

## Clinical manifestations of childhood asthma persisting until the age of seven

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### ABSTRACT

**Background** Asthma is a chronic illness commonly found in children. We aimed to find out the clinical manifestations of childhood asthma persisting until the age of seven and the influencing factors.

**Methods** A review was performed at the outpatient clinic of the Department of Child Health Cipto Mangunkusumo Hospital Jakarta, from January 1992 to December 2001, on children with asthma who still had symptoms until the age of seven.

**Results** During the period of 10 years, there were 322 children with clinical symptoms of asthma persisting until the age of 7. One hundred and forty-six (45.3%) met the inclusion criteria, consisting of 75 (51.4%) boys and 71 (48.6%) girls. The average age was 11.7 years. There were 101 (69.2%) patients with rare episodic asthma, 26.0% with frequent episodic asthma, and 4.8% with persistent asthma. Age of onset was mostly beyond 3 year-old (51%). Besides asthma, atopic diseases noted in these patients were allergic rhinitis in 85 (58.2%) and atopic dermatitis in 42 (28.8%). Logistic regression found that cigarette smoke exposure (adjusted OR 4.72, 95%CI 2.05;10.87,  $p=0.000$ ), allergic rhinitis (adjusted OR 3.44, 95%CI 1.40;8.45,  $p=0.007$ ), and atopic dermatitis (adjusted OR 2.37, 95%CI 1.01;5.72,  $p=0.048$ ) had significant association with the degree of asthma.

**Conclusion** Of 146 children who still had asthma until the age of seven, there were 69% with rare episodic asthma, 26% with frequent episodic asthma, and 4.8% with persistent asthma. Factors presumably influencing this manifestations were cigarette smoke exposure, allergic rhinitis, and atopic dermatitis [*Paediatr Indones* 2004;44:1-6].

**Keywords:** risk factor, persisting asthma, children, the age of seven, cigarette smoke exposure, allergic rhinitis, atopic dermatitis

**A**sthma is a chronic illness commonly found in children with various prevalence rates (1-30%).<sup>1,2</sup> In the course of the illness, 52% of patients will have remission as

they get older.<sup>3</sup> Out of those who have the asthma symptoms by the age of seven, 28.3% will still have the symptoms by the age of 11, and 16.5% by the age of 16.<sup>4</sup> Interaction between atopic and environmental factors highly determines the clinical course of the disease.<sup>5-7</sup> Factors influencing the clinical course of asthma are atopy, age, sex, age of onset, degree of illness, degree of pulmonary function impairment, response to bronchodilators, duration of illness, contact to allergens especially inhaled allergens, and delay of anti inflammation drugs treatment.<sup>8-10</sup> The prediction of the morbidity of asthma might be more definitely determined if pulmonary function impairment can be assessed.<sup>11,12</sup> Early intervention to prevent sensitization and relapse should be done in order to improve the prognosis of childhood asthma.<sup>8,13</sup> This study aimed to find out the clinical manifestations of childhood asthma persisting until the age of seven and its influencing factors.

### Methods

We reviewed 322 asthma patients who still had the illness beyond the age of seven at the time they

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visited the outpatient Clinic of Allergy-Immunology and Pulmonology Divisions, Department of Child Health, Medical School, University of Indonesia-Cipto Mangun-kusumo Hospital, Jakarta, during a 10-year period (January 1992 to December 2001). The inclusion criteria were asthma patients aged beyond 7 years-old who still had the symptoms, age of onset below 7 years, and had complete clinical data about relapses of the asthma during the last 1 year. The criterion of exclusion was patients who did not visit the clinic for at least 1 year.

Data were grouped based on age, sex, age of onset, other atopic illnesses besides asthma, atopy in the family, age at the initiations of formula and semi-solid or solid food, cigarette smoke exposure, results of skin test, and results of pulmonary function test. Clinical manifestations were grouped into the degree of asthma. The definition of asthma and degree of asthma were based to the National Consensus of Childhood Asthma 2002.<sup>14</sup> Data were analyzed to assess the crude odds ratio of each factor (independent variables) related to the degree of asthma by using bivariate analysis. Thereafter a multivariate analysis (logistic regression model) was performed to assess the adjusted odds ratio and statistical significance by using 95% confidence intervals (95%CI). SPSS for windows release 10.0 computer program was used. A p value of <0.05 was considered significant.

