Factors for high-risk asthma in Taiwanese children

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Summary

Background: **Asthma is one of the major causes of death in otherwise healthy young individuals. However, many of these deaths may have been prevented by more aggressive treatment. To determine factors correlated with a high risk of death in Taiwanese children with atopic asthma.**

Methods: **Taiwanese children aged 5-18 years, diagnosed with atopic asthma were enrolled in the study. Atopic asthma was diagnosed and immunoglobulin E (IgE) specific to antigens from any 1 of 8 allergens was measured (i.e. *Dermatophagoides pteronyssinus, Dermatophagoides farinae*, cat and dog dander, cockroach, egg white, milk and fish). High-risk asthma was defined as asthma requiring admission to a hospital or a visit to an emergency department. The study tried to determine the association of high-risk asthma with allergy-related parameters (e.g. asthma severity, asthma score, total serum IgE levels, serum levels of allergen-specific IgE, eosinophil count) and pulmonary function in Taiwanese children.**

Results: **One thousand one hundred and twenty-two Taiwanese children were evaluated. Those with higher asthma severity, asthma symptom score, serum levels of IgE specific to *D. pteronyssinus* and *D. farinae*, higher total serum IgE levels, and lower $FEF_{25-75\%}$ (forced expiratory flow, 25-75%) values were considered to be members of the high-risk asthma group.**

Conclusions: **The characterization of risk factors has enabled us to identify high-risk asthma in Taiwanese children, which will facilitate the treatment of these children in the future.*(Asian Pac J Allergy Immunol 2010;28:250-5)***

Key words: *high-risk asthma, atopic asthma, children, asthma severity, IgE, eosinophil count, pulmonary function*

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Introduction

Asthma is the most common chronic disease among children. According to the World Health Organization, approximately 300 million people currently have asthma and approximately 250,000 patients die each year.[1] Aside from its increasing prevalence, the severity of asthma also seems to be increasing in pediatric and adolescent patients, based on the observed increase in rates of consultations and visits into clinics, hospitals, and emergency departments.[2]

Between 1980 and 1999, the mortality attributable to asthma in children aged 5-14 years nearly doubled, which is a substantially greater increase than that observed in older adolescents and adults.[2] Many of these asthma deaths may have been avoided if the patients have been treated more aggressively. Hence, it is important to establish a list of risk factors to identify asthma patients who may have serious adverse outcomes.

The aim of this study was to determine the factors correlated with high-risk in Taiwanese children with atopic asthma. The findings would facilitate the identification of high-risk patients, to guide their treatment and prevent asthma-related morbidity and mortality.

Methods

Study population and design

This retrospective six-year study (2004-2010) which was conducted in Taiwan on patients with physician-diagnosed atopic asthma. The participants were 5-18 years old (n = 1122; 735

Table 1. Classification of asthma severity

	Frequency of symptoms		% predicted	Variability
	Day	Night	FEV_1/PEFR	PEFR%
Intermittent	<1/wk	≤2/m	≥80%	<20%
Mild persistent	≥1/wk <1/day	>2/m	≥80%	20-30%
Moderate persistent	Daily	≥1/wk	60-80%	>30%
Severe persistent	Daily	Frequent	≤60%	>30%

Classified according to the Global Initiative for Asthma [GINA] guidelines
Intermittent: 1 point
Mild persistent: 2 points
Moderate persistent: 3 points
Severe persistent: 4 points

Table 2. Asthma Symptom Score

Cough score (night time)
0 = absent
1 = mild (cough was present but did not disturb sleep)
2 = moderate (patient awoke once because of cough)
3 = severe (patient awoke more than once because of cough)
4 = extremely severe (patient experienced insomnia on most nights)
Shortness of breath score (early in the morning)
0 = absent
1 = mild (occasional shortness of breath that did not require medication)
2 = moderate (occasional shortness of breath that required medication)
3 = severe (frequent shortness of breath that required medication)
4 = extremely severe (persistent shortness of breath that required multiple doses of medication)
Wheeze or dyspnea score (day time)
0 = absent
1 = mild (occasional wheeze)
2 = moderate (occasional wheeze and dyspnea that did not disturb normal activities)
3 = severe (persistent wheeze and dyspnea that hampered normal activities)
4 = extremely severe (wheeze and dyspnea that left the patient totally unable to perform normal activities)
Cough score (day time)
0 = absent
1 = mild (occasional cough that did not disturb normal activities)
2 = moderate (frequent cough that did not disturb normal activities)
3 = severe (frequent cough that disturbed normal activities)
4 = extremely severe (persistent cough)

boys and 387 girls). There was no experimental intervention involved.

