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Respiratory Medicine

"ASSOCIATION OF LUNG FUNCTION WITH BLOOD EOSINOPHILS AND TOTAL SERUM IGE IN ADULT ALLERGIC ASTHMA"

Dr. Lavina V. Mirchandani *	M.D (TB and Chest Diseases), D.N.B (Respiratory Medicine), DHA. Associate Professor (ex), Department of Pulmonary Medicine, Dr. D.Y.Patil University, College of Medicine, Nerul , Navi Mumbai.*Corresponding Author
Dr. Ibrahim Siddiqui	MBBS Resident, Department of Pulmonary Medicine, Dr. D.Y.Patil University, College of Medicine, Nerul, Navi Mumbai.
Dr. Girija Nair	M.D (TB and Chest Diseases) Professor and Head, Department of Pulmonary Medicine,Dr. D.Y.Patil University, College of Medicine, Nerul, Navi Mumbai.

ABSTRACT **Background:** In allergic phenotype of asthma, IgE is involved early in the inflammatory cascade followed by eosinophilic inflammation and airway remodelling. This study aims to find the correlation between lung function and these biomarkers in adult allergic asthmatics.

Methodology: Spirometry, total serum IgE levels and blood eosinophil counts were determined in 43 adult allergic asthmatics and the association between these biomarkers and airway obstruction as represented by the forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) ratio (FEV1/FVC %) was analysed.**Results:** For both pre- and post-bronchodilator spirometry, patients with FEV1/FVC ratio < 70%, had significantly higher total serum IgE levels as well as blood eosinophil counts ($p \leqslant 0.05$), compared to patients with FEV1/FVC ratio ≥70%.

Conclusion: Total serum IgE and blood eosinophil counts show strong association with airway obstruction in allergic asthmatics and can be used to modulate asthma management.

KEYWORDS : Allergic Asthma, Biomarkers, Spirometry

INTRODUCTION:

Bronchial Asthma is a heterogeneous disease characterized by airway inflammation, reversible airway obstruction and bronchial hyper responsiveness to a multiplicity of stimuli. It manifests clinically by paroxysms of cough, dyspnoea, wheezing and chest tightness that may vary over time and intensity and resolve spontaneously or as a result of therapy. It presents as an obstructive type of ventilator defect usually diagnosed from a reduced forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) ratio (FEV1/FVC %) on spirometry. The inflammatory cascade unleashed by allergic and non-allergic triggers in asthma patients is complex, resulting in many phenotypes and endotypes of asthma and making its management extremely challenging. Molecular phenotypes have been identified revealing specific biomarkers which help in targeted personalized asthma management [1]. Ascertaining the association of simple biomarkers to airway obstruction will further help in defining the subgroup of patients who will benefit from targeted therapies. This study done on the allergic phenotype of asthma patients determines the association of obstruction on spirometry with two easily measurable biomarkers viz blood eosinophil counts and total serum IgE levels.

MATERIALS AND METHODS:

A cross-sectional study was conducted on outpatients at an urban tertiary hospital over a period of about one year from 2014 onwards wherein 43 patients aged above 18 years and diagnosed with stable allergic asthma on the basis of clinical history, examination, X-ray findings and skin prick testing, were enrolled after obtaining written informed consent and fulfilling inclusion and exclusion criteria. Smokers, persons < 18 years old, lactating and pregnant women, patients with positive skin prick test for aspergillus were excluded from the study. Patients were also excluded if they had past history of pulmonary TB or any other respiratory illness, were on oral steroids or on oral antihistaminic drugs within two weeks prior to study or had experienced acute exacerbations within 4 weeks before the study began. Regular treatment with inhaled bronchodilators and inhaled corticosteroids was continued in all patients. After a written informed consent, each patient underwent spirometry pre and post bronchodilator, a standard allergen skin prick test (SPT), estimation of their peripheral blood cell counts, blood eosinophil counts and total serum IgE levels on the day of enrolment in the study. Correlation between Total Serum IgE and FEV1/FVC Ratio pre and post bronchodilator and similarly between blood eosinophil counts and FEV1/FVC Ratio pre and post bronchodilator was tested using the two tailed unpaired t test. A value of $p < 0.05$ was regarded as a statistically significant difference.

RESULTS:

In the present study, of the 43 patients, 24 (55.8%) were male and 19 (44.2%) female and the mean age was 34.07 years. All patients had early onset history of asthma symptoms, had history of recurrent colds, sneezing on exposure to either dust, odours, change of weather and 42% had family history of asthma. All patients had polysensitization to various allergens on SPT. Depending on the FEV1/FVC ratio patients were divided as those with ratio above 70% and those below or equal to 70%. This was done with both pre-bronchodilator and post-bronchodilator FEV1/FVC %.

The mean total serum IgE in FEV1/FVC % >70% pre and post bronchodilator group was 800.34 and 893.54 respectively while in the FEV1/FVC % ≤ 70% pre and post bronchodilator group it was 1599.26 and 1744.86 respectively. On comparison between the pre bronchodilator FEV1/FVC % >70% group with pre bronchodilator FEV1/FVC % ≤ 70%, it was found that the difference in the total serum IgE levels between the two groups was statistically significant ($p < 0.05$). Similarly, the difference in total serum IgE levels between the post bronchodilator FEV1/FVC % >70% group with post bronchodilator FEV1/FVC % ≤ 70% was also statistically significant.

