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Allergic and Nonallergic Asthma in Children: Are They Distinct Phenotypes?

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ABSTRACT

The aim of current study is to describe clinical similarities and differences between atopic and non-atopic asthma in children.

In a cross-sectional study, 95 asthmatic children (75 allergics and 20 nonallergics) were included in the study. Demographic, clinical, and familial history were compared between two groups.

There was no significant differences between variables like sex, age of onset (p=0.75), severity (p=0.70), and family history among the two groups (p=0.42). Patients with allergic asthma were significantly older than those with non- allergic asthma (11.28±3.19 and 9.75±2.35 years, respectively, p=0.02).

The controversy lingers over the presence of a completely distinct phenotype of non-atopic asthma in children. Our study suggested that phenotypes of allergic and non-allergic asthma in children were not entirely distinct.

Keywords: Allergic; Asthma; Children; Non allergic; Phenotype

INTRODUCTION

Asthma is a chronic inflammatory disorder mostly associated with atopy and bronchial hyperreactivity (BHR). Since the introduction of non-atopic asthma by Rackemann in 1945,[1] there has always been debate over its existence and specifications. Non-atopic asthma was primarily explained in old females with sinusitis, nasal polyps, and aspirin sensitivity,[2,3] asserted as a dissimilar entity from adult atopic asthma.[4] Initially, non-atopic asthma is defined when patient has no personal or family history of allergy and a negative skin prick test in response to common aeroallergens.[4] Comprising as much as 10% of asthmatics, non-atopic asthma is different from more

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typical form of asthma in adult (Table 1).[4,12,19,20]

Further researches showed much more similarities in pathophysiology of these two phenotypes[5] and therefore their complete distinctions were called into question. On the other hand, there is abundant information regarding adult non-atopic asthma while there is small number of data in children. The aim of current study was to seek for clinical similarities and discrepancies between atopic and non-atopic asthma in children.

Table 1. Clinical characteristics of non atopic asthma in adults

Prevalence	Less common than atopic asthma
Sex	Usually Female
Age of onset	Usually late onset
Severity	More severe than atopic asthma
Triggers	Viral infections
	Irritants
Symptoms	Cough
	Wheezing
	Chest tightness
Family history of asthma	Less common than atopic asthma

MATERIALS AND METHODS

The study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences. Information about the study was given comprehensively both orally and in written form to all study participants and their parents. Written informed consents were obtained from the study participants and their parents.

Patient Selection and Data Collection

In a prospective cohort study, 95 asthmatic children with asthma were enrolled in a one-year period from 2011 to 2012. Inclusion criteria were participants of 6 to18 years of age with diagnosis of asthma based on GINA guideline.[6] Children with positive skin prick test (SPT) to at least one aeroallergen were considered atopic, and children with negative SPT, family history, and personal history of allergy were non-atopic.

Detailed personal and family history of atopy were obtained and physical exam was performed. History of all possible triggers such as respiratory infections, cold air and irritants was also obtained. Day care history was defined as a child-care setting where six or more unrelated children attended. Low birth weight (LBW) was defined as birth weight lower than 2500 g. Birth order was obtained based on formal identity card documents and age of onset of asthma symptoms was asked from parents. Pulmonary function test, lab tests and SPT were performed at the first visit.

Skin Prick Test (SPT)

SPTs were performed with 25 common aeroallergens belonging to five groups (based on common aeroallergens in our region): mites, molds, pollens, animal dander, and insects. Histamine and saline were used as positive and negative controls, respectively. After 15 minutes, the diameter of wheal reaction was measured. Positive results were considered as a wheal diameter of at least 3 mm greater than the negative controls.

Statistical Analysis

Student t-test (for parametric variables) or Mann-Whitney U test (non-parametric variable) was used to compare variables. Statistically significant variables in the univariate analyses were entered into a logistic model to define independent predictors of non-atopic asthma. A p-value of <0.05 was considered statistically significant.

RESULTS

Demographic Characteristics

A total of 95 individuals were included in this study. Mean age±SD of participants was 10.96 ± 3.09 years. Of the included patients, 40% (n=38) were female. Based on the description above, 75 (78.9%) patients were classified as allergic asthma, whereas 20 (21.1%) as non-allergic asthma. Patients' demographics and their distribution between the allergic and non-allergic group are summarized in Table 1. Patients with allergic asthma were significantly older than those with non-allergic asthma (11.28 ± 3.19 versus 9.75 ± 2.35 years, respectively, p=0.022). Age of onset of disease in atopic group was 6.55 ± 4.9 years while this age for non-atopic group was 6.11 ± 4.21 years (p=0.750). Mann Whitney U test showed that the birth order was not significantly different between two groups (p= *0.430*). Positive history for LBW, and cesarean section (p=0.769 and 0.217, respectively)

Table 2. Characteristics of subjects with allergic and non-allergic asthma

Varibles	Allergic asthma (n=75)	Non-allergic asthma (n= 20)	*P* value
Demographics			
Age (Mean±SD) (years)	11.28 ± 3.19	9.75 ± 2.35	0.022
Age of onset (years)	6.55 ± 4.9	6.11 ± 4.2	0.750
Birth order; median (range)	1 (1-11)	1 (1-5)	0.430
Female gender (%)	60%	60%	1.000
Low birth weight (%)	13.3%	15%	0.769
Asthma Symptoms			
Cough (%)	93.3%	95%	1.000
Dyspnea (%)	48%	55%	0.578
Diffuse wheezing (%)	52%	35%	0.176
Family history of asthma			
Maternal (%)	13 (17.3%)	2 (10%)	0.424
Paternal	16 (21.3%)	3 (15%)	0.529
Asthma severity			
Mild persistent	53.3%	55%	0.701
Moderate persistent	41.3%	35%	0.701
Severe persistent	5.3%	10%	0.701

were not significantly different between the two groups of study (Table 2). Moreover, gender distribution was not different between those with allergic asthma and those with non-allergic type.

