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The Role Of Eosinophilic Cationic Proteins, Total IgE And Eosinophilia In Children With Bronchial Hyperresponsiveness

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ABSTRACT
Bronchial hyperreactivity (HRB), is defined as an excessive bronchial constriction that acts as an exaggerated bronchoconstrictor of the airways. This occurs as a secondary action of a nonspecific stimuli.
Taking as a starting point asthmatic patient, as the patient responds by bronchoconstriction action of various stimuli, the concept of bronchial hyperractivity gradually began to take shape. Bronchial hyperractivity (HRB) can be considered a major, heterogeneous phenomenon, depending on several conditions, in term of etiology and which gathers the features of a genuine syndrome if we consider the complexity of the mechanisms which produce and countless clinical implications.

Keywords: wheezing, child,bronchial hyperractivity

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Introduction

The most common chronic respiratory pathology in children is recognized as being asthma. One of the most frequent simptoms associated with this is the bronchial hyperresponsiveness. Bronchial hyperreactivity (HRB) can be considered a major heterogeneous,phenomenon, depending on several conditions, in term of etiology and which gathers the features of a genuine syndrome if we consider the complexity of the mechanisms which produce and countless clinical implications [1,2,3].

The research of HRB is strongly related to asthma. HRB is involved in both the immediate and late asthmatic reaction. It is considered that acute HRB, which occurres due to contraction of bronchial smooth muscle is responsible for the acute asthmatic reaction, while chronic HRB is involved in the chronic symptoms of asthma.

Objectives

The present study evaluates eosinophilic inflammation in children with bronchial

hyperresponsiveness and identifying the determinants of onset of bronchial asthma, which is why we turned to dosing cationic proteins of eosinophils (ECP) from serum as a marker of eosinophilic inflammation, which can predict persistent wheezing over five years and therefore the diagnosis of bronchial asthma.

So that objective in the main paper it is to discuss the usefulness of eosinophilic cationic inflammation in obstructive respiratory pathology in children.

Material and method

The study had a prospective cohort character and was conducted on a total of 199 patients with wheezing, that have been followed for a period of four years between 2009-2013.

Study was conducted in the Clinical Pediatric department of the Constanta Clinical Emergency Hospital.

The ages of the patients in the study ranged from 2-4 years old, where they presented for a recurrent episode of wheezing.

Children where evaluated using a questionnaire to asses the following parameters:

- age, sex, origin;
- mother's age, mother's education, the organization of the family (mothers's marital status), socioeconomic conditions, addictions of parents in pregnancy/ postpartum;
- previous history of hereditary disease;
- previous personal physiological history (gestational age, birth weight, conducting vaccination calendar);
- type of food
- atopic environment
- associated comorbidities
- number of episodes of bronchial obstruction prior to introduction into the study.

Results

The distribution of patients by eosinophilic cationic proteins values

Eosinophilic cationic protein was evaluated in 183 patients. Of these, 119 were subsequently diagnosed with asthma, and 64 were not diagnosed with bronchial asthma at the revaluation.

The average value of eosinophilic cationic protein for the group of patients who developed bronchial asthma was 24.34 mg/L (standard deviation of 12.14 mg/L). It is noted from the outcome that the average value of the eosinophilic cationic protein is increased compared with the maximum laboratory value, of 11 mg/L. In patients who were not diagnosed with asthma calculated a mean value of 14.92 mg/L, with standard deviation of 11.96 mg/L. (Table I)

Table I. Descriptive analysis of eosinophilic cationic protein values

Caegory	Asthma	Wheezing	Total
N	119	64	183
Mean	24.34	17.97	22.11
Median	21.6	13.65	18.6
Std. Deviation	12.14	11.967	12.426
Variance	147.39	143.21	154.41
Skewness	0.65	1.936	0.98
Kurtosis	-0.366	4.973	0.633

Comparing medican values for the two groups is observed that in patients who developed bronchial asthma has a value of almost 60% compared to the group of patients who did not develop asthma (Table II).

The distribution of cationic protein value is presented for both groups compared in figure no 1.

It is evident that both distributions are asymmetrical to the left, most of the values are below the value of 20 g/L.

