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Research Article

IN CLINICAL PRACTICE IGE LEVELS AS A BIOMARKER FOR THE MANAGEMENT OF BRONCHIAL ASTHMA PATIENTS IN INDIA

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ABSTRACT

Allergen-specifcIgE is the predominant biomarker for allergic asthma. IgE binds to FcεRI, which is expressed by several cells including mast cells, basophils, eosinophils, and B lymphocytes. Te subsequent binding of allergens to allergen-specifcIgE activates the release of proinfammatory mediators. It was also determined that serum IgE levels were associated with airway hyper-responsiveness, even in patients without a history of asthma symptoms or atopy. Therefore, a study was undertaken to estimate the serum IgE level in bronchial asthma patients, and to correlate the severity of airway obstruction with serum IgE level in bronchial asthma patients. This cross-sectional study was carried out in Tertiary Care Hospitals of NRI Medical College and General Hospital Chinakakani and Sri Lakshmi Narayana Institute of Medical Sciences, Pondicherry. Our Results concludes that the serum IgE level in bronchial asthma patients is elevated and it increases with the increase in the severity of airway obstruction which paves the way for better understanding about the nature of disease and disease progression. Serum IgE level increases as the severity of airflow obstruction increases. It helps to classify the Bronchial asthma patients based on IgE and to guide anti IgE therapy for the patients with difficult to treat allergic asthma and to assess its response.

Keywords: -Allergic asthma-; Serum IgE; Severity of obstruction; Spirometry-IgE therapy.

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INTRODUCTION

Asthma is a condition of bronchial hyper-reactivity associated with inflammation. It is a chronic inflammatory disease that ranges from mild to the severe form. Asthma affects 1–18% of the population globally and it is estimated that >300 million people in the world have asthma. Of this, 5–10% have severe asthma. Although the severe form affects a smaller proportion of patients, it is responsible for a larger component of the overall disease burden. [1,2]

Severe asthma is a chronic inflammatory disease with a marked heterogeneity [see Figure 1, adapted from Brusselle et al., 2014] in etiology, pathophysiology, and clinical aspects, leading to the identification of different phenotypes (early onset atopic/allergic, eosinophilic, exercise-induced, obesity, and paucigranulocytic).[3] Subsequently, considering the molecular mechanisms underlying the pathophysiology of bronchial inflammation, the concept of endotypes has been studied to develop targeted therapy.[4] For many years, from a pathogenic perspective, the focus of research has been on the role of T-cells in the initiation and perpetuation of inflammation T helper 2 (Th2) cells have beenidentified

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as the cells involved in controlling immunoglobulin E (IgE) production due to the generation of interleukin (IL)-4 and IL-13 and influencing the functioning of eosinophils through the actions of IL-5.[5]

In severe asthma, biomarkers can be applied to determine the patient's phenotype and help evaluate treatment response, thereby improving the precision therapeutic approach to severe asthma. Biomarkers can be diagnostic or predictive in nature, and applying these biomarkers to identify phenotypes has been very purposeful. For example, early-onset allergic asthma is characterised by the presence of allergen-specific (IgE, and late-onset hypereosinophilic asthma is characterised by elevated peripheral blood and sputum eosinophils.[5-8] Eosinophil and IgE levels can be used as diagnostic biomarkers for these phenotypes. However, blood eosinophils are commonly present in early-onset allergic asthmatics, and allergen-specific IgE may be present in late-onset, hyper-eosinophilic asthmatics. Therefore, these commonly used biomarkers may give clues as to the phenotype or endotype.[8-9]. Biomarkers can be diagnostic or predictive in nature, and applying these biomarkers to identify phenotypes has been very purposeful. For example, early-onset allergic asthma is characterised by the presence of allergen-specific IgE, and late-onset hypereosinophilic asthma is characterised by elevated peripheral blood and sputum eosinophils. Spirometry is the gold standard for diagnosis of bronchial asthma. Forced expiratory volume in one second (FEV1) from spirometry is a reliable for diagnosing airflow obstruction. A reduced FEV1 may be found with many other lung diseases, but a reduced ratio of FEV1 to forced vital capacity (FVC) indicates airflow limitation. IgE has also been shown to be a major contributing factor for the development of bronchial hyper responsiveness in asthmatics[5] . Serum levels of allergenspecific and total IgE are strongly associated with the clinical grade of sensitization and disease severity in allergic patients[6] . Atopy is a tendency to produce an excessive amount of IgE antibodies when exposed to allergens. Bronchial asthma is a type 1 hypersensitivity reaction where combination of allergens with IgE antibodies produces the airway inflammation and asthmatic symptoms. Serum IgE levels also shows association with degree of airflow obstruction[6] .

