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Original Article

Sensitization to indoor allergens and frequency of asthma exacerbations in children

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Abstract

Background The rapid increase in asthma incidence has implicated the importance of environmental influences over genetic influences. Sensitization to perennial indoor allergens has been associated with increased asthma symptoms.

Objective To examine the correlation between sensitization to indoor allergens and frequency of asthma exacerbations in children.

Methods A cross-sectional study was carried out on asthmatic children aged 6 to 12 years in the Department of Child Health, Udayana University Medical School /Sanglah Hospital, Denpasar. Degree of sensitization was assessed by mean wheal diameter (positive defined as 3 mm greater than negative control) for seven common indoor allergens. Frequency of asthma exacerbation for three consecutive months prior to data collection was retrospectively reviewed.

Results Positive skin test results for one or more allergens were found in 84 of 89 (94%) asthmatic children. Higher frequency of asthma exacerbations weakly correlated with the number of allergens with positive sensitization (r=0.284; P=0.007). Mean wheal diameter of each allergen did not correlate to the frequency of asthma exacerbations. In addition, the frequency of asthma exacerbations was independent for parental and sibling atopic history, preceding respiratory infections, use of asthma controllers and passive environmental tobacco smoke exposure.

Conclusions Sensitization to common indoor allergens correlates weakly with frequency of asthma exacerbations. **[Paediatr Indones. 2011;51:207-12]**.

Keywords: *asthma exacerbation, sensitization, indoor allergen*

Asthma, a chronic inflammatory disorder of the airways, is the most prevalent chronic disorder, and often starts in childhood.[1] This disorder may negatively affect children physically, emotionally and socially, and impair quality of life.[2,3] The rapidly increasing incidence of asthma in all age groups shows the importance of environmental over genetic factors in the pathogenesis of asthma.[4] Atopy can be demonstrated by increased total or specific serum IgE and by a positive response to skin-prick tests (SPT) using standardized allergens. Available epidemiological evidence suggests that the population-based proportion of asthma cases attributable to atopy is 40 to 90%.[2,5,6] Due to the fact that most people, particularly children, spend the greater part of the day indoors, it is not surprising that increased attention has been focused on the role of foreign proteins that accumulated indoors.[7,8] Sensitization to indoor allergens has been associated with increased airway responsiveness, and exposure to particular allergens may exacerbate asthma or cause symptoms to persist. Common indoor allergens

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include domestic mites, animal allergens, cockroach allergens, and fungi.[2,9,10]

The association between sensitization and asthma applies only to persistently exposed to perennial allergens, i.e. indoor allergens, and has been identified only in adults. Few studies have focused on the most common indoor allergens in children living in tropical climates, which contributes to respiratory infections as they are suspected triggers of asthma exacerbations.[5,9,11-14] Therefore, we conducted a study to examine the correlation between sensitization to common indoor allergens and the frequency of asthma exacerbations. We also investigated the correlation between mean wheal diameters of each allergen and the frequency of asthma exacerbations.

Methods

From March 2009 to June 2010, we performed a cross-sectional study on children with asthma, referred to the outpatient clinic of the Respirology Division, Department of Child Health, Udayana University/ Sanglah Hospital Medical School, Denpasar. Subjects were aged 6 to 12 years and informed consent was obtained from parents or guardians. We excluded patients with extensive atopic dermatitis, prior use of anti-histamine drugs in the preceding seven days, immunotherapy treatment, known immunodeficiency (such as malignancy), chronic respiratory disorders other than asthma, nephrotic syndrome, kidney failure and increased pulmonary vascularisation associated with congenital heart diseases. Subjects were recruited by consecutive sampling.

At the first visit, the diagnosis of asthma was established by a pediatric respirologist on the basis of clinical symptoms relating to the characteristic bronchospasm. Patients' parents or guardians completed questionnaires on demographic data, frequency of asthma exacerbations during the period of three months prior to data collection, family and patient's allergic history, use of controllers, and passive environmental tobacco smoke exposure.

All subjects underwent SPT by the prick-puncture method using micropuncture points (Stallerpoint®), with standardized, glycerinated, full-strength aeroallergens (Stallergene®). SPT included the following allergens: house dust mites (*Dermatophagoides pteronysinnus, Dermatophagoides farinae*) 100 IR/ml & 100 IR/ml, cat (*Felis domesticus*) 100 IR/ml, dog (*Canis familariasis*) 100 IR/ml, fungi (*Alternaria, Cladosporium*) 1000 IC/ml & 1000 IC/ml and German cockroach (*Blatella germanica*) 1000 IC/ml. All micropuncture points and allergen extracts were products of Stallergenes S.A-Antony, France. A panel was considered valid if the mean diameter of the negative glycero-saline control at 15 to 20 minutes was at least 3 mm smaller than that produced by the positive histamine control (histamine hydrochloride 10 mg/ml). Wheal diameters equal to or greater than the histamine control were considered positive. Longest diameter of the wheal (D) was measured, as well as the diameter perpendicular to the former (d), using a transparent standardized ruler. Measurement of mean wheal diameter was calculated as (D+d):2. The wheal was outlined using a pen and the outline transferred to a permanent record with transparent tape. This study was approved by the Ethics Committee of the Udayana University Medical School /Sanglah Hospital, Denpasar.