Asthma Symptoms and Triggers

Frequency of all three cardinal symptoms of asthma (cough, dyspnea and wheezing) was not statistically different between the allergic and non-allergic patients (Table 2). Of these variables, cough was the most frequent symptom in both groups (Table 2).

Certain asthma triggers such as recurrent respiratory infections, passive smoking, persistent exposure to irritants (air pollution, cold air, perfume, detergents), and emotional stress were assessed between the two groups. None of the variables showed a significant difference in prevalence between the allergic and non-allergic cases. Recurrent respiratory infections were the most prevalent triggers in both groups.

Asthma Severity Classification

Severe persistent asthma frequency showed no significant difference between the groups (p=0.7) (Table 2). The percentages of patients with mild and moderate persistent asthma (GINA categories) were not also statistically significant between two groups (Table 2).

We also classified symptoms of asthma into seasonal and perennial, in which 67(70.5%) cases had seasonal symptoms and 23 (24.2%) cases demonstrated perennial symptoms. In atopic group, 52 (73.2%) patients had seasonal symptoms, whereas 21.1% of non-atopic cases had seasonal symptoms. Neither the proportions of seasonal symptoms nor perennial symptoms were statistically different between the two groups.

DISCUSSION

Non-atopic asthma has been typically described as late onset type of asthma mainly observed in adults. Although major progress has been made in understanding of non-atopic asthma in pediatrics but it is still more enigmatic in children.[7] This study was performed to address ambiguities in clinical aspects of non-atopic asthma in children

Our study showed that patients with allergic asthma were significantly older than patients with non-allergic disease. Castro- Rodriguez, et al study also found that children with atopic asthma were older than non atopic.[8] Atopy is a risk factor for persistent asthma in adolescence[9] therefore non-atopic asthma incidence decreases by age.[10] This could explain the age difference of these two groups. On the contrary, other studies have shown no age difference between atopic and non-atopic asthma in children.[11,12]

The age of onset of asthma was not different between allergic and non-allergic asthma in our study. Despite the conclusive differences in age of onset in adults,[13,14] results from children studies vary,

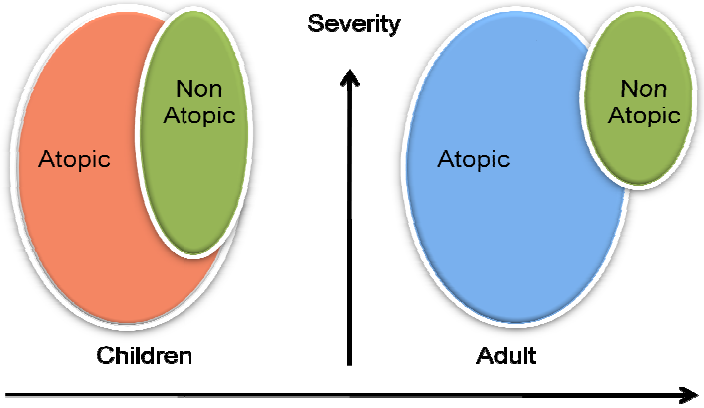

Figure 1. Allergic and nonallergic asthma phenotype in children and adult

reasonably explained by the complexity of the pathophysiology, which causes several variables to change at the same time. Other studies have also shown no association between age of onset and type of asthma particularly in children.[15] In Castro- Rodriguez et al study,[8] age of onset of symptoms was significantly earlier in children with non-atopic asthma than atopic asthma. This discrepancy could be due to the possibility that non-atopic and atopic asthma are not two completely distinct phenotypes in children with more overlaps in children than adults (Figure 1).

Asthma severity in children showed no significant difference between allergic and non-allergic asthma in our study. Severity is one of the most distinctive features to separate allergic and non-allergic asthma in adults and more severe forms are observed in adults with non-allergic asthma.[11-13] However, severity of symptoms is not much different between allergic and non-allergic asthma in children. Castro-Rodriguez et al study did not find any difference in asthma severity in children with atopic and non-atopic asthma[8] the same as Inouye et al study. Accordingly, Cline et al.[16] did not find any significant association between asthma severity and existence of atopic or non-atopic background in children. In fact, severity is defined as an intrinsic severity of the disease process and not related to treatment or triggers.[17] Therefore, lack of difference in severity between atopic and non-atopic asthma in children is in contrast to adults probably due to intrinsic similarities of these two phenotypes in children.

The importance of positive family history in classifying patients to allergic and non allergic asthma is outlined in adults. The original classification of non-atopic asthma by Rackemann proposed stronger familial association in atopic asthma than in non-atopic asthma in adult.[18] Strong genetic predisposition to atopy and allergy indicates that atopic asthma in adults is more family associated phenotype. In this regards, we did not have a statistically significant result which showed that genetic predisposition was not strongly associated with atopic asthma in children. Another possibility is that genetic predisposition of atopic asthma in children may actually be the same as non-atopic asthma.

It is now well established that upper respiratory tract infections (URTI) are the most common cause of acute exacerbations in allergic and non-allergic asthma.[19] Our finding also showed that URTI was the most common trigger in both groups. Besides, the proportion of asthma triggers showed no statistically significant difference between the two groups in our study. This finding is in congruence with previous reports.[20] Indeed, similar mast cell activation in both extrinsic and intrinsic asthma has been suggested as a possible explanation for this finding[21] which seems that pathophysiology of both atopic and non-atopic asthma are mainly the same in children.

The controversy lingers over the presence of a completely distinct phenotype of non-atopic asthma in children. Our study suggests that phenotypes of allergic and non-allergic asthma in children were not entirely distinct.

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