ATOPIC AND NON-ATOPIC ASTHMA PHENOTYPES IN CHILDREN

Gülşah Duyuler Ayçın
Department of Pediatric Allergy Immunology, Adana City Training and Research Hospital Adana, Turkey

ABSTRACT

Introduction*: Asthma is a heterogeneous disease manifested by various clinical phenotypes in children and adults. Two common phenotypes are allergic (atopic) and non-allergic (non-atopic), with more than 50% of asthma in adults, and an estimated 80% of childhood asthma being the allergic type. The aim of this study was to compare the atopic and non-atopic distinctions among patients with asthma between the ages of 5 and 17 by evaluating their clinical features and severity of asthma, and by demonstrating the significance of eosinophilia and IgE values.*

Materials and methods*: History, physical examination and laboratory results of patients with asthma were evaluated in this retrospective chart analysis conducted in Erzurum, Turkey. Atopic and non-atopic discrimination were performed, and clinical features, eosinophil count, and total IgE results were compared.*

Results*: According to the receiving-operating characteristic (ROC) analysis, the cut-off value for eosinophil was 395 mm³, and total IgE was 150IU/ml. Values > 395 mm³ in peripheral blood were accepted as the threshold value, and they were significantly higher in the atopic group (p=0.004). A total IgE level > 150IU / mL was accepted as threshold value, and comparing those levels in the atopic and non-atopic groups showed a highly significant difference (p<0.001). Obesity was significantly higher in the non-atopic group (p = 0.04).*

Conclusion*: These results encourage further study with variable phenotypic presentations to better tailor treatment-specific treatment options for children with asthma.*

Keywords: *Asthma, child, atopy, phenotypes, eosinophil.*

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Introduction

Asthma is a heterogeneous disease manifested by various clinical phenotypes in children and adults[1]. The two forms of asthma are allergic (atopic) and non-allergic (non-atopic), and > 50% of asthma in adults and an estimated 80% of childhood asthma have the allergic form[2]. The prevalence of asthma in children varies by country, race, environmental factors, and methods used to measure it, but in developed societies, prevalence was found to range between 4-23%, as measured by the International Asthma and Allergy Study in Childhood (ISAAC) method[3].

It has been shown that in Turkey, the prevalence of asthma varies between 2.8% and 14.5%[4].

In most cases, allergic asthma is associated with the IgE antibody, but the concept of asthma phenotypes is a complex one. The Severe Asthma Research Program (SARP), a multicenter network examined asthma in adults and children by lung function and age of onset. They studied phenotypic clusters in five groups of patients, as well as the underlying pathophysiological mechanisms, and observed that the overlap is not clear[5]. In children, phenotyping is determined on the basis of multiple variables, namely presence and absence of atopy, severity of the disease,

triggers of symptoms, airway inflammation patterns, and response to drugs, especially for severe asthma[6,7,8].

The aim of this study was to compare the atopic and non-atopic distinctions of patients with asthma between 5 and 18 years of age by evaluating the clinical features, severity of asthma, and demonstrating the significance of eosinophilia and IgE values.

Material and methods

The files of all patients between the ages of 5 and 17, who were diagnosed with asthma at the pediatric allergy immunology clinic at the Erzurum Regional Training and Research Hospital in Erzurum, Turkey from October 2017 through October 2018, were retrospectively analyzed. Patients included in the study were those diagnosed with asthma, and had a history of recurrent wheezing and positive bronchodilator reversibility tests. The patients were followed up by the same physician, and the following data were noted: age, gender, height, body weight, history of asthma (asthma attack requiring hospitalization in the last year, triggering factors in previous episodes), night cough (except for gastroesophageal reflux and allergic rhinitis), atopy, asthma in family, onset of asthma before two years of age by anamnesis, physical examination, pulmonary function test (PFT), skin prick test (SPT) results, eosinophilia, and total immunoglobulin E (IgE). Specific IgE information for inhaled allergens were recorded and evaluated retrospectively. The severity of asthma in patients was evaluated as mild, moderate, or severe according to the criteria set forth by the Global Strategy for Asthma Management and Prevention [1]. PFT and SPT with 11 standard aeroallergen were performed (Allergopharma, Reinbeck, Germany): Dermatophagoides pteronyssinus, Dermatophagoides farinea, Alternaria, Clodasporium, Aspergillus, Candida albicans, tree pollen mixture 1, tree pollen mixture 2, grass pollen mixture, weeds, cockroach, and 10mg/ml histamine phosphate as positive control, and 0.9% saline as the negative control. The presence of 3 mm or more indurations was accepted as positive.