Interobserver reliability was measured between the two eligible pediatric residents who performed the SPT for 105 wheal measurements of 15 patients. The expected Kappa value was between 0.61 and 1 for observer agreement. Demographic characteristics and prevalence of sensitivity to each allergen were analyzed. The correlations between frequency of asthma exacerbation and sensitization to indoor allergens, as well as between mean wheal diameter of each allergen and the frequency of asthma exacerbations were determined using the Spearman's correlation test. Associations of each confounding factor and frequency of asthma exacerbations were analysed by Mann-Whitney test. The analyses results were not significant, hence subsequent multivariate analysis was not performed.

Results

A total of 89 asthmatic children met our inclusion criteria. No subjects were excluded. The calculated Kappa value for interobserver agreement was 0.84, indicating very good agreement.[15] Descriptive statistics for the 89 study subjects are shown in **Table 1**. There were 57 (64%) boys and 32 (36%) girls. The

median age was 93 months (interquartile range: 81-117 months), with mean age was 100 months. Only 5 (6%) subjects had negative allergy panels.

As many as 50.5% of the subjects showed sensitivity to three or more indoor allergens. Positive sensitization to increased types of indoor allergens weakly correlated to increased frequency of asthma exacerbations (r=0.284; P=0.007). The mean wheal diameter of individual indoor allergens did not significantly correlate to frequency of asthma exacerbations, as presented in **Table 2**. Univariate analysis of the confounding factors did not reveal any significant influence on the frequency of asthma exacerbations, as shown in **Table 3.**

Table 1. Demographic and clinical characteristics

Variables	Number of subjects (n=89)
Sex (male), n (%)	57 (64)
Median age, months (range)	93 (87 to 117)
Positive skin test sensitization, n (%)	84 (94)
Positive skin test by allergen, n (%)	
Dermatophagoides pteronyssinus, n (%)	66 (74)
Dermatophagoides farinae	64 (72)
Blatella germanica	34 (38)
Canis familariasis	21 (24)
Felis domesticus	18 (20)
Alternaria	13 (15)
Cladosporium	9 (10)
Median frequency of asthma exacerbations, (range)	2 (0 to 5)
History of atopy, n (%)	
Atopy in one parent	50 (56)
Atopy in both parents	34 (38)
Other atopic manifestations in patient, n (%)	80 (90)
Environmental tobacco smoke exposure, n (%)	53 (60)
Use of controller, n (%)	7 (8)
Respiratory infections, n (%)	49 (55)

Table 3. Factors relating to asthma exacerbations

Variables	P¶
Atopy in sibling	0.457
Atopy in one parent	0.557
Atopy in both parents	0.600
Respiratory infections preceding asthma exacerbations	0.382
Use of controller	0.202
Environmental tobacco smoke exposure	0.674

¶: Mann-Whitney U test

Discussion

Previous studies have shown varying results on atopy in asthmatic children, with 80 - 97% atopic to indoor and outdoor allergens,[11,12,16] and 60.3 - 67.35% atopic to indoor and food allergens.[17,18] We observed the highest sensitization to house dust mites, *Dermatophagoides pteronysinnus* (74%) and *Dermatophagoides farinae* (72%). Previous studies both in subtropical and tropical countries, have shown similar results.[2,11-14,16-18]

We found a weak positive correlation between sensitization to increased types of indoor allergens and frequency of asthma exacerbations (r=0.284; P=0.007). Previous study showed a negative association between increased sensitization to indoor allergens and asthma severity in adults. Asthma severity was determined based on several parameters, including frequency of asthma exacerbations and FEV_1 which is reduced during asthma exacerbations. This association was not significant in other indoor allergens tested with SPT (*Alternaria*, house dust mite, cockroach).[12] Schwindt *et al.*[19] reported a significant association between asthma severity and cumulative atopy level, calculated from the total SPT score to indoor and outdoor allergens (P=0.03). Analysis of

Table 2. Correlation between mean wheal diameter of each indoor allergen and frequency of asthma exacerbations

Allergen		r	P¶
Median *Der p*, mm, (interquartile range)	3.5 (1.5 to 5.5)	0.052	0.630
Median *Der f*, mm (interquartile range)	3.5 (1.5 to 5.5)	0.137	0.199
Median *Fel d*, mm (interquartile range)	2.5 (1.1 to 3.9)	0.024	0.823
Median *Can f I*, mm (interquartile range)	2.3 (0.9 to 3.7)	0.158	0.140
Mean *Bla g I*, mm (SD)	2.6 (1.2)	0.140	0.190
Median *Alternaria*, mm (interquartile range)	2.0 (0.5 to 3.5)	0.178	0.094
Mean *Cladosporium*, mm (SD)	1.9 (1.0)	0.005	0.964