Therefore, the present study was designed to study the serum IgE levels in Bronchial asthma patients, and to correlate the severity of airway obstruction with serum IgE level in Bronchial asthma patients.

MATERIAL AND METHODS:

This cross-sectional study was carried out in Tertiary Care Hospitals of NRI Medical College and General Hospital Chinakakani and Sri Lakshmi Narayana Institute of Medical Sciences, Pondicherry. The sample size was 150 (Based on previous study with standard deviation -44, Confidence interval - 95% and Relative error-10%) [7].Patients attending the Pulmonary Medicine OPD with symptoms of episodic onset of cough, breathlessness, chest tightness and wheezing were subjected to spirometry and those patients who had spirometric values showing reversibility of more than and/or equal to 12% in forced expiratory volume in 1s (FEV1), or at least 200mL from baseline after inhalation of salbutamol (4×100 mcg) given by metered dose inhaler using a spacer device was included in the present study. Patients who were <18 years old were excluded from the study.Smokers and patients with acute severe asthma, sputum positive pulmonary tuberculosis, COPD and asthmatics using bronchodilators were also excluded from the study

Approval from the institutional ethical committee and fully informed written consent from the patient were obtained before starting the study. Patients in the age group of 20 to 60 years are included in the study. Patient's Name, Age, Sex is noted, and detailed history is taken in each patients regarding the duration of the asthma symptoms, frequency and severity of the exacerbation, smoking history and previous medical history.

Chest X-Ray, Complete blood count, ESR, Electrocardiography, Sputum for AFB and Gram's stains were done for study subjects. A detailed explanation of the purpose of the study, procedure adopted and the safety measures undertaken while doing spirometry were clearly given to patients participating in our study. Spirometry including reversibility testing was performed according to ATS recommendation using spirometer. Serum IgE was estimated in patients who were diagnosed as bronchial asthma.Estimation of serum IgE was done using QuantiaIgE which is a turbidimetric immunoassay for estimation of immunoglobulin IgE in human serum.

Chi square was used to test the hypothesis, association of levels of serum IgE with severity of airway obstruction on bronchial asthma patients, Pearson bivariate correlation coefficient was used to quantify the extent of correlation between spirometric parameters with serum IgE level among bronchial asthma patients. For all statistical analysis $p<0.05$ was considered as statistically significant.

Table 1: Distribution of severity of airway obstruction among the cases

Severity of Obstruction	FEV1	No. of Cases n = 150	Percentage
Mild	>70	24	16
Moderate	60 - 69	18	12
Mod. Severe	50 - 59	36	24
Severe	36 - 49	44	29.33
Very severe	<35	28	18.67

Table 2: Distribution of symptoms among the cases

Symptom	No. of Cases n= 150	Percentage
Dyspnoea	88	58.67
Cough	74	49.33
Wheeze	54	36

Table 3: Distribution of cases based on IgE levels

IgE (IU/ml)	No. of Cases	Percentage
101-200	16	10.67%
201-300	26	17.33%
301-400	40	26.67%
401-500	68	45.33%

Table 4: Age wise distribution of IgE in cases

Age (in years)	IgE(IU /ml)			
	101 - 200	201 – 300	301 - 400	401 - 500
21 -30	4	6	16	14
31 -40	2	6	6	14
41 - 50	10	6	14	22
51 - 60	0	8	4	18
	16	16	40	68

Table 5: Gender wise distribution of IgE in cases

Gender	IgE (IU/ml)				Mean IgE
	101-200	201 - 300	301-400	401 - 500	
Male	8	12	16	36	380.13
Female	8	14	24	32	369.97

Table 6: Distribution of serum IgE levels based on the severity of obstruction among the cases

FEV1	IgE (IU/ml)			
	101-200	201-300	301-400	401-500
Mild	8	2	6	8
Moderate	0	6	10	2
Moderately Severe	2	6	16	12
Severe	2	10	8	24
Very Severe	0	4	6	18

Table 7: Mean distribution of IgE (IU/ml) according to age

Age (in years)	No. of cases	Mean IgE(IU/ml)
21- 30	40	363
31 -40	28	384
41-50	52	369.42
51 - 60	30	388.66
	150	374.3+/- 11.4