Corroborating appearance histogram Shapiro-Wilk test result, becomes apparent that eosinophilic cationic protein distribution values differs significantly

from the normal distribution. As a result, it is more useful to compare the use of the median, and the non-parametric statistical comparison test Mann-Whitney Test.

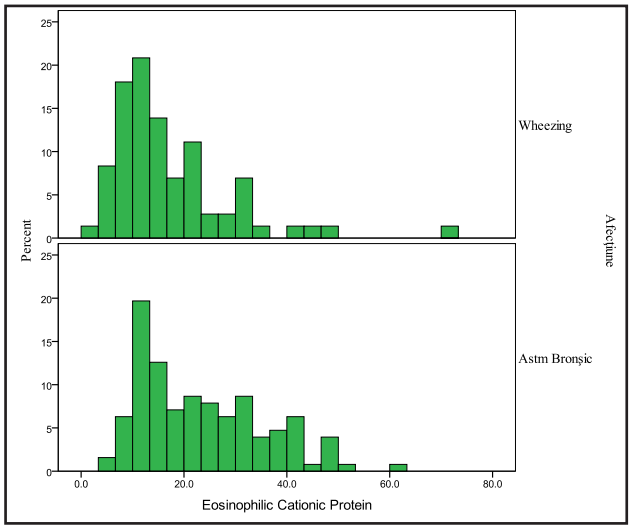

Figure 1 Eosinophilic cationic protein distribution values

The difference observed between the two groups is statistically significant, U = 2470.5, z = -3.914, p <0.001.

When Chi-square test is applied, it indicates a statistically significant association between eosinophilic cationic protein values and the occurrence of asthma. (P = 0.0002). Basically, a child with wheezing presenting elevated eosinophilic cationic protein is significantly higher risk of being diagnose with asthma than a child with normal levels of eosinophilic cationic proteins.

The distribution of patients by IgE values

The average values of IgE in patients who were later diagnosed with bronchial asthma are increased, averaging 117.73 IU/ml and the median value of 95 IU/ml. The standard deviation for this is 79.194 IU/ml. For the second group is the average of 67.62, standard deviation 69.185 IU/ml and the median value of 44.00 IU/ml. (Table II) its is therefore apparent in both cases a very high dispersion values, appearance presented in Figure 2.

Chi-square test indicated a statistically significant associations between IgE values and the emergence of the type of bronchial asthma that the patients followed in the study. (P = 0.001)

Table II Descriptive analysis of IgE values

Category	Asthma	Wheezing	Total
N	126	72	198
Mean	117.738	67.625	99.515
Median	95	44	80
Std. Deviation	79.19426	69.1859	79.30169
Variance	6271.731	4786.688	6288.759
Skewness	1.471	2.63	1.633
Kurtosis	2.472	6.658	2.674

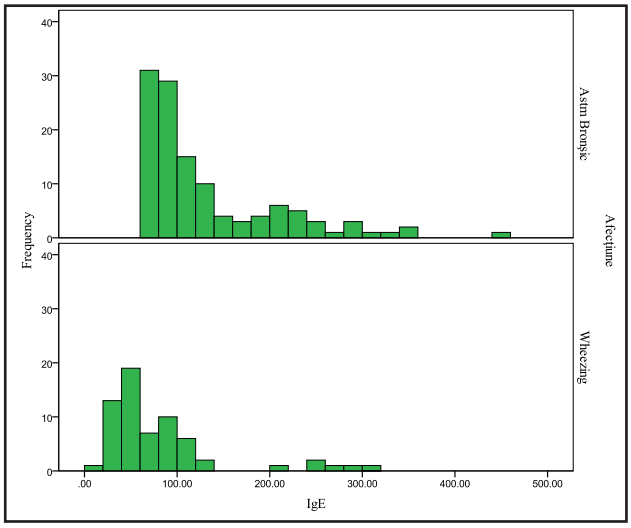

Figure 2 Distribution IgE values

Distribution of the patients based on baseline eosinophils values

The mean value for the group of patients who developed asthma is 3.55% (standard deviation 3.52), while for the group of patients who have been diagnosed with bronchial asthma had an eosinophil average percentage of 5.67% (standard deviation 5.37).