¶: Spearman's correlation test

each allergen by Schwindt *et al.*[19] showed a significant association in fungi only, and not in the other aeroallergens. Separately, a significant association was also observed between sensitization to cat allergen and asthma severity.[20] However, significant associations of sensitization to house dust mites, dog and cockroach, to asthma severity was not reported. The combination of sensitization and high concentration of exposure was significantly associated with more severe asthma only for the cockroach allergen. This association was not seen in house dust mites, dog, and cat allergens. This pediatric asthma study reported a significant difference in asthma severity between total positive SPT to four allergens compared to total negative SPT, in spite of a wide range in confidence interval.[20]

Further studies have confirmed the significance of sensitization combined with high levels of exposure.[9,11,21] Almost all allergens associated with asthma in tropical climates were perennial and mainly indoors. This perennial exposure causes chronic pulmonary inflammation and bronchial hyperreactivity.[4] A prior study in Denpasar identified the concentration of house dust mites in homes of asthmatic and non-asthmatic children to be higher than levels needed for sensitization. The level of house dust mites in asthmatic children's houses was significantly higher than that in those of non-asthmatic children.[22] However, this level was much lower than that reported in previous studies in subtropical climates.[23-25] Housing types may contribute to this difference.[14] In tropical countries, particularly in Bali, houses tend to have large, open ventilation. In contrast, prior research in subtropical countries tend to have closed housing, especially during the fall and winter, when indoor air becomes temperate and humid. Also these homes may have more rugs and upholstery which may trap allergens.[2,4]

In comparing Denpasar to other large cities in Indonesia, such as Surabaya and Jakarta, the environmental air is less polluted in Denpasar. Air pollutants may also contribute to asthma severity.[2] Due to the characteristics of indoor allergens, such as house dust mites and cockroaches, allergen levels detected in indoor air are dependent on air disturbances.[2,4,10] Air disturbances, levels of allergen exposure and housing ventilation were not evaluated in our study.

We observed no significant correlation between mean wheal diameter of each allergen and the frequency of asthma severity. Also, there was no significant correlation between parental and sibling atopy and frequency of asthma exacerbations. The relationship between atopy and asthma is complex.[13] A larger mean wheal diameter was correlated with more severe asthma only in adults.[12] The role of genetics in asthma also is not simple, and atopy is merely a factor associated with genetic variability.[2] Prior studies mainly focus on genetic factors or environmental factors.[26] But the genetic-environment interaction plays a major role in the pathogenesis of asthma.[27] In addition, we did not observe an association between the use of controllers and frequency of exacerbations. None of our subjects were taking anti-leukotriene, a controller that might influence a subject's response to SPT.

There are many factors contributing to pediatric asthma, including outdoor and indoor allergens, air pollutants, drugs, obesity, exercise, humidity, nasal polyposis, and viral, mycoplasma, or chlamydial respiratory infections.[10] Approximately 80% of asthma exacerbations in children are triggered by viral respiratory infections, particularly by rhinovirus.[28] In 55% of our subjects, one or more asthma exacerbations in the period of three months prior to data collection were preceded by respiratory infection. The symptoms of respiratory infections were considered significant if they started within two days prior to asthma exacerbations. However, our analysis failed to show any significant association between preceding respiratory infections and the frequency of asthma exacerbations ($P=0.382$).

We also observed no significant influence of environmental tobacco smoke exposure on the frequency of asthma exacerbations. As many as 60% of our subjects reported environmental tobacco smoke exposure, but this data was subject to information bias. Prior studies have shown the poor accuracy of data acquired from questionnaires, particularly data on tobacco smoke exposure.[29] Previous data have established the influence of tobacco smoke exposure on poorer asthma control.[30] The influence of tobacco smoke exposure on increased SPT reactivity was also previously reported.[31] Although sensitization to indoor allergens has been considered more important compared to outdoor allergens in asthmatic children,[32] the possibility that asthma

severity in our patients was influenced by the latter could not be excluded.

In our study, we chose to emphasize the sensitization to indoor allergens in pediatric asthma patients. We conclude that increased types of IgE-mediated skin reactions towards indoor allergens weakly correlated to increased frequency of asthma exacerbations, in addition to the known role of other contributing factors. Our results did not show increased reactivity to any single, specific allergen resulting in increased frequency of asthma exacerbation. However, children with frequent asthma exacerbations, which is indirectly associated with more severe asthma, were more easily sensitized. Therefore, these patients are more prone to airway inflammation induced by allergens, potentially due to active immunological responses to perennial allergens. SPT as the main diagnostic tool of atopy in asthma cases could be beneficial to the management of asthmatic patients, as it may allow for avoidance of allergens and/or specific immunotherapy.[2] Future studies are needed to improve the design of pulmonary function tests and SPT of family members. Our study could serve as a basis for further investigation of the role of sensitization to indoor allergens in the severity of pediatric asthma.

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