PHENOTYPE OF CHARACTERISTICS IN ASTHMA CHILDREN NON - ALLERGIC AND ALLERGIC

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ABSTRACT

Introduction: *In allergic children asthma, increased blood or tissue eosinophilia, total concentration or specific IgE, fraction exhaled nitric oxide are frequently reported. It reflects the inflammatory characteristic of disease. Phenotype classification non allergic and allergic asthma helps to optimize the diagnosis and treatment.*

Objective: *This study to investigate possible difference atopy status, blood eosinophilia, total IgE concentration, F_ENO in allergic and non-allergic asthma children.*

Methods: *It was a prospective study asthma patients who had been treated at the National Hospital of Pediatrics. Eosinophil count, IgE concentrations, lung function, and measurements of nitric oxide in exhaled breath (F_ENO) were done at the beginning of the study. If the patient has positive skin prick test, we class allergic asthma patient and patient with negative skin prick test was non-allergic asthma patient.*

Results: *141 patients with an average age of 9 years, 63.8% of male. 75.9% had a history of allergy, in which allergic rhinitis is the most common comorbidity (67.4%). Positive skin test of Df, Dp and Blomia house dust mites were 78.0%, 75.9%, and 68.8%, respectively. Total IgE and blood eosinophil level were high (732.2UI/L and 5.9%). F_ENO concentrations were 24.0±19.6ppb. Compare with non-allergic children asthma, allergic children had higher degree of blood eosinophilia 630 ± 494 G/L vs 344.0 ± 320 G/L ; total concentration IgE 748.0 UI/mL vs 353.0 UI/mL ($p = 0.024$ and $p = 0.014$ respectively). F_ENO showed that patient with allergic asthma higher than non-allergic (25.3 ± 1.8 vs 15.8 ± 4.0; $p = 0.055$). Patients with positive respiratory allergen have individual high percentage 90.7% vs negative patient 70.6% with $p = 0.003$. There was no significant difference in FEV1 value, gender, BMI, asthma level between non-allergic and allergic asthmatics.*

Conclusion: *Bronchial asthma children with similar severity and respiratory function may be associated higher inflammatory factors in allergic asthma compared to non-allergic asthma.*

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1. INTRODUCTION

Since the beginning of the concept of immunity - allergy are divided into two groups Th1 and Th2, bronchial asthma has been associated with Th2 - induced allergic manifestation, hypersensitivity reactions, hypersensitivity reactions, eosinophilia and corticosteroid response. But studies have shown that it is just the majority, not all cases, in this direction [1]. In children, asthma according to the dominant Th2 pathway meets from 45 to 88% in clinical [2].

Asthma is characterized by local infiltration and activation of a variety of inflammatory and immuno-effector cell. The finding that eosinophils are toxic to human lung tissue and that their presence in the bronchial mucosa may correlate with morphological damage to the bronchial [3].

Non-invasive markers to assess them presence and the intensity of airway inflammation in children have been made. Measurements of several blood markers of inflammation have been reported in the monitoring of asthma [4] as well as fraction exhaled nitric oxide (F_ENO) has been proposed as to assess airway inflammation in asthma [5].

The aim of the study is to investigate possible difference atopy status, blood eosinophilia, total IgE concentration, F_ENO in allergic and non-allergic asthma children.

2. STUDY SUBJECTS AND METHODOLOGY

2.1. Study subjects

Patients (6 - 17 years old) diagnosed with asthma at the Department of Immunology Allergy of National Children's Hospital from May 2014 to May 2016.

Selection criteria for study subjects

- Between the ages of 6 and 17 years.

- Have not been in asthma control (newly treated patients) or quit at least 1 month of preventive treatment.

- Properly realized all clinical and functional techniques as directed.

Exclusion criteria

With one of the following criteria: patients with asthma accompanied by other severe diseases; patients with severe asthma attacks; patients being treated with systemic corticosteroids (oral, injectable).

Criteria for diagnosis of asthma

Apply 2014 Global Initiative for Asthma (GINA) guidelines for children >5 years old to diagnose asthma, asthma severity, asthma exacerbation.

2.2. Methods

Study design

It was a prospective study with the intervention for asthma preventive treatment with inhaled corticosteroid according to GINA 2014 guidelines.