The patients were divided into two groups: atopic or non-atopic. Patients with a positive skin test and specific IgE result for inhaler allergens were considered atopic. For the PFT measurement, values found using spirometry in combination with the computer-based M.E.C. PFT Systems Pocket–Spiro® (Brussels, Belgium) and the (European Community for Coal and Steel) (ECCS) reference normal values were determined as the percentage of the estimated normal value[9]. After initial measurement, 400 micrograms of salbutamol were inhaled and after 15 minutes, forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and peak expiratory flow (PEF) were measured again. A 12% or 200 ml increase in FEV1 value showed the presence of a reversible obstruction. PFT and reversibility tests were performed in all patients.

Total IgE and specific IgE panels (hx1, gx2, tx100, mx1) were studied by using fluorometric enzyme immunoassay (FEIA) and ImmunoCAP Total IgE kits. A cut-off value >0.35IU/mL was accepted for specific IgE panels. In the atopic and non-atopic groups, the following information was gathered: onset of asthma before two years of age, obesity, severity of asthma, cough variant asthma, nocturnal cough, exercise-induced asthma, infection-related attack (upper respiratory tract infection - URTI), cigarette and perfume-induced attack, hospitalization for an asthma attack ≥1 in the past year, family history of asthma, eosinophil count, IgE level, FEV1, and reversibility values. Patients with chronic lung disease or congenital heart disease were not included in the study.

A ROC curve analysis was performed for total IgE and eosinophil values. Also, a sensitivity and specificity analysis was performed with a 95% confidence interval for eosinophil and IgE values in both the atopic and non-atopic groups.

This study was carried out with the approval of the Ethics Committee of the Erzurum Regional Training and Research Hospital (Erzurum BEAH KAEH 2018/decision no. 17-166). Informed consent was obtained from the parents of all patients. Statistical analysis was performed with the SPSS18.0 (Statistical Package for Social Sciences) program and comparisons were made by chi-square test, Fisher Exact Test and the Mann-Whitney Utest. Statistical significance was determined as $p<0.05$. Categorical variables were reported as mean ± standard deviation, and numbers or percentages, respectively.

Results

A total of 115 patients were included in the study, with ages ranging from five years (60 months) to 17.5 years (210 months). The mean age was 124.77 months (10.38 years). Of this group, 62 patients (53.9%) were male. The mean age was 126.17±45.15 months (10.51 years) in the atopic patients and 122.65±43 (10.22 years) months in the non-atopic group. No differences were detected between groups in terms of age and

gender. There were 69 patients (60%) in the atopic group and 46 patients (40%) in the non-atopic group. There was no difference between the groups in terms of asthma starting at the age of two years, as based on patient history. Among patients included in the study, mite allergy was detected in 22 patients (19.1%), pollen allergy was detected in 45 patients (39.1%) and mold allergy was detected in two patients (1.7%). Body mass index (BMI) >30kg/m^2 was found in eight of the 115 patients. Obesity was significantly higher in the non-atopic group (p=0.04). There were no significant differences between the atopic and non-atopic groups in terms of asthma severity, or cough variant asthma (Table1).