The participants' medical histories were evaluated using a standard questionnaire. Their parents or guardians helped in answering the questions fully and accurately. Demographic data (i.e. age, gender, height, and weight), clinical data (i.e. asthma severity and asthma score), and laboratory data (e.g. serum total and allergen-specific immunoglobulin E [IgE] levels, eosinophil count, and pulmonary function) were obtained through interview and evaluation.

Children with atopic asthma were defined as patients diagnosed with asthma who had IgE specific to antigens from 1 to 8 allergens with class-1 or higher, namely, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat and dog dander, cockroach, egg white, milk, and fish. High-risk asthma was defined as asthma requiring hospital admission or an emergency department visit within the year before enrollment in the study. All other patients with asthma were classified as having low-risk asthma.[3]

An association between high-risk asthma and various allergy-related parameters, namely, asthma severity, asthma score, serum levels of allergen-specific IgE, total serum IgE levels, eosinophil count, and pulmonary function, was also evaluated.

All appropriate institutional review boards approved this study and each participant or the parent or legal guardian provided written informed consent.

Asthma severity and asthma score

Asthma severity was classified into four categories according to the GINA (global initiative for asthma) guidelines and based on the level of symptoms, degree of airflow limitation, and pulmonary function variability (Table 1).[3] These were intermittent, mild persistent, moderated persistent, and severe persistent. Each asthma severity score ranges from 1 to 4 points. The asthma symptoms score and possible total score ranged from 0 to 16 points (Table 2).

Total and allergen-specific serum IgE

Venous blood samples were drawn from all participants at the start of the study for measurement of total serum IgE levels and serum IgE specific to antigens from the 8 allergens stated above, using the Pharmacia CAP System. The sensitivity of the specific IgE detection was 0.35 kU/L and values greater than or equal to 0.35 kU/L were considered positive. The CAP classes were scored as follows: 0.35-0.70 kU/L, class 1; 0.71-3.5 kU/L, class 2; 3.6-7.5 kU/L, class 3; 7.6-17.5 kU/L, class 4; 17.6-50 kU/L, class 5; and >50 kU/L, class 6. The sensitivity of total IgE detection was 1 IU/ml and values ≥1 IU/ml were considered positive.

Blood eosinophil count

Venous blood samples were also obtained from all participants at the beginning of the study

Table 3. Association between high-risk asthma and asthma severity and score

Parameter	Group	Mean (SD)	*p*
Severity (point)	high-risk (412)	3.23 (0.82)	0.000*
	low-risk (710)	2.96 (0.88)	
Score (point)	high-risk (412)	6.90 (3.90)	0.000*
	low-risk (710)	5.10 (3.27)	

*p<0.05 by Mann-Whitney test

for determination of eosinophil counts . The timing of the blood sampling was during an unstable phase of the patient's asthma (all had clinical symptoms of asthma).

Pulmonary function measurements

Pulmonary function tests included assessments of the PEFR (peak expiratory flow rate, %), FEV_1 (forced expiratory volume in 1 sec), and $FEF_{25-75\%}$ (forced expiratory flow, 25-75%). All pulmonary-function tests were performed using the SensorMedics 2130 spirometer.

Statistical analyses

Statistical analyses were performed by the independent-*t* test and Mann-Whitney test. The results were considered statistically significant at $p < 0.05$. All statistical analyses were performed using the SPSS statistical software version 12.0.

Results

Of the 1122 participants, 412 (37%) and 710 (63%) patients belonged to the high-risk and low-risk groups, respectively.

Asthma severity and asthma score

There was a significant association between asthma severity and score and high-risk asthma. Asthma severity in the high-risk group was significantly higher than that of the low-risk group (Mean ± SD: 3.23 ± 0.82 vs. 2.96 ± 0.88, $p < 0.05$). The high-risk group also had higher asthma scores (6.90 ± 3.90 vs. 5.10 ± 3.27, $p < 0.05$) (Table 3).