The study was presented to the Ethics Council of National Hospital of Pediatrics and approved in May 2014.

141 patients were enrolled and performed skin prick test (SPT). If the patient has positive skin prick test, we class allergic asthma patient and patient with negative skin prick test was non-allergic asthma patient.

Patient classification

Qualified pediatric patients will be selected for the study groups.

Patient classification: follow 1 and 4 asthma severity and asthma control of GINA 2014.

Data collection

All the patients were asked for medical information and clinical examination: to determine asthma status and levels. Family and patients' history of allergies: allergic rhinitis, allergic conjunctivitis, eczema, urticaria, drug allergy, food allergy, and asthma.

Laboratory tests

Blood count: counting the number of white blood cells, eosinophilia by automatical machine.

Total amount of IgE in the blood: by luminescence chemistry techniques.

Skin prick test: negative control is a saline

solution 0.9%; Positive control is histamine 1mg/ml. Six respiratory allergens are made: Dermatophagoides Pteronyssius (Dp), Dermatophagoides Farinae (Df), Blomia tropicalis (Blo), hair and epidermis of dogs, cats, cockroaches. Test is positive when reddish area ≥ 3x3mm.

Respiratory function test

Performed by Koko instrument at Respiratory Functional Testing room of the Central Pediatric Hospital and record the values of FVC, FEV_1, FEV_1/FVC, PEF, FEF_{25-75}.

Measurement of NO in exhaled breath

Performed with Hypair NO with exhalation flow rate of 50 mL/sec; measuring twice and getting the mean. Classification of NO elevations as recommended by ATS in children: F_ENO <20ppb: normal; 20-35 ppb: increased; >35ppb: highly increased [6]

2.3. Statistical analyses: SPSS 22.0 software was used. Qualitative variables are expressed in terms of numbers and percentages. Quantitative variables are represented by mean and SD. Checking the standard or non-standard distribution of variables was realized with Skewness - Kurtosis test.

3. RESULTS

Of the 141 children enrolled in the study were performed skin prick test. Clinical characteristics of the patient were shown in table 1.

Table 1. Clinical characteristics of study subject

Subject characteristics	n = 141
Age	9.0 ± 2.3
Gender, Female (Male), %	36.2 (63.8)
BMI, kg/m^2	17.2 ± 3.2
Individual allergy, %	75.9
Skin eruption ,%	15.6
Allergis rhinitis,%	67.4
Conjuntivis,%	11.3
Eczema, %	22.0
Drug allergy, %	5.7
Food allergy, %	5.7
Family allergy history, %	70.2
Asthma levels %	
Level 1	1.4
Level 2	49.7
Level 3	48.9
Level 4	0
Asthma at admission (current) %	
Yes	56.0
No	44.0

Average age of study group: 9 years old with the average BMI of 17.2 The ratio of male/female is 1.8/1; most of patients have allergic history with the percentage of 75.9, in which patients with allergic rhinitis are the most common: 67.4%; 70.2% of families have parents; The majority of patients have asthma with level 2 and 3 asthma with a rate of 49.7% and 48.9%, respectively. 56.0% of patients have acute asthma symptoms at varying levels (Table 1).

Table 2. Laboratory features of study subject

Laboratory features of patients	n	
Eosinophils, %	135	5.9 ± 4
IgE, UI/mL Median (min – max)	125	732.2 (14.6- 6088.0)
Bronchial F_ENO, ppb	137	24.0 ± 19.6
FEV_1, % compare to theory	128	77.2 ± 19.0
FEV_1/FVC, % compare to theory	128	82.7 ± 8.6

The respiratory function of the patient decreased slightly, with FEV1 of 77.2 ± 19.6% compared to the theory (Table 2). Nitric oxide levels in exhalation increased by 24.0 ± 19.6 ppb. F_ENO is increased highly. IgE levels and eosinophils are higher than normal.

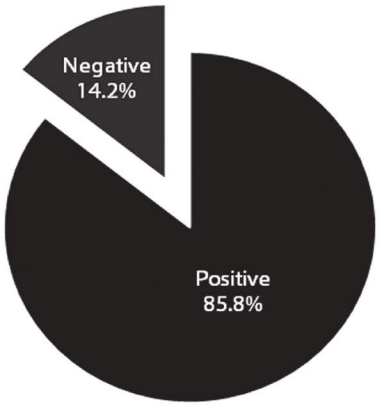

Figure 1. Character of Skin Prick Test

The percentage of positive Skin Prick Test are 85.8%.