Results:

Table 1: Distribution of severity of airway obstruction among the cases
Table 2: Distribution of symptoms among the cases
Table 3: Distribution of cases based on IgE levels
Table 4: Age wise distribution of IgE in cases
Table 5: Gender wise distribution of IgE in cases
Table 6: Distribution of serum IgE levels based on the severity of obstruction among the cases
Table 7: Mean distribution of IgE (IU/ml) according

DISCUSSION:

The discovery of IgE in 1966 brought a change. The era shifted into the investigation of genetics, functions and clinical applications of this immunoglobulin. It was established that IgE has unique properties as it can induce rapid pathological responses and it can act as a highly sensitive immunological amplifier. It became well established that IgE levels are increased in patients affected by atopic conditions and that IgE provides the critical link between the antigen recognition role of the adaptive immune system and the effector functions of mast cells and basophils at mucosal and cutaneous sites of environmental exposure. These functions have made IgE an attractive target for pharmacological intervention, with IgE blockade having clinical potential across many different therapy areas. Despite focusing on IgE for several years, there has been relatively little consideration of pathways outside that of mast cells and the acute phase reaction.[61] In the early 1990s, the discovery of Th2 lymphocytes and their role in controlling IgE production and in the late phase of allergic inflammation reduced the biological importance of IgE antibodies. Thus, traditionally, IgE antibodies were believed to be responsible for the classic “early phase” of an allergic reaction and considered to have only a minor (peripheral) role in the “late phase” reaction. During this period, IgE lost some “popularity” and was only considered of importance from a diagnostic perspective to confirm forms of allergic asthma through the skin and in vitro testing. Total IgE did not have any diagnostic significance. Despite decreased interest in IgE antibodies, several studies achieved decidedly important results regarding not only the biological role of IgE but also the therapeutic effects of IgE-blocking mAbs.[11] This was the turning point in defining the biological role of IgE and, in 2003, the introduction of omalizumab, a humanised mAb that selectively binds to IgE, for the treatment of moderate-to-severe persistent allergic asthma, marked a milestone in both mAb and anti-IgE therapy for asthma.[12-13].

It was found that that serum IgE value increased with the increase severity of airway obstruction and it was to be statistically significant $p<0.05$ as observed in a

study conducted within the age group of 20-60 years[14] . This suggests that treatment of bronchial asthma patients warrants necessary correlation between IgE levels and severity of obstruction. Patients with severe asthma have a higher mean IgE level than patients with moderate or mild asthma hence IgE levels increased as asthma severity increased . The same trend is reflected in both older and younger bronchial asthma patients . The severity of bronchial asthma in obese patients is indicated by the increase in the levels of IgE[15]. It was noted that serum IgE is elevated in bronchial asthma patients and a significant correlation was found between total IgE and lung function which is measured as bronchial responsiveness to inhaled methacholine[14]. A study on asthmatic children in Australia revealed that higher IgE levels in patients with more severe persistent asthma compared with those with mild, episodic asthma [16-17] . The reports of all the studies cited in the foregoing paragraph corroborate with our finding that serum IgE levels increased as the severity of asthma increased.

In our study, male patients had higher IgE levels compared to female patients and the same had been reported in an earlier study conducted among the age group of 6 or older. A study on the association of age, gender and smoking with total IgE and specific IgE, it was found that among non-smokers geometric mean total IgE was higher in men than women but unrelated to age[14]. A study on the epidemiology of immunoglobulin E levels in a defined population revealed that age-adjusted geometric mean IgE levels The most probable reason for the higher prevalence of IgE levels in men is cigarette smoking. In our study, the mean serum IgE value of bronchial asthma patients was 374.3 IU/ml that is higher than the general population as noted by previous studies. The mean total IgE level of the population was found to be 106.6 IU/ml whereas higher mean total IgE level was observed patients with severe asthma have a higher mean IgE level. Thus the earlier studies cited above show that serum IgE is higher in bronchial asthma patients that are similar to our study