Clinical features	Atopic (n: 69 60%)	Non-Atopic (n:46 40%)	P value°
Gender			
Female	38 (55.07%)	24 (52.2%)	P=0.07
Male	31 (44.9%)	22 (47.8%)	
Age	126.17 ± 45.15	122.65 ± 43	p=0.08
Under 2 years onset	24 (34.2%)	13 (28.2%)	
Over 2 Years onset	45 (65.2%)	33 (71.7%)	P= 0.46
Obesity			
BMI <30 kg/ m^2	67	40	
BMI >30 kg/ m^2	2 (2.9%)	6 (13%)	P= 0.04
Asthma severity			
Mild	38 (55.1%)	21(45.6%)	P= 0.22
Moderate	24 (34.8%)	14 (30.4%)	
Severe	7 (10.1%)	11 (23.9%)	
Cough Variant Asthma			
Yes	1	1	
No	68	45	P= 0.64
Cough at night			
Yes	41 (59.4%)	28 (60.9%)	P= 0.51
No	28 (40.6%)	18 (39.1%)	
Exercise induced asthma			
Yes	32(46.4%)	31(67.4)	P= 0.03
No	37(53.6%)	15(32.6%)	
Attack due to infection			
Yes	27 (39.1%)	27 (58.7%)	P= 0.03
No	42 (60.9%)	19 (41.3%)	
Trigger with cigarette and perfume			
Yes	32 (46.4%)	20 (43.5%)	P= 0.45
No	37 (53.6%)	26 (56.5%)	
≥1 Asthma attack hospitalization in the last year			
Yes	14 (20.2%)	15(32.60%)	P=0.10
No	55 (79.71%)	31 (67.39%)	
Family history of asthma			
Yes	34 (49.27%)	11 (23..91%)	P=0.04
No	35 (50.72%)	35 (76.08%)	

Table 1: Clinical features in atopic and non-atopic asthma groups.
°*Fisher Exact Test*

In our study, 63 of the 115 patients (54.7%) had a history of coughing, wheezing, dyspnea, and need for ventolin use after exercise. When atopic and non-atopic groups were compared, there was a significantly higher rate of exercise induced asthma in the non-atopic group (p = 0.03). There was no difference between the atopic and non-atopic phenotypes in the study groups in terms of symptoms of cough at night (except for gastroesophageal reflux and allergic rhinitis) (Table 1).

The history of an attack with infection was higher in the non-atopic group and the difference was found to be statistically significant (p = 0.03) (Table1). In terms of triggering caused by smoking and perfume, there was no significant difference between the groups. Hospitalizations for an asthma attack ≥1 in the past year were evaluated, and no significant difference was found between the two groups. Family history of asthma was high in the atopic group, and there was a statistical significance between the two groups (p = 0.04).

Values > 395mm3 in peripheral blood were accepted as a threshold, and were significantly higher in the atopic group (p = 0.004) (Table 2). Total IgE levels above 150IU/mL were accepted as threshold, and levels in the atopic and non-atopic groups differed significantly (p < 0.001) (Table 2).

	Atopic	Non- Atopic	P value°
Eosinophil			
Eosinophil mean (mm^3)	604.44	270.64	P<0.001
Under 395 mm^3	29	32	P=0.004
Over 395 mm^3	40	14	P=0.004
Total IgE			
Total IgE mean IU/ml	392.56	121.02	P<0.001
Under 150 IU/ mL	16	34	P<0.001
Over 150 IU/ mL	53	12	P<0.001
PFT			
FEV1	83.79 ± 15.81	83.21 ±19.71	P=0.826
Reversibility	13.17±10.11	18.33±15.55	P=0.008
FVC	81.21±15.67	81.21± 18.98	P=0.06
PEF	64.40 ±19.81	65.74 ± 21.91	P=0.06

Table 2: Eosinophil, IgE, and PFT Results in Atopic and Non-Atopic Groups.
°*Fisher Exact Test*

