0.41	2.08	0.364;11.919
Positive skin prick test	2.70	**0.01**	14.82	1.963;111.947
Eosinophilia	0.75	0.41	2.12	0.354;12.705

B= logistic regression coefficient; OR = Odds ratio; 95%CI = 95% confidence interval

In allergic rhinitis, mucosal mast cells or basophils are induced by allergen, resulting in nasal reactions (early and late types). These reactions will cause itching, mucosal edema, hypersecretion, or mucosal damage that will disturb mucociliary transport. Malfunction of mucociliary transport will raise the probability of sinusitis. Postnasal drip resulting from sinusitis causes inflammation of bronchial mucosa and increases AH.

A study on 27 allergic rhinitis patients found that 15 patients had AH.[21] Backer *et al*[10] found that atopic diseases such as asthma, allergic rhinitis, and atopic dermatitis in children are significantly associated with AH (p=0.001). However, they did not find AH in children with urticaria. In our study we found that 6 of 9 recurrent chronic cough patients who had allergic rhinitis had AH; whereas AH prevalence in recurrent chronic cough patients who had atopic dermatitis and in those with urticaria was 6/12 and 9/19 respectively. Statistically, atopic dermatitis and urticaria were not associated with AH. Multivariate logistic regression analysis showed that there was no association between allergic rhinitis and AH.

Cigarette smoke is the main air pollutant. According to Miltzer, cigarette smoke contains chemicals such as nicotine, tar, and carbon monoxide which can be hazardous to the respiratory epithelium.[22] The damage to respiratory epithelium causes epithelial cell unable to prevent inhalant allergen penetration to go further into the airway mucosa and react with target cells. Unimpaired epithelial cells produce *neural endopeptidase* (which is able to neutralize P substance) and *epithelial derived relaxing factor* (EpDRF). Both prevent bronchoconstriction, edema, and inflammation of the airways. The damage to mucosal epithelial cells was increased by inflammatory mediators.[15,16,23] Constant contact with cigarette smoke affects FEV_1. The effect of cigarette smoke occurs not only in active smokers, but also in children of smoking parents (passive smokers).[22]

Martinez *et al*[24] stated that the prevalence of AH in male children of smoking parents was significantly higher compared to that in those of non-smoking parents (OR=4.3, p=0.009). Frischer *et al*[25] showed that AH occurs more often in children exposed to maternal smoking in their first year of life (OR=2.82; 95%CI 1.25;6.34; p<0.01) and Forastiere *et al*[26] reported that maternal and paternal smoking are strong predictors of AH.

In our study, AH prevalence in recurrent chronic cough patients with passive smoking was 14/19. In univariate analysis, AH was significantly associated with passive smoking and use of mosquito-coil, whereas in multivariate logistic regression analysis, we found only passive smoking as an independent associated factor of AH (OR=11.97; 95%CI 1.231;116.458; p=0.03).

Backer *et al*[27] found that the degree of AH by inhaled histamine is significantly related to history of asthma in the two first-degree relatives (p<0.001). Caultas and Slamet showed that the prevalence of asthma in children whose parents both had atopy was higher than those with atopy in only one parent.[22] In our study, AH prevalence in recurrent chronic cough children with history of atopy in father, mother, and both parents was 10/18, 11/22, and 5/6, respectively. In univariate analysis, it was found that AH was significantly associated with history of atopy in father, mother, and both parents, while in multivariate logistic regression analysis, history of atopy in father was the only independent associated factor of AH (OR=22.75; 95%CI 1.757;294.683; p=0.02). These results may be due to the small number of subjects with history of atopy in both parents in our study.

Postma *et al*[28] concluded that a trait for an elevated level of serum total IgE is coinherited with a trait for AH and that the gene governing AH is located near a major locus that regulates serum IgE levels on chromosome 5q31-q33. This data provides strong evidence of one or more susceptibility loci on chromosome 5q31-q33 that contribute to AH and atopy.

In our study, AH prevalence in recurrent chronic cough children with positive skin prick test was 16/24. In univariate analysis, it was found that positive skin prick test was significantly associated with AH and in multivariate logistic regression analysis we found positive skin prick test as an independent associated factor of AH (OR=14.82; 95%CI 1.963;111.947; p=0.01).

Martinez *et al*[24] reported that AH is significantly associated with atopy (positive skin prick test) (p=0.001). Peat *et al*[9] concluded that atopy (positive skin prick test) is the most important risk factor for AH in all ages.

In asthma, the number of eosinophils increases in the bronchial submucosa. Thus, the degree of AH

is associated with the number of eosinophils in the wall of airways. Eosinophilia indirectly induces AH. The presence of both eosinophilia and AH indicates a more activated immunologic process in the airways. Eosinophilia may reflect a higher number of eosinophils in the airway mucosa.[8] The association between higher peripheral blood eosinophil counts and AH was found in some studies.[29-31] In our study, AH prevalence in recurrent chronic cough children with eosinophilia was 14/29. In univariate analysis, eosinophilia was significantly associated with AH in children with recurrent chronic cough, but in logistic regression analysis we found that eosinophilia was not an independent factor of AH. These results are possible because eosinophilia can be caused by helminthic and allergic diseases;[32] helminthic infection is still prevalent in our area.

In conclusion, AH prevalence in children with recurrent chronic cough without history of wheezing is 33%. Independent associated factors of AH in recurrent chronic cough children are positive skin prick test, history of atopy in father, and passive smoking. We advise family members to stop smoking inside the house. More studies with case-control or cohort design should be done to control the confounding variables.

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