Serum levels of allergen-specific IgE

Serum levels of IgE specific to *D. pteronyssinus*, *D. farinae*, cockroach and dog dander antigens were significantly associated with high-risk asthma. The high-risk group had higher serum levels of IgE specific to *D. pteronyssinus* (4.60 ± 1.59 vs. 4.17 ± 1.68, $p < 0.05$), *D. farinae* (4.37 ± 1.57 vs. 4.02 ± 1.67, $p < 0.05$), dog dander (0.44 ± 0.89 vs. 0.28 ± 0.71, $p < 0.05$), and cockroach antigens (0.35 ± 0.74 vs. 0.29 ± 0.75, $p < 0.05$) than those in the low-risk group. There was no significant association between high-risk asthma and the serum levels of IgE specific to antigens from other allergens (including cat dander, egg white, milk, and fish) (Table 4).

Table 4. The association between high-risk asthma and serum class levels of allergen-specific IgE

Allergen	Group	Mean (SD)	*p*
D. pteronyssinus (class)	high-risk (412)	4.60 (1.59)	0.000*
	low-risk (710)	4.17 (1.68)	
D. farinae (class)	high-risk (412)	4.37 (1.57)	0.000*
	low-risk (710)	4.02 (1.67)	
Cat (class)	high-risk (412)	0.22 (0.88)	0.217
	low-risk (710)	0.16 (0.58)	
Dog (class)	high-risk (412)	0.44 (0.89)	0.000*
	low-risk (710)	0.28 (0.71)	
Cockroach (class)	high-risk (412)	0.35 (0.74)	0.021*
	low-risk (710)	0.29 (0.75)	
Egg (class)	high-risk (412)	0.27 (0.62)	0.744
	low-risk (710)	0.28 (0.63)	
Milk (class)	high-risk (412)	0.28 (0.65)	0.801
	low-risk (710)	0.27 (0.62)	
Fish (class)	high-risk (412)	0.03 (0.22)	0 .973
	low-risk (710)	0.05 (0.30)	

*p<0.05 by Mann-Whitney test

Levels of specific IgE to dog dander and cockroach were both negative (class level <1). In both the high-risk group and the low-risk group, the number of patient sensitized to dog dander or cockroach allergen was small (despite there being a significant difference between the two groups). Hence, using specific IgE to dog dander or cockroach as a risk factor for high-risk asthma is not useful in clinical practice.

Eosinophil count and total serum IgE levels

There was a significant association between total serum IgE levels and high-risk asthma but not between eosinophil count and high-risk asthma. Total serum IgE levels in the high-risk group were higher than those in the low-risk group (786.56 ± 1110.52 vs. 596.32 ± 862.87, $p < 0.05$) (Table 5).

Pulmonary function

There was a significant association between $FEF_{25-75\%}$ value and high-risk asthma. The $FEF_{25-75\%}$ values in the high-risk group were significantly lower than those in the low-risk group (48 ± 20 vs. 53 ± 20, $p < 0.05$). There was no significant association between high-risk asthma and PEFR (%) and FEV_1 values (Table 6.).

Table 5. Association between high-risk asthma and eosinophil count and total serum IgE levels

Parameter	Group	Mean (SD)	*p*
Eosinophil count (%)	high-risk (412)	4.75 (4.79)	0.920
	low-risk (710)	4.77 (3.80)	
IgE(IU/mL)	high-risk (412)	786.56 (1110.52)	0.001*
	low-risk (710)	596.32 (862.87)	

*p<0.05 by *t* test

Table 6. Association between pulmonary function and high-risk asthma

Parameter	Group	Mean (SD)	*p*
PEFR (%)	high-risk(412)	92.30 (29.75)	0.166
	low-risk(710)	95.02 (32.50)	
FEV_1 (L)	high-risk (412)	99.58 (21.00)	0.208
	low-risk (710)	102.41 (42.64)	
$FEF_{25\sim75\%}$ (L/s)	high-risk (412)	48.18 (19.90)	0.000*
	low-risk (710)	52.62 (20.12)	

*p<0.05 by *t* test

Discussion

Patient selection was based on a single medical center, where the chronic care of asthma is provided by the bureau of national health insurance. The rate of high-risk asthma in young patients is high at 37% of this age group. This is the reason why it is necessary to determine the risk factors for high-risk asthma and define the high-risk group more accurately.

The classification based on severity is useful in making decisions regarding management during the initial patient assessment. The term "asthma severity" indicates both the severity of the disease and the patient's responsiveness to treatment.[1] The results suggest that asthma severity and symptom score can be indicators of asthma risk, in that patients with higher asthma severity or symptom score are at a higher risk for adverse outcomes.