## Results

### Subjects' characteristics

During the period of 10 years (January 1992 to December 2001), there were 322 children with clinical symptoms of asthma persisting until the age of 7. One hundred and forty-six (45.3%) met the inclusion criteria consisting of 75 (51.4%) boys and 71 (48.6%) girls.

The average age was 11.7 years. A hundred and one children (69.2%) suffered from rare episodic asthma, 26.0% with frequent episodic asthma, and 4.8% with persistent asthma. Age of onset were mostly in the age-group of beyond 3 years old (51.4%). Other atopic diseases noted in these patients were allergic rhinitis in 85 (58.2%) and atopic dermatitis in 42 (28.8%) (Table 1).

Family history of atopy was present in 108 (74.0%) subjects; 92 (63.0%) had family history of asthma. History of parental asthma were obtained in 40 (27.4%). Pulmonary function test was only done in 47 (32%) subjects; 25 out of them showed abnormal results. Passive cigarette smoke exposure was found in 64 (44.0%) subjects. Skin test to house dust mites (HDM) was positive in 118 (81.0%) and to house dust were positive in 119 (81%) (Table 1).

### Bivariate analysis

Bivariate analysis was performed to assess the crude odds ratio (crude OR) of each factor (independent variable) related to the degree of asthma. Compared to the patients in the group of rare episodic asthma, patients in the group of frequent episodic asthma and in the group of persistent asthma were more likely to have the following factors i.e., (1) abnormal result of pulmonary function test, (2) positive exposure to cigarette smoke, (3) allergic rhinitis & atopic dermatitis as accompanying illness, (4) positive skin test to house dust mites and to house dust. These factors might affect the clinical manifestations of asthma persisting until the age of seven (Table 1). Bivariate analysis showed that factors presumed to have influenced the manifestations of asthma persisting until the age of seven were (1) positive exposure to cigarette smoke (crude OR 5.2, 95%CI 4.58;6.62,  $p=0.000$ ), (2) asthma with allergic rhinitis (crude OR 3.5, 95%CI 2.28;4.26,  $p=0.001$ ), (3) asthma with atopic dermatitis (crude OR 2.5, 95%CI 1.12;4.26,  $p=0.004$ ), (4) positive skin test to HDM (crude OR 3.2, 95%CI 2.17;4.42,  $p=0.050$ ) and (5) positive skin test to house dust (crude OR 2.2; 95%CI 1.1;3.4,  $p=0.06$ ) (Table 2).

### Multivariate analysis

The extent of relationship between one risk factor and another was assessed using multivariate analysis. Logistic regression showed that factors significantly associated with the manifestation of asthma persisting until the age of seven were (1) cigarette smoke exposure (adjusted OR 4.72, 95%CI 2.05;10.87,  $p<0.0001$ ), (2) asthma with allergic rhinitis (adjusted OR 3.44, 95%CI 1.40;8.45,  $p=0.007$ ), and (3) asthma with atopic dermatitis as accompanying illness (adjusted OR 2.37, 95%CI 1.01;5.72,  $p=0.048$ )