The mean absolute eosinophil count (AEC) in FEV1/FVC % >70% pre and post bronchodilator group was 331.82 and 357.14 respectively while in the FEV1/FVC % ≤ 70% pre and post bronchodilator group it was 600 and 660 respectively. On comparison of the AECs between the pre bronchodilator FEV1/FVC % >70% group with pre bronchodilator FEV1/FVC % ≤ 70%, it was found that the difference between the two groups was statistically significant ($p < 0.05$). Similarly, the difference in AEC between the post bronchodilator FEV1/FVC % >70% group with post bronchodilator FEV1/FVC % ≤ 70% was also statistically significant. The statistical analysis with precise values is summarized in Table1 below.

Table 1: Correlation between total serum IgE, absolute blood eosinophil count and spirometry in Allergic Asthma in two groups viz FEVI/FVC% >70% and FEVI/FVC% ≤ 70%

GROUPS	MEAN TOTAL SERUM IGE	MEAN ABSOLUTE BLOOD EOSINOPHIL COUNT /µl (AEC)	t-TEST FOR EQUALITY OF MEANS

			t VALUE IGE BETWEEN 2 GROUPS	p VALUE IGE BETWEEN 2 GROUPS	t VALUE AEC BETWEEN 2 GROUPS	p VALUE AEC BETWEEN 2 GROUPS
PRE-BRONCHODILATOR FEV1/FVC% > 70% N=22	800.34	331.82	-2.456	0.018	-3.540	0.001
PRE-BRONCHODILATOR FEV1/FVC% ≤ 70% N=21	1599.26	600				
POST-BRONCHODILATOR FEV1/FVC% > 70% N=28	893.54	357.14	-2.502	0.016	-3.908	0.0003
POST-BRONCHODILATOR FEV1/FVC% ≤ 70% N=15	1744.86	660				

DISCUSSION:

Bronchial Asthma is a syndrome encompassing distinct phenotypes and endotypes based on factors such as onset of disease, predominant cellularity, obesity, exercise induced, molecular mechanisms causing T2 high or T2 low and other as yet unidentified elements. Allergic (or atopic) asthma is now recognised as a specific phenotype of asthma representing over 60% of cases whereas non atopic eosinophilic phenotype represents about 25–30%[2].

Allergic asthma is a T2 high form of asthma which implicates signalling of IL4, IL13 and IL5. IL4 and IL13 leads to increased IgE synthesis by B cells while IL5 has a stimulatory effect on eosinophils. Thus while IgE is involved early in the inflammatory cascade in T2 high endotype of asthma, eosinophilia can be considered as a consequence of the whole process[3]. Hence total serum IgE and blood eosinophil levels should be higher in allergic asthma and can serve as important biomarkers. However, eosinophils may be the pro inflammatory and epithelial damaging cells in both allergic and non-allergic asthma[4].

Traditionally IgE antibodies are believed to be responsible for the classic "early phase" of an allergic reaction but its biological role is complex as it has a considerable role not only in the "late phase" reaction by activation of Th2 cells and production of chemokines, but also by affecting eosinophil functions and directly activating airway smooth muscle cells to produce cytokines, chemokines and extracellular matrix proteins resulting in smooth muscle hypertrophy and hyperplasia and airway wall remodelling[5].

Eosinophil differentiation and activation is mainly regulated by IL5, but other cytokines like Granulocyte–macrophage colony stimulating factor (GM-CSF), IL-3, prostaglandin D2 (PGD2) and indirectly IgE also enhance eosinophil functions[6]. The ongoing inflammation due to accumulation of eosinophils and release of toxic proteins by eosinophils results in bronchial wall damage and airway remodelling.

Thus both IgE and eosinophils are fundamental to the inflammatory response, bronchoconstriction and airway remodelling seen in asthmatic airways. Hence in this study we studied the relationship between the objective parameter of ratio of patient's FEV1 to FVC in % and absolute blood eosinophil count (AEC) and total serum IgE levels. In our adult allergic asthmatic patients, it was observed that the values of total serum IgE levels and AEC were significantly higher ($p < 0.05$) in the group having obstruction on spirometry as envisaged by FEV1/FVC % ≤ 70%, compared to those with FEV1/FVC % >70%. This significant difference was seen in both pre and post-bronchodilator spirometry.

Similarly, other studies have reported that higher eosinophil counts correlate well with reduction in FEV1% and also to the response to inhaled steroids[7]. In fact, high blood eosinophil counts are reported to be associated with airflow obstruction in adults with and without asthma[8]. Many studies have reported a correlation of higher serum IgE levels with lower values of FEV1 and FEV1/FVC[9]. But there are studies which have found no statistically significant differences between patients with high and low IgE levels regarding the baseline values of FEV1, FVC and FEF25-75%[10].

Our study has definitively shown that in the specific subset of allergic asthma patients there is a significant correlation of blood eosinophil counts and total serum IgE levels with obstruction on spirometry. Having objective parameters like the two easily reproducible, readily measured biomarkers mentioned could help in deciding specific therapies targeted at eosinophils or IgE so that patients are better controlled and airway remodelling and chronic obstruction is prevented.

CONCLUSION:

The Asthma syndrome is intricate and complex necessitating a more evolved approach at a cellular level for its management. Though there have been tremendous advances in the understanding of the pathophysiology, genetic, cellular and molecular pathways of Asthma, leading to better modalities for its management; even today we still rely on asthma symptoms for classifying the control of asthma and tailor treatment according to it. In our study the strong association of obstruction on spirometry, both pre and post bronchodilator, with higher values of blood eosinophil counts and total serum IgE in the subset of allergic asthmatics validates the role of these biomarkers in endotype categorization and asthma management

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