Early allergen sensitization is associated with increased risk of persistent asthma.[4-8] More importantly, sensitization to indoor aeroallergens is the factor that shows the strongest association with asthma.[6,9-14] Ronmark *et al.* have noted that the prevalence of allergic sensitization in school children in Northern Sweden has increased significantly between 1996 to 2006.[15] They also observed that the pattern of response (age of patient at the time of development and type and number of specific allergens involved), not the presence or absence of specific IgE antibodies, has a fundamental effect on the clinical expression of asthma.[16]

Early exposure to dust mite allergens is a significant factor in the development of asthma.[6,10-12,14] Sensitization to house dust mite and cat dander allergens is also associated with frequent hospital visits in older children.[17,18] Sporik *et al.* have found that sensitization to cat or dog dander allergens is strongly associated with bronchial hyper-reactivity.[19] A major study in the northeastern region of the United States of America has shown the importance of cockroach allergen exposure and sensitization in asthma severity among inner-city children.[20]

However, other studies have produced conflicting results. For instance, several studies on African-American children living in poverty do not show sensitization to cat allergens as a risk factor for asthma.[6] Carlsten C *et al.* have found that sensitization to dog allergen is not a predominant risk factor for asthma.[12] Exposure to indoor allergens causes asthma and allergy, but this effect may depend on the dose and type of allergen, as well as the underlying genetic susceptibility of the child.[14] Few studies mention the relationship between allergen sensitization and asthma risk. In the current study, patients with IgE specific to *D. pteronyssinus* and *D. farinae* belonged to the high-risk asthma group.

A strong association between asthma and elevated total serum IgE levels has been reported in cross-sectional and prospective studies.[9-11,21] Siroux *et al.* have noted that the total serum IgE level is positively associated with asthma-related hospitalization in a 12-month period before enrolment in the study. Their findings are consistent with our observations.[10] Total serum IgE level is positively correlated with high-risk asthma. However, Gergen *et al.* examined the association between total IgE levels and asthma in the National Health and Nutrition Examination Survey and noted that total IgE levels are associated with asthma only among persons who have positive results for at least 1 allergen-specific IgE.[22]

A few studies have examined the relationship between blood eosinophil count and asthma severity in children. These studies show a positive correlations between blood eosinophil counts and the severity of asthma symptoms.[23] A prospective study involving more than 1000 patients with

asthma has shown that peripheral blood eosinophil count >0.45 x 10^9 per liter is associated with a more than a 7-fold increase in the relative risk of asthma-related death.[24] However, eosinophil counts were not related to asthma severity in a study in which asthma patients were monitored form childhood to adulthood.[25] Our results showed no association between eosinophil count and high-risk asthma. This may be explained by the fact that blood eosinophils do not exactly reflect eosinophilic airway inflammation[26] and neutrophils, rather than eosinophils, may be the predominant cells in high-risk asthma.[27]

In otherwise healthy asthmatics patients, the assessment of pulmonary function often yields normal values that may underestimate the severity of their disease.[28] This indicates that the assessment of symptoms, such as the frequency of nocturnal awakenings, need for rescue short-acting beta-agonist bronchodilation, amount of school or work missed, and impact on overall quality of life, often reveals greater asthma severity than that reflected by pre- or post-bronchodilator spirometry. [28]

Many clinicians consider spirometry to be the best or most objective assessment for asthma severity and/or control. The FEV_1 and PEFR (%) values are conventionally used as measures of airflow limitation caused by bronchoconstriction. However, children at all levels of asthma severity can have relatively unimpaired FEV_1 values when they are clinically stable.[29] In children, the distal airways are definitely affected and normal FEV_1 values are typically seen in many children with asthma due to increased peripheral airway resistance in the absence of or before significantly large airway involvement.[29]

Several studies have shown abnormalities in $FEF_{25-75\%}$ values in asthmatic children with normal FEV_1 values.[29] Luigi DB *et al*. found that reduced $FEF_{25-75\%}$ values in intermittent allergic asthma patients are significantly higher than the FEV_1 and PEFR values.[30] Accordingly, only the $FEF_{25-75\%}$ value correlates with high-risk asthma in children. There is no significant association between high-risk asthma and FEV_1 and PEFR (%) values in this study.

In conclusion, Taiwanese children with higher asthma severity, asthma score, serum levels of IgE specific to *D. pteronyssinus* and *D. farinae* antigens, and total serum IgE levels, and lower $FEF_{25-75\%}$ values belong to the high-risk asthma group. Assessing these high-risk factors will facilitate the identification of high-risk asthma patients in Taiwanese children, leading to better treatment.

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