As eosinophils, also IgE is a product of the T2 inflammation pathway. IgE levels are usually associated with specific sensitization to several allergens, both seasonal and perennial, but also with inflammatory, immunologic or hematologic disorders [18]. IgE levels are important both total and specific one, particularly the second is crucial for the identification of allergen sensitization as possible triggers of asthma. Just IgE was the target of the first monoclonal antibody in severe asthma, Omalizumab, able to bind the C3 region of IgE Fc fragment, determining a reduction of free IgE available to bind their receptors on cells [19]. Generally, the clinical utility of measuring total IgE serum levels is limited by its low specificity. Total IgE, contrary to what could be expected, does not consistently discriminate among asthmatic populations between atopic and non-atopic. Among patients from the International Severe Asthma Registry (ISAR) patients with atopy had a median IgE value of 535 KU/L compared to non-atopic 224.3 KU/L [20]. Even applying cluster analysis combining clinical physiological and biological traits, total IgE was not able to discriminate among the different groups [21]. The sensitivity and specificity of total IgE as a predictor of airway eosinophilia are quite weak and an AUC of 0.62 has been reported. At a sensitivity of ≥ 95% FENO, B-EOS and total IgE had a comparable specificity, but the sensitivity of total IgE was significantly lower compared to the other biomarkers (0.47).

A broader application of total IgE is that of identifying patients with T2 inflammation. Actually, gene expression analyses reported that subjects with Th2-high asthma had higher serum IgE levels than Th2-low (244 IU/ml vs 125 IU/ml) [22]. In an unselected population of patients with severe asthma, a cut-off of IgE> 150 IU/mL was chosen as one of the type2 biomarkers being detectable in 42% of patients [23]. The International Severe Asthma Registry (ISAR) applied a lower cut-off of ≥75 kU/L, which yielded a prevalence of 59% of IgEpositive patients. The likelihood of having another T2 positive biomarker was 59 and 65% respectively for B-EOS and FENO. This study reported a cluster of patients, accounting for 6% of the whole population, that is characterized by very high levels of IgE (1,932 kU/L), which is clinically associated with the youngest age, the longest duration of asthma, obesity, and poor lung function (58).

Even if IgE is the biomarker for the eligibility for omalizumab treatment of severe asthmatics, a role as a response predictor to omalizumab in different severe allergic asthma populations was not demonstrated. The response to omalizumab, in terms of ACQ clinical variation, was not associated with IgE levels [24]. A Spanish real-life study observed a greater decrease of IgE after omalizumab interruption in the failure group, suggesting that the faster IgE decreases, the earlier asthma relapses [25]. Accordingly, the Xolair Persistency Of Response After Long-Term Therapy (XPORT) trial showed that discontinuation of omalizumab was associated with a decrease in total IgE levels and an increase in free IgE levels as well as an increase in basophil expression of the high-affinity IgE receptor [26]. Dupilumab demonstrated its clinical efficacy in patients with both severe allergic asthma, defined by total serum IgE> 30 IU/mL and > 1 perennial aeroallergen-specific IgE>0.35 kU/L at baseline, and not allergic. A reduction in total serum IgE occurred for both the allergic and non-allergic patients. A baseline total IgE> 700 IU/mL did not influence the rate of adjusted annualized severe exacerbation rate [27-28]. Given these observations, the

major clinical applications of this biomarker are to predict the response to anti-IgE therapy and to determine the optimal dosage of omalizumab.

The identification and daily use of standardised and defined biomarkers remain a long and winding journey but perhaps a suitable alternative will be a definition of different panels of asthma with clarity on different biomarkers that can be used depending on the eligibility of patients. The path to understanding the disease of asthma is far from complete. With new research, new targets emerge on a regular basis. With new targets, newer biomarkers will also be developed. Hence, much research is the need of the hour to develop an ideal biomarker that has a diagnostic as well as predictive value and is easy to quantify at affordable costs. As total serum IgE is not allergen-specific and may be influenced by several extrinsic factors and pathologic conditions, sIgE may be considered a more reliable biomarker both for asthma diagnosis and severity assessment

CONCLUSION:

Our Results concludes that the serum IgE level in bronchial asthma patients is elevated and it increases with the increase in the severity of airway obstruction which paves the way for better understanding about the nature of disease and disease progression. This also helps us to guide the anti IgE therapy for the patients with difficult to treat allergic asthma and to assess its response. However serum IgE level is also elevated in various atopic disorders which compounds its utility largely. Further study is needed to better clarify their role, individually or in combination, in the diagnosis and treatment of severe asthma but so far three readily applicable biomarkers (blood eosinophils, FeNO and IgE) have been extensively studied, which remain to have clinical significance. Future clinical trials of novel asthma therapies should include the use of biomarkers in their design, which may lead to a more stratified approach to therapy and improve outcomes

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