There is a higher percentage value of eosinophils in the blood count of the patients which did not develop bronchial asthma. (Table III)

Table III A descriptive analysis of the values of eosinophils

Category	Asthma	Wheezing	Total
N	48	30	78
Mean	3.557	5.673	4.371
Median	3.3	5.1	3.7
Std. Deviation	3.5231	5.3696	4.4169
Variance	12.412	28.833	19.509
Skewness	1.015	1.124	1.329
Kurtosis	1.004	0.584	1.771

By analyzing the distribution values of (Figure No. 3) it is observed that the values of eosinophils present similar distributions, with most cases showing values below 5%.

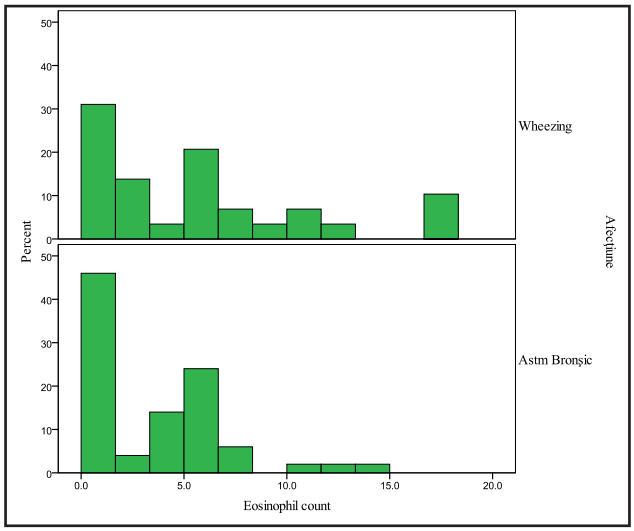

Figure 3. Distribution of eosinophils values

Since eosinophils values do not meet the normal distribution of values for comparison using a non-parametric test, as that used in the present case the Mann-Whitney test.

Eosinophil values did not differ significantly between the two groups, U = 389, z = -1.548, p = 0.122. Therefore it can not be stated with suddicient confidence that there are differences between the values of eosinophils in the two groups of patients.

Possible screening tests

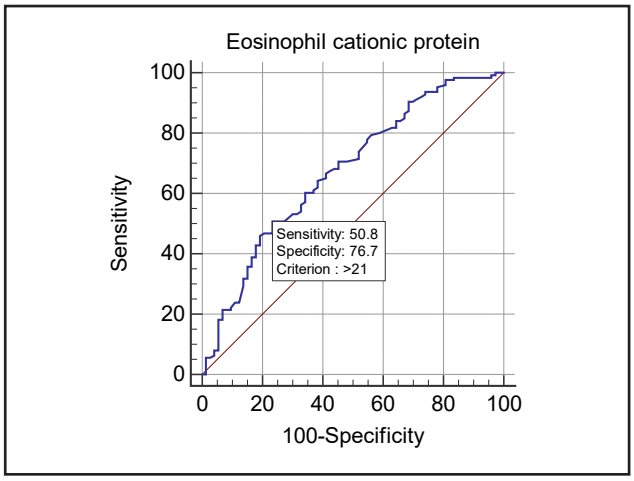

Figure 4 ROC for Eosinophil cationic protein

It is noted that the optimal test results are obtained when the right threshold of ECP's determination shall be a considered value of 21 µg/L. Patients with values greater than 21 µg/L have an increased risk of developing asthma. For this threshold, the sensitivity is 50.8 and specificity of 76.7.

The area under the ROC curve is a measure of the accuracy of the test. As the surface becomes greater, the accuracy of the test is higher. For eosinophil cationic protein analysis, the area under the ROC curve is 0.67, indicating poor accuracy, about significant result (p <0.001).