**TABEL 1.** DISTRIBUTION OF SUBJECTS' CHARACTERISTICS

Characteristics	Number of subjects	Degree of asthma			Total
		Rare episodic asthma	Frequent episodic asthma	Persistent asthma	
		101 (69.2%)	38 (26.0%)	7 (4.8%)	146 (100%)
		n	n	n	n (%)
1 Sex	Boys	46	24	5	75 (51.4)
	Girls	55	14	2	71 (48.6)
2 Age of onset	<1 year-old	21	11	2	34 (23.3)
	1-3 year-old	26	9	2	37 (25.3)
	≥3 year-old	54	18	3	75 (51.4)
3 Atopic history	Only asthma	28	5	-	33 (22.6)
	Asthma + Allergic rhinitis	50	29	6	85 (58.2)
	Other atopics illness	23	14	5	42 (28.8)
4 Family history	Atopy (+)	74	29	5	108 (74.0)
	Asthma	64	23	5	92 (63.0)
	Allergic rhinitis	23	10	2	35 (24.0)
	Atopic dermatitis	4	7	2	13 (8.9)
5 Family history of asthma	Only father	12	3	-	15 (10.2)
	Only mother	14	4	-	18 (12.3)
	Father & mother	4	2	1	7 (4.7)
	Siblings	18	4	-	22 (15.1)
	Paternal grand father	15	7	2	24 (16.4)
	Paternal grand mother	7	2	-	9 (6.2)
	Maternal grand father	6	4	1	11 (7.5)
	Maternal grand mother	14	2	1	18 (12.3)
6 Initiation of	Cow's milk formula initiation <6 months	57	25	5	87 (59.5)
	Additional food initiation 6 month's	62	27	7	96 (65.7)
	Egg <6 month's	34	15	7	56 (38.3)
	Sea fish <12 month's	38	23	5	67 (60.4)*
	Tomato <6 month's	25	14	3	42 (35) <sup>l</sup>
7 Pulmonary function test (Done in 47 patients)	Abnormal	4	18	3	25 (53.1)
	Obstructive	1	1	-	2 (4.2)
	Restrictive	3	8	9	12 (25.5)
	Obstructive & restrictive	-	9	2	11 (23.4)
8 Passive smoking	Positive	32	27	5	64 (43.8)
9 Skin test	Positive	88	35	7	130 (89.0)
	Inhaled allergens	23	33	7	123 (84.2)
	House dust mite	77	34	7	118 (80.8)
	House dust	79	34	6	119 (81.5)
	Pet dander	35	10	1	46 (31.5)
	Food allergens	26	10	1	37 (25.3)

Note: \*Out of 111 subjects; <sup>l</sup>Out of 120 subjects

(Table 2). Positive skin test to HDM and to house dust did not show any significant associations.

## Discussion

The major limitation of this study was the different treatment received by the subjects before and after the launching of Children Asthma National Consensus. A high percentage of patients failed to meet the inclusion

criteria, causing the study results unable to represent the whole clinical manifestations of asthma persisting until the age of seven. The average age of onset was 2.8 years whereas the age of onset of the majority of subjects (51%) was beyond 3 year-old (Table 1). This suggests that age of onset beyond 3 years is a determining factor whether someone tends to have illness persisting through later age.

Martinez *et al* found that 51.5% of subjects who developed wheezing prior to the first 3 years of life got

**TABLE 2.** CRUDE AND ADJUSTED ODDS RATIO OF INDEPENDENT VARIABLES AS FACTORS PRESUMED TO INFLUENCE THE DEGREE OF ASTHMA (FREQUENT EPISODIC AND PERSISTENT ASTHMA COMPARED WITH RARE EPISODIC ASTHMA)

Independent Variables	Bivariate			Multivariate		
	Crude OR	95%CI	P	Adjusted OR	95%CI	P
Passive cigarette smoking	5.24	4.58; 6.62	0.000	4.72	2.05;10.87	0.000
Asthma + allergic rhinitis	3.52	2.28; 4.26	0.001	3.44	1.40;8.45	0.007
Asthma + atopic dermatitis	2.51	1.12; 4.22	0.004	2.37	1.01;5.72	0.048
Skin test to HDM (+)	3.24	2.17; 4.42	0.050	1.28	0.28;5.89	0.758
Skin test to house dust (+)	2.21	1.11; 3.4	0.063	1.26	0.26;6.28	0.793

recovery by the age of six.<sup>15</sup> In this study, clinically, male sex seems to be the factor affecting the degree of asthma, although it was not statistically proven. This was different from the previous studies showing that the prognosis of asthma in boys was better than that in girls.<sup>16</sup> The tendency of the ratio shifting toward girls suggests that there is a tendency of worse prognosis at the postpubertal age in girls compared to boys. This difference of prognosis between male and female is likely to be linked to the anatomy of the airway. In boys, the development of chest musculatures and the enhancement of lung capacity at pubertal period are faster than girls.<sup>16,17</sup>

Asthmatic patients aged beyond 6 years-old are usually accompanied by other atopic illnesses such as allergic rhinitis, which is the most frequent atopic illness accompanying asthma (58.2%).<sup>18,19</sup> Our study shows a significant correlation between allergic rhinitis accompanying asthma and the severity of asthma (adjusted OR 3.44; 95%CI 1.40;8.45,  $p=0.007$ ) (Table 2). The close relationship between asthma and rhinitis leads to a single disease entity, called rhinobronchitis or a united airway disease.<sup>18,19</sup> Settupane *et al* found that the risk of developing asthma was 3 times higher in allergic rhinitis patients compared to those who were not.<sup>20</sup> Nasobronchial reflex which causes an increased resistance in the lower respiratory tract is thought to be one of the mechanisms of this relationship.<sup>21</sup>