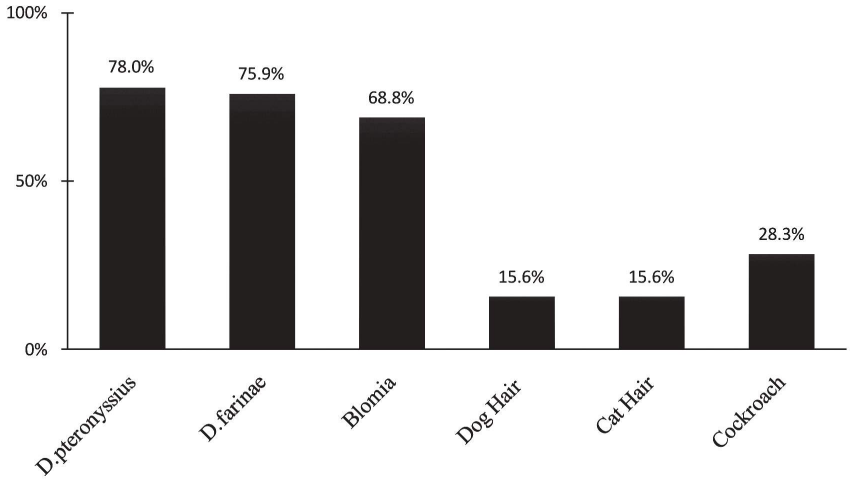

Figure 2. Subjects who tested positive to different respiratory allergens

Most patients are allergic to respiratory allergens, most commonly allergic to indoor dust mites of Dp, Df, Blomia, 78.0%, 75.9% and 68.8%, respectively.

Table 3. Clinical characteristics of non-allergic and allergic asthma

Characteristics \ SPT		Negative n=20	Positive n=121	P
Gender	Male (%)	13 (14.4)	77 (85.6)	0.906
	Female (%)	7 (13.7)	44 (86.3)	
BMI	$\overline{X} \pm SD$	17.1 ± 4.0	17.2 ± 3.0	0.936
Individual allergy	No (%)	10 (29.4)	24 (70.6)	0.003
	Yes (%)	10 (9.3)	97 (90.7)	
Asthma levels	1 (%)	0	2 (100.0)	0.093
	2 (%)	12 (17,1)	58 (82,9)	
	3 (%)	8 (11,6)	61 (88,4)	

There is no difference about: gender, BMI, or severe asthma in patients with positive and negative skin prick test with p> 0.05. Patients with positive respiratory allergen as house dust mites, dog hair, cat hair or crockroach have individual high percentage 90.7% vs negative patient 70.6% with signification p < 0.05 (Table 3).

Table 4. Laboratory features of non-allergic and allergic asthma

Characteristics \ SPT		Negative	Positive	p
FEV_1, % *compare to theory*	$\overline{X}$ + SD	83.7 ± 15.2	76.1 ± 19.3	0.106
	n	19	109	
IgE, *UI/mL*	Median (min – max)	353.0 (14.6-2167)	748.0 (28.1-6088.0)	0.024
	n	18	107	
Eosinophils, *G/L*	$\overline{X} \pm SD$	344 ± 320	630 ± 494	0.014
	n	20	115	
F_ENO, *ppb*	$\overline{X}$ ± SE	15.8 ± 4.0	25.3 ± 1.8	0.055
	n	18	119	

Compare with non-allergic children asthma, allergic children had significantly higher degree of blood eosinophilia 344.0 ± 320 G/L vs 630 ± 494 G/L; total concentration IgE 353.0 UI/mL vs 748.0 UI/mL with p = 0.024 and p = 0.014 respectively. NO measurements showed that patient with allergic asthma higher than non-allergic but no significant difference (25.3 ± 1.8 vs 15.8 ± 4.0; p= 0.055). There was no significant difference in FEV1 value between non-allergic and allergic asthmatics.