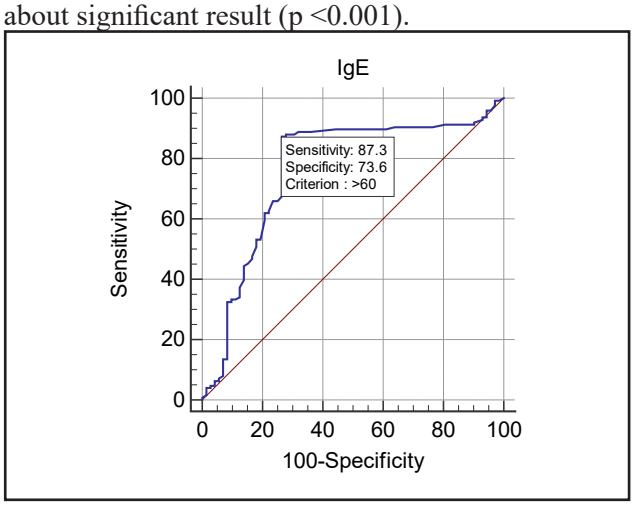

Figure 5 ROC for IgE

The optimal test results are obtained if the limit value analysis as adopted is considered a value of 60 IU/ml. For this value, sensitivity is calculated and obtain a value of 83.7% and specificity of 73.6%.

The area under the ROC curve has a value of 0.76, which is statistically significantly different compared to the reference value (p <0.00001). This value indicates that the test has an average value in the screening of bronchial asthma reactivity is increased, with a result being highly statistically significant.

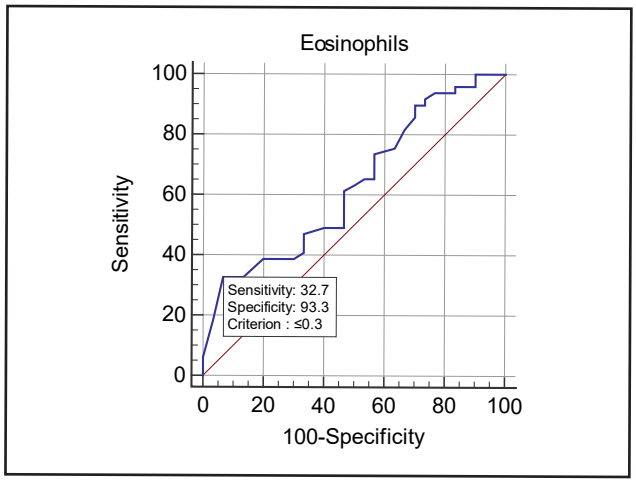

Figure 6 ROC for Eosinophilia

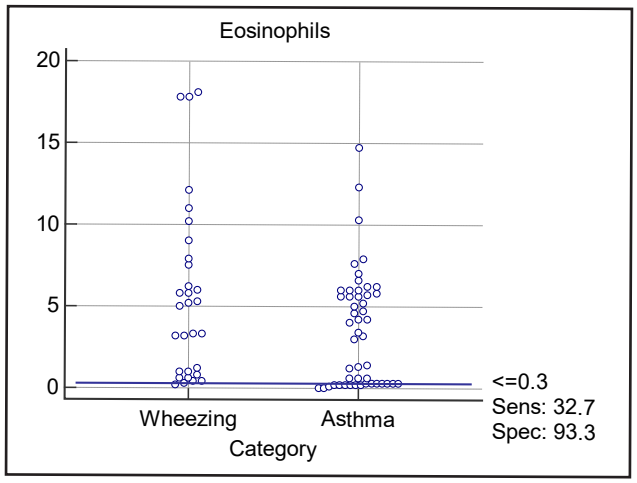

Figure 7 Dot diagram eosinophils

The optimal test results are obtained when the threshold for eosinophils count is considered value of <= 0.3. Patients with values over 0.3 has an increase risk of developing bronchial asthma. For this threshold, the sensitivity value is 32 and specificity is 93.1.

The area under the ROC curve is a measure of the accuracy of the test. As greater the surface is, the accuracy of the test is higher. For the analysis of eosinophils, the area under the ROC curve is 0.62, indicating a poor accuracy, resulting in statistical significance (0.0434).