Atopic dermatitis developed within the first year of life is considered to be a predictor of later development of asthma.<sup>3,22</sup> Studies of asthma in children demonstrated a continuous pattern of relationship between allergen sensitization process and the development and natural course of allergic disease (allergic march).<sup>3,23,24</sup> Sensitization to inhaled allergen that has already began during infancy is a strong risk factor to asthma.<sup>25,26</sup> Our study found that atopic dermatitis was the second most frequent (28.8%) accompany-

ing atopic illness after allergic rhinitis. Clinically and statistically significant relationship was found between atopic dermatitis accompanying asthma and severity of asthma (adjusted OR 2.37; 95%CI 1.12;5.72;  $p=0.048$ ) (Table 2).

Exposure to cigarette smoke has a major influence in the persistence of asthma symptoms.<sup>27,28</sup> Markjaroenpong *et al* found that cigarette smoke exposure increased the risk of having nocturnal symptoms 3 times higher.<sup>29</sup> Cunningham *et al* found that cigarette smoke exposure increased the risk of developing persistent wheeze (OR 1.4; 95%CI 1.1 ; 1.8).<sup>27</sup> Our study found that 44% of the subjects were exposed to cigarette smoke. Clinically and statistically significant relationship was found between positive cigarette smoke exposure and more severe asthma (adjusted OR 4.72; 95%CI 2.05;10.87,  $p=0.000$ ) (Table 2).

Early initiation of cow's milk formula is related to earlier development of atopic dermatitis. Oddi *et al* found that exclusive breastfeeding discontinuation before the age of 4 months would increase the risk of asthma developed prior to the age of six (OR 1.28; 95%CI 1.01;1.62).<sup>30</sup> Exclusive breastfeeding for 6 months will suppress the development of food allergy until the age of 1 year and dermatitis until the age of 3.<sup>30,31</sup> Data of the age of formula initiation in our study were uncertain because of lack of cow's milk consumption data in mothers who breastfed their infants. Oeling *et al* reported that 8.5% of asthma in children was caused by food allergens. Sensitization was occurred in the first year of life, and the most frequent cause was egg.<sup>32</sup>

Early food allergen exposure has an important role in the course of asthma. Illi *et al* found that the risk of developing asthma by the age of 7 would increase if allergen sensitization already occurred within the first year of life (OR 10.12; 95%CI 3.81;26.88).<sup>23</sup>

Price *et al* found that among atopic dermatitis patients, the prevalence of food allergen sensitization prior to the age of 2 was very high (84%) compared to that at the older age. Among them there was also a significant high antibody titer to food allergen (egg, soy, and peanut).<sup>33</sup> In our study, the number of subjects who got additional food prior to the age of six months (65.7%) was higher than that at the older age. To be noted, before the 6 months exclusive breastfeeding program, the recommendation for additional food initiation was at the age of 4 months.

The severity of asthma is known to be related to the intensity and duration of allergen exposure. Arsyad *et al* found that HDM sensitization was a risk factor for asthma by the age of 4 (OR 8.07; 95%CI 4.6;14.1).<sup>13</sup> Avoidance to HDM allergen exposure was proved to lessen the asthma symptoms and restore the lung function.<sup>26,34</sup> Our study found that the prevalence of positive skin test to house dust was (81.5%) and HDM (80.8%). Bivariate analysis showed the relationship between positive skin test to HDM (crude OR 3.24; 95%CI 2.17;4.42;  $p=0.050$ ) and the degree of asthma, but such relationships could not be seen in the multivariate analysis, so that they need to be explored further.

Duration and intensity of the disease are closely linked to the development of impairment of pulmonary function, which influence the later course of the disease.<sup>10,12</sup> Data of pulmonary function test in our study was only obtained from 32% of the total subjects. Because of missing data of pulmonary function test was more than 20%, so it can not be explored further with multivariate analysis.

In summary we found that out of 146 children who still had their asthma until the age of seven, 101 (69.2%) had rare episodic asthma, 26.0% frequent episodic asthma, and 4.8% persistent asthma. Factors that might influence the manifestations were cigarette smoke exposure, allergic rhinitis, and atopic dermatitis. Positive skin test to HDM clinically seemed to be the influencing factor, but the results was not statistically significance, so they need to be explored further.

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