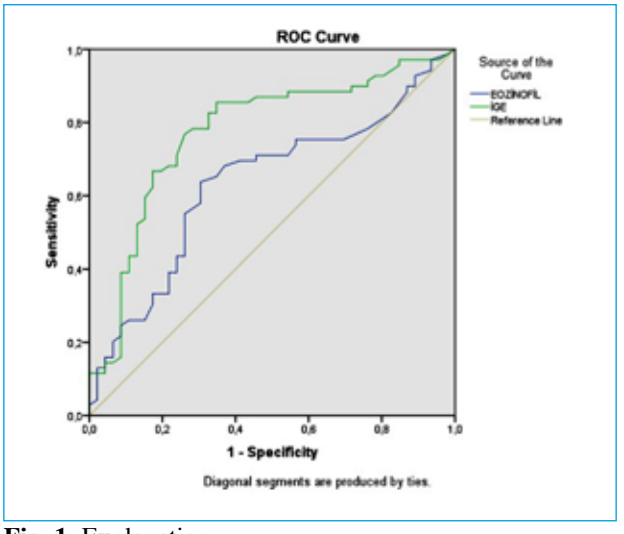

Fig. 1: Explanation.
ROC analysis eosinophil and IgE values.
Threshold value for blood eosinophil count 395mm3. The sensitivity and specificity of eosinophil counts > 395mm3 were 43% and 77% respectively.Threshold value for IgE 150 IU/ ml sensitivity was 60% and specificity was 85% (p<0.001).

The table also shows that in evaluating results of the PFT, only the reversibility values between the two groups were significant (p = 0.008). In the atopic group, the mean value of reversibility was 13.17±10.11, as compared to 18.33+15.55 in the non-atopic group (Table 2). ROC analysis was performed to determine the threshold values of eosinophil and IgE values in predicting atopy. The mean IgE in our study equaled 280.62±393.28 IU/ml, and the cut off value for IgE level was determined as 150 IU/ml. Sensitivity was 60% and specificity was 85% (p<0.001). In the study group, the number of eosinophils was 468.02±973.76. The threshold for predicting atopy for eosinophil was determined to be 395mm3. The sensitivity and specificity of eosinophil counts > 395mm^3 were 43% and 77% respectively (p<0.001) (Figure1).

Discussion

This study took a comprehensive look at factors influencing atopic and non-atopic asthma, and included factors such as: gender, age, obesity, asthma severity, cough variant asthma, cough at night, exercise induced asthma, attack due to infection, trigger from cigarette and perfume, > 1 asthma attack hospitalization in the last year, and family history of asthma.

We started with the premise that a phenotypic analysis in children is essential for successful treatment management, and for organizing and personalizing the diagnosis and treatment of asthma[10]. The allergen-induced (atopic) phenotype may occur at any age, but more often starts in early childhood[11]. We hypothesized that asthma was more prone to early onset in the atopic group, but this finding was not statistically significant. In our study, 69 (60%) of the 115 patients were atopic and 46 (40%) were in the non-atopic group. A study similar to ours, with 53 asthmatic patients aged between 3-14 years detected atopy in 50.9% of the study population[12].

A multicenter study by Jarvis et al. reported no association between obesity and allergic sensitization[13], but other studies have shown a relationship between non-atopic asthma and obesity[14]. Similarly, in our study, obesity was significantly higher in the non-atopic group.

Regarding clinical asthma severity, a study by Liam et al. found no difference between atopic and non-atopic individuals[15]. Likewise, in our study, the patients were evaluated in three groups in terms of asthma severity-mild, moderate, and severe-and no significant relationship was found between asthma severity and atopy.

As for patients with cough variant asthma, the cough is the main symptom. According to Gibson et al, this diagnosis should be confirmed either by spirometry with a positive bronchodilator response, or by positive bronchial provocation challenge[16]. In our study, two out of 115 asthma patients, one in the atopic group, and one in the non-atopic group, were evaluated as cough variant asthma. There was no difference between groups, possibly due to the very small numbers.

Nocturnal asthma and exercise asthma occur in the majority of patients who are not treated, and these are not two separate phenotypes. Exercise asthma is seen in 10% of athletes[17]. In our study, when atopic and non-atopic groups were compared, there was a significantly higher rate of exercise induced asthma in the non-atopic group (p=0.035). In the studies conducted with various provocation tests, exercise-induced bronchospasm was reported with a ratio of 45-90% in asthmatic children[18].