4. DISCUSSION

4.1. Patients' general characteristics

In our study, the percentage of boys is 63.8%, consistent with previous studies. According to

Almqvist, boys have a higher risk of asthma than girls do (OR = 1.4 to 1.6) [7] or the percentage of boys with asthma is nearly double that of girls. Maybe, differences in the development of lungs and airways in genders may play an important role: at birth, boys' lungs are smaller than girls' are, but at mature age, male lungs are larger than females. In addition, hormonal changes during puberty, different reactions of the genders to environmental factors may cause different rates of asthma in the genders.

Asthma patients have average BMI of 17.2, which is smaller than the standard of 18.5, almost no obesity was found in the study. Up to 70.2 % of patients had a history of allergy, with one of the following: eczema, allergic rhinitis, allergic conjunctivitis, recurrent urticaria, medicine allergies, and food allergies. This goes well with previous studies, which have shown that over 50% asthma in children is allergic asthma[8]. In these cases, allergic rhinitis is the most common co-infection, accounting for 67.4%, with nasal Nitric Oxide increased highly by 1836 ± 830ppb.

According to Duong-Quy et al., nasal F_ENO concentrations greater than 834 ppb have high sensitivity and specificity (92.59% and 96.97%) for the diagnosis of allergic rhinitis [9]. Because of the high coinfection, for better asthma control, allergic rhinitis is a problem that needs to be addressed in parallel.

The majority of patients in the study have mild to moderate persistent asthma (49.7% and 48.9%) with mild FEV1 respiratory depression by 77.2%, compared to the theory. Fractional exhaled nitric oxide (F_ENO) is a non-invasive, safe, and reliable technique for assessing airway inflammation. Many studies have shown a link between F_ENO and eosinophils in sputum, in blood, bronchial fluid or in lung biopsy. Thus, F_ENO reflects eosinophilic inflammation in bronchial asthma and is used as a monitor for inflammation in asthma. In our study, F_ENO concentrations were 24.0 ppb, higher than usual children were (normal F_ENO <20 ppb in healthy children). As recommended by ATS, F_ENO increase is a good indication for increased eosinophilia inflammation and response to corticosteroids [10].

Beside that the total IgE concentration in the study highly increases by 732.2 UI/mL, peripheral blood eosinophilia also increases by 6%. This is a sign of Th2 allergy asthma, the dominant phenotype in children.

Currently, 130 types of households dust mites in 27 different families have been found, but only 12 types are ecologically related to human beings. Among these types, D.pteronyssinus is most commonly seen in houses of patients with asthma and allergic rhinitis. Positive skin eruption test is most common in households dust mites, the most common respiratory allergies in tropical countries like Vietnam. Allergy to pet hair such as dogs and cats is not high. Thus, indoor environment control is an important factor in order to avoid asthma onset and better control.

4.2. Non-allergic and allergic patient' characteristics

A study of patients with positive skin tests from a single respiratory allergen (D. pteronyssius, D.farinae, Blomia, hair and epidermis of dogs, cats, cockroaches.) showed that there was no difference gender male and female; body mass index BMI; asthma severity; respiratory function FEV1 compared with the negative skin test group as in the previous study[11]. However, patients with positive skin tests (allergic asthma) had a

higher prevalence of allergic disease than non - allergic asthma ($p < 0.05$).

In our study, eosinophils, IgE, and F_ENO in children with positive skin tests highly compared with those with negative skin test were 630 versus 344 G/L, respectively; 748 vs 353 UI/mL; 25.3 vs 15.8ppb.

In the study of Silvestri, there were eosinophilia differences between 500 and 125 G/L for both positive and negative skin test groups; the F_ENO difference between the two groups was 23.9 and 7.9ppb (with $p = 0.0001$). According to Enrique and Bella, in children with positive skin tests, the concentration of F_ENO increased than children negative SPT [12]. Eosinophilia, IgE, and F_ENO increase in allergic children may be due to differences in the pathology of two forms of asthma that trigger inflammatory and inflammatory cells. The authors found differences in the composition of T cells, cytokines in the airways of patients with allergic and non-allergic asthma [13].

Conclusion, asthma is a syndrome rather than a disease with various forms of onset, on pathogenesis, on inflammation, and on prognosis and treatment. Phenotypic classification non allergic and allergic asthma, therefore, helps optimize the diagnosis and treatment.

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