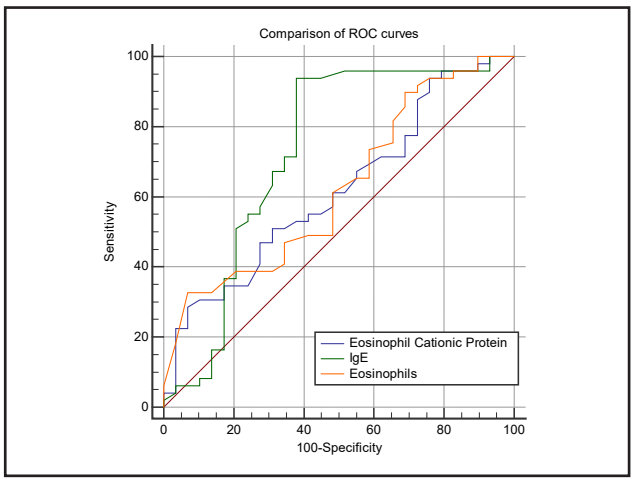

Figure 8 Comparison of ROC curves

In cases in which the accuracy of the test is indicated by the area under the ROC curve, it can be seen that the test for immunoglobulin E shows the highest accuracy in identifying children with increased bronchial hyperactivity, which will later develop bronchial asthma.

Discussion

ECP's level in biological fluids are indicative of the activation and degranulation of eosinophils, specifically, in currently use for the clinical examination and diagnosis of inflammatory diseases.

The children who's analysis resulted in high levels of ECP were the ones who met the afore mentioned criteria. Of 164 subjects with elevated eosinophilic cationic protein, 144 were later diagnosed

with spirometry of AB. This idea is supported by apublished studies [4,5]

According to another study by Ingram et al. 1995 [6] on a group of wheezing children in age between 2 and 4 years, the serum ECP was similar to the value obtained in my study (24.34 mg/L). this idea is supported in another study published by J. Rvilla [7], which highlights that the ECP has an average value of 22.48 g/L in children with persistent wheezing. We have found that those subjects with higher levels of ECP (21 μg/L) had a significantly higher risk of being diagnosed with asthma after the age of 5 years.

In case of that wheezing is a heterogeneous symptom with manifestations transitory or permanent, should it be assessed since the first visit **atopic** and other elements that can sustain/ maintain wheezing. The existence of unmediated IgE asthma causes the dosage of serum total IgE to have a predictive importance in association with ECP.[8]

In Keleş's study of 2012 [8], conducted on a sample of 108 patients, separated into 2 groups: patients with transient wheezing and group 2 containing persistent wheezings. Mean serum IgE was 97.1% in group 1 and 16.9% in group 2 with $p>0.01$, dates that sustain the necessary idea of dosing IgE in children with clinical manifestations of asthma to establish predictability evolution in these events.

Related to sanguine eosinophilia, it can be said that the increased level of eosinophils from peripheral blood is found in a variety of conditions including: parasited, infectious processes, allergies, cancers, primary haermatological affections and other less defined diseases.[9]

Global asthmatic research began to focus towards other different mechanisms from those known so far, considering that condition of the pathophysiological processes involved in the occurrence of asthma is not fully understood. Literature of specialization, begins to support the idea that there are a number of non allergenic asthma cases. [10]

Conclusions

The dosage of eosinophilic cationic protein in serum may be a useful marker in the estimation of eosinophilic inflammation in the airways in patients with wheezing. My study suggests that eosinophilic inflammation is present from the first episodes of wheezing in children who develops asthma at age of 5.

Subjects with increase levels of ECP (21μg/L) had a significantly increased risk of diagnosis of asthma after the age of 5 years.

The determination in total serum IgE, ECP and eosinophils present a basic point in predicting the clinical evolution in manifestations of allergic type by the bronchial asthma.

In my study, the total number of patients presented most of the time with high values of IgE. The test has a specificity of 73.6 and a sensitivity of 83.7 for a threshold of 60 IU/ml. The amount of area under the ROC curve indicate that the test has an average screening value in bronchial asthma in children with increased bronchial reactivity, the result being highly statistically significant.

Values of eosinophils below 0.3, the possibility that a patient is healthy is 93.1%.

In conditions when the accuracy of the test is indicated by the area under the ROC curve, it can be observed that the test for immunoglobulin E shows the highest accuracy in the identification of children with increased bronchial hyperactivity, which will later develop asthma.

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