Our research found that triggering infection with URTI in the non-atopic group was significantly higher than in the atopic group (p=0.03). In a survey conducted on primary school children, 50.9% of 116 asthmatics were reported to have been triggered by URTI[19].

There was no difference between the groups in terms of smoking and perfume triggers. In a questionnaire-based study conducted in primary children by Ozmen et al, 41.1% were reported to be triggered by cigarette smoking[19].

Regarding > 1 hospitalization due to asthma attack in the last year, we found that 29 patients (25.21%) across both groups were hospitalized, but this was not a significant finding. In comparison, family history of asthma was significantly higher in the atopic group (p=0.04). This factor, and contact with allergens are important factors for the development of allergic asthma[11]).

The mean total IgE was 392.56 IU/ml in the atopic group and 121.02 IU/ml in the non-atopic group, showing a significant difference (p < 0.001). This finding aligns with another study of 53 children with asthma. The mean eosinophil count was 357.5mm^3 in asthmatic patients, and there was a significant difference with the control group. In the same study, total IgE levels were significantly different versus the control group (p=0,006)[12]. Eosinophil is the center of T2 inflammation and is the dominant inflammatory cell in the respiratory tract of children with severe asthma. Although it is not a standard cut off for eosinophilic inflammation, a

sputum eosinophil cell count of more than 2-3% of the total number of cells or a blood eosinophil count of 300 mm^3 has been used as a threshold value[20].

In a study with children, conducted by Terhan et al, those who had > three wheezing attacks in a one-year follow-upwere defined as the frequent wheezing group (n = 29), and those with < three attacks since the index attackwere defined as the infrequent wheezing group (n = 28)[21]. When a ROC curve analysis of the cut-off value of blood eosinophil count for predicting the frequent wheezing group was examined, values of blood eosinophil count > 390mm^3 in predicting frequent wheezing were found to have a sensitivity of 51.7% and specificity of 78.1% (p=0.019). For total IgE level, threshold level was found to be 154IU/ml. Sensitivity and specificity were 20.7% and 96.4%, respectively. In our study, when the ROC curve analysis of the cut-off value of the IgE in predicting the atopy was examined, sensitivity and specificity of total IgE level > 150IU/ml was detected as 60% and 85% (p<0.001), respectively. The threshold value of eosinophil for predicting atopy was found to be 395mm^3. The sensitivity and specifity of eosinophil count of 395/mm3 and above values were 43% and 77%, respectively (p<0.015)(Figure 1). Moreover, the number of eosinophils above 395mm^3 was significantly higher in patients with atopic asthma. The mean IgE mean was 392.56IU/ml in atopic patients and was significantly higher than the non-atopic group.

PFT values did not differ between the two groups. Reversibility values were significantly higher in the non-atopic group (p=0.08). In one study, no significant difference was found between atopic and non-atopic individuals in terms of the severity of clinical asthma[15], while in other research, patients with atopic asthma were found to have better respiratory function, but more frequent attacks versus non-atopic patients[11].

The limitation of this study may be that it could not be determined as to whether an infection is viral or bacterial in patients with URTI triggered by asthma attack.

For the planning of treatment and monitoring of asthmatic patients, it is necessary to determine the risk factors, the severity of asthma, and to conduct a detailed allergic evaluation. In our study, in terms of atopic and non-atopic phenotypes, we found that attacks due to exercise and infection are more common in non-atopic patients, reversibility was significantly higher in non-atopic patients, and if the total IgE level > 150IU/ml and the eosinophil level > 395mm^3, it may be useful to continue investigating into the diagnosis of atopic asthma. These results encourage further study with variable phenotypic presentations to better tailor treatment-specific options for children with asthma.

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Corresponding Author:
Gülşah Duyuler Ayçin
Department of Pediatric Pediatric Allergy Immunology
Adana City Training and Research Hospital Adana / Turkey
Email: drduyu@gmail.com
(Turkey)