Original Research Article

Serum immunoglobulin E and absolute eosinophil count as markers of severity in childhood asthma

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ABSTRACT

Background: Asthma is a chronic inflammatory condition of the airways resulting in increased airway reactivity to a variety of stimuli like allergens, irritants, viruses and exercise. There is a strong association between the exposure of allergens and development of asthmatic symptoms. A hypersensitivity reaction initiated by immunologic mechanisms mediated by Immunoglobulin E (IgE) antibodies occurs in allergic asthma. IgE and eosinophils play an important role in the inflammatory process resulting in bronchial hyperresponsiveness. The aim of this study was to evaluate serum total IgE levels and Absolute Eosinophil Count (AEC) as markers of disease activity and study their association with the severity of bronchial asthma in children.

Methods: A prospective study was conducted in the paediatric department of a tertiary care hospital in Ahmedabad, Gujarat, India from July 2017 to December 2018. Children between 4-14 years of age diagnosed as having bronchial asthma were included in the study. Serum total IgE levels and absolute eosinophil count were done in all the study participants and their correlation with the severity of asthma was assessed.

Results: Of the total 109 patients of asthma, 44(40.4%) had intermittent asthma, 30(27.5%) mild persistent, 25(22.9%) moderate persistent and 10(9.2%) severe persistent asthma. Serum total IgE levels were raised above the normal limits for age in 94(86.2%) patients and increased AEC was found in 61(56 %) patients. Both serum total IgE levels and AEC increased significantly ($p < 0.0001$) with increasing severity of asthma.

Conclusions: Serum total IgE levels and AEC can be used to predict the severity of asthma in children.

Keywords: Absolute eosinophil count, Allergy, Asthma, Immunoglobulin E

INTRODUCTION

Asthma is a chronic inflammatory condition of the lung, characterized by bronchial hyperresponsiveness and reversible airway obstruction. It is the most prevalent chronic respiratory disease among children and causes considerable morbidity and mortality. An increase in the prevalence of bronchial asthma has been noted over the last few decades. The prevalence of asthma in children varies from 3.5-29.5% in different geographic areas in India.^{1,2} The Global Initiative for Asthma (GINA) guidelines defines

asthma as a heterogeneous disease characterized by chronic airway inflammation and respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.³

The etiology of childhood asthma is complex and multifactorial. A combination of environmental factors (like air pollution, tobacco smoke and urbanization) and inherent biologic and genetic susceptibilities have been implicated.¹ Asthmatic patients have increased airway

reactivity to a variety of stimuli such as allergens, irritants, exercise, cold air and viruses. There is a strong association between the exposure of allergens and development of asthmatic symptoms. The single most important risk factor for the development of asthma is atopy which is a tendency to produce excessive amounts of Immunoglobulin E (IgE) antibodies when exposed to allergens. A hypersensitivity reaction initiated by immunologic mechanisms mediated by IgE antibodies occurs. The allergens stimulate the induction of T Helper type 2 (Th2) cells and other immune cells, which produce proinflammatory cytokines and chemokines which mediate the inflammatory process. Among these cytokines, Interleukin (IL) 4 promotes IgE production by B cells while IL5 increases the production and maturation of eosinophils. Subsequently, acute and late phase reactions occur due to IgE mediated reaction to the allergens and results in bronchoconstriction. IgE plays a central role in the initiation and propagation of the inflammatory cascade and thus the allergic response.^{4,5}

Serum IgE is a trace protein and normally accounts for <0.001 % of total serum immunoglobulins. Serum total Immunoglobulin E (tIgE) levels vary with age with maximum levels seen during childhood, typically between the age of 8 to 12 years. Despite the fact that initially tIgE had been strongly linked to asthma in epidemiological studies, it was given progressively less attention in asthma until the arrival of anti IgE therapy.⁴ Blood eosinophils are known to be an indirect marker of airway inflammation in asthma and peripheral blood Absolute Eosinophil Count (AEC) has been widely used to demonstrate the allergic etiology of the disease.

Paediatric asthma is an enormous challenge for clinicians, not only for diagnosis but also in terms of prognosis and follow-up, particularly in infants and young children in whom lung function tests are difficult to perform. An inflammatory biomarker, giving additional information, would of immense help in daily clinical practice. It is desirable to have a biomarker which is able to predict the development asthma in the future, diagnose asthma, aid in the choice of therapy and provide guidance during follow-up. A large number of studies have been conducted to study the utility of various biomarkers such as serum tIgE, AEC, sputum eosinophils, skin prick tests, allergen specific IgE and Fractional Exhaled Nitric Oxide (FENO) in asthma.⁶ As IgE and eosinophils play an important role in the inflammatory process in asthma, authors undertook this project to evaluate serum total IgE levels and AEC as markers of disease activity in children with bronchial asthma. Authors' aim was to study the association of serum total IgE levels and absolute eosinophil count with the severity of bronchial asthma in children.

METHODS

A prospective study was conducted in the paediatric department of a tertiary care hospital in Ahmedabad, Gujarat, India from July 2017 to December 2018.

Institutional Ethical Committee approval was taken for conducting the study and informed consent was taken from the parents/guardian.

Inclusion criteria

- Children between 4-14 years of age diagnosed as having bronchial asthma as per GINA guidelines were included in the study.³

Exclusion criteria

- Children with respiratory conditions like pulmonary tuberculosis, cystic fibrosis, tropical pulmonary eosinophilia and congenital malformations of the respiratory tract were excluded.
- Those with congenital heart disease, neurological conditions, Gastro-oesophageal reflux disease, viral infections, parasitic infestations and immunocompromised states were also not included in the study.

A detailed history was taken, and each patient was thoroughly examined, and findings noted in a predesigned proforma. Severity of asthma was assessed based on the frequency and severity of exacerbations, day and nighttime symptoms, limitation of normal activity, treatment required to control the symptoms and lung function tests. Patients were classified based on severity of asthma into 4 groups-intermittent, mild persistent, moderate persistent and severe persistent asthma.^{7,8} Family history of asthma was noted and the presence of comorbidities like allergic rhinitis and atopic dermatitis was recorded. Serum total IgE levels and absolute eosinophil count were done in all the study participants. Serum tIgE levels were estimated by chemiluminescent immunoassay which uses monoclonal antibodies specifically directed against IgE. The IgE levels were measured using IgE II reagent kit in Cobas e411 analyzer, Roche. AEC was determined by examination of the peripheral blood smear. Serum tIgE levels were considered raised if they were above the normal values for age.⁹ AEC was considered raised if the value was >450 eosinophils/ μ l.¹⁰

Statistical analysis

The data collected was analyzed with the help of SPSS version 20.0. Results were expressed as mean $\pm$ standard deviation (mean $\pm$ SD). Statistical analysis was done by student's t test and one-way Analysis of Variance (ANOVA) test. The mean values of serum tIgE and AEC were compared between the groups of asthma. A p value <0.05 was considered statistically significant.

RESULTS

Here, 109 children aged 4-14 years with bronchial asthma were included in the study. The mean age of the children

was 8.2 ± 3.3 years. Maximum children (47.7%) were in the 4-7 years age group. 79(72.5%) patients were males while 30(27.5%) were females. Male: female ratio was 2.6:1 with significant male predominance. Serum tIgE levels were raised above the normal limits for age in 94(86.2%) patients. AEC was raised in 61(56 %) patients. 57(52.3%) patients had increased levels of both serum tIgE and AEC. 53(48.6%) children had a family history of asthma. 96.2% of patients with positive family history had elevated serum tIgE levels. Mean serum tIgE levels in patients with a family history of asthma was 860.5 ± 622 IU/ml against 433.9 ± 493.2 IU/ml in those without a family history. 58.5% of patients with a positive family history had elevated serum AEC. 28(25.7%) patients of asthma had associated allergic rhinitis while 6(5.5%) had atopic dermatitis. Characteristics of the patients with asthma are shown in Table 1.

Of the total 109 patients of asthma, 44(40.4%) had intermittent asthma, 30(27.5%) mild persistent, 25(22.9%) moderate persistent and 10(9.2%) severe persistent asthma. Mean serum tIgE levels were 231.9 ± 182.6 IU/ml in intermittent, 557.9 ± 318.2 IU/ml in

mild persistent, 1399 ± 693.1 IU/ml in moderate persistent and 2031 ± 553.9 IU/ml in severe persistent cases. Serum tIgE levels increased with increasing severity of asthma and this was statistically significant ($p < 0.0001$) when the values were compared within the groups. The increasing level of serum tIgE was found to be statistically significant when compared between each of the groups ($p < 0.0001$ between intermittent and mild persistent cases and also between mild persistent and moderate persistent cases and $p < 0.05$ between moderate persistent and severe persistent cases).

Mean serum AEC (eosinophils/ μ l) was 411.3 ± 299.5 in intermittent, 438.6 ± 232.9 in mild persistent, 582.9 ± 377.4 in moderate persistent and 1147.7 ± 893.1 in severe persistent cases. Mean AEC increased with increasing severity of asthma and this was statistically significant ($p < 0.0001$) when the values were compared within the groups. Both serum tIgE levels and AEC showed significant increase with increasing severity of asthma. The correlation of serum tIgE levels and AEC with severity of asthma is shown in Table 2.

Table 1: Characteristics of the patients with bronchial asthma.

Characteristics		Number of patients (n=109)	Percentage of patients (%)
Age (years)	$4 \leq 7$	52	47.7
	$> 7 \leq 10$	22	20.2
	$> 10 \leq 14$	35	32.1
Gender	Male	79	72.5
	Female	30	27.5
Family history	Present	53	48.6
	Absent	56	51.4
Associated comorbidities	Allergic rhinitis	28	25.7
	Atopic dermatitis	6	5.5
Serum total IgE levels	Increased	94	86.2
	Normal	15	13.8
Absolute eosinophil count	Increased	61	56
	Normal	48	44

Table 2: Correlation of serum immunoglobulin E levels and absolute eosinophil count with severity of asthma.

Severity of Asthma	Number of Patients (%)	Serum tIgE (IU/ml) Mean $\pm$ STD Significance	AEC (cells/ μ l) Mean $\pm$ SD Significance
Intermittent	44 (40.4)	231.9 ± 182.6	411.3 ± 299.5
Mild Persistent	30 (27.5)	557.9 ± 318.2	438.6 ± 232.9
Moderate Persistent	25 (22.9)	1399 ± 693.1	582.9 ± 377.4
Severe Persistent	10 (9.2)	2031 ± 553.9	1147.7 ± 893.1

F=74.81
 $p < 0.0001$
F=10.38
 $p < 0.0001$

DISCUSSION

In this study of 109 children with bronchial asthma, the ratio of males: females were 2.6:1 with a significant male predominance. Other studies have noted a male: female ratio varying from 1.4:1 to 2.3:1.¹¹⁻¹³ This shows that the

male gender is at increased risk for asthma and this is probably related to narrower airways and increased airway tone which predisposes them to enhanced airflow limitation in response to a variety of stimuli. This difference disappears after the age of 10 years when airway diameter/length ratio is the same in both sexes,

because of changes in thoracic size that occurs in puberty in males but not in females.¹⁴

Bronchial asthma is a chronic inflammatory disease with a marked heterogeneity in pathophysiology and aetiology. The heterogeneity of bronchial asthma may be related to the inducing mechanism (allergic vs non-allergic), histopathological background (eosinophilic vs non-eosinophilic), and the clinical manifestations, particularly in terms of severity and frequency of exacerbations. Bronchial asthma is commonly sustained by allergic sensitization, which leads to bronchial hyperresponsiveness and acute bronchoconstriction in response to specific and non-specific triggers.⁵ There is a strong association between exposure of allergens and development of asthmatic symptoms. Allergic (or atopic) asthma represents the most frequent type of asthma representing over 60% of cases.⁵ Raj et al, noted that 55.6% of asthmatic children had sensitization to one or more aeroallergens suggesting atopy.¹⁵ Atopic or allergic asthma is a phenotype of asthma which is characterized by allergic sensitization and T helper cells play a major role in the initiation and perpetuation of inflammation. After exposure to allergens, Th2 type T cells induce cytokines and interleukins like IL-4 in genetically susceptible individuals which promote the production of IgE by B cells. IgE primed mast cells release chemical mediators responsible for immediate bronchoconstriction, as well as subsequent recruitment of eosinophils and late-phase inflammatory response.^{4,5} IgE through its high affinity IgE receptors is a critical regulator of Th2 response and airway inflammation.

Many studies have been done to compare the serum tIgE levels in asthmatic children with those in normal children. It has been noted that the mean serum tIgE levels in children with asthma was significantly higher than those in normal controls (p value <0.001).¹⁶⁻¹⁹

In this study serum tIgE levels were above the normal limit for age in 86.2% patients with asthma. Chandran et al, Chaudhary et al, and Lama et al, found raised serum tIgE levels in 75%, 71.4% and 63.3% of asthmatic children respectively.^{11,16,18} There is a strong relationship between increased serum tIgE levels and asthma prevalence.²⁰ Authors noted an increase in the levels of serum tIgE as the severity of asthma increased and this was statistically significant. Other studies have also shown significant increase in the serum tIgE levels as the severity of asthma increased. Serum tIgE levels were lowest in children with intermittent asthma and progressively increased with increasing severity and were highest in patients with severe persistent asthma.^{12,21-23}

Carrol et al, demonstrated a clear relationship between the stages of increasing asthma severity and elevated levels of serum tIgE. They found significantly higher tIgE levels in asthmatic patients requiring hospitalization compared to non-hospitalized asthmatics. Significantly higher tIgE levels were found in those with forced

expiratory volume in the first second (FEV1) <80% compared to patients with FEV1 >80%.²⁴

Kovac et al, observed that the serum tIgE concentration was much higher in severe persistent asthma compared to other grades of asthma.²⁵ A study done by Sciuca et al, in children with recurrent wheeze, showed that raised levels of tIgE was directly proportional to the increased risk of bronchial asthma in them.²⁶ Studies have shown that tIgE levels are associated with the severity of symptoms, risk of exacerbations and remodelling of the airways.⁶ There is an association between the prevalence of asthma and the total serum tIgE levels, independent of specific reactivity to common allergens or symptoms of allergy.¹⁸

Serum tIgE indicates predisposition to atopic status. Measurement of serum tIgE levels can serve as a low-cost investigative tool to differentiate between allergic and nonallergic asthma which can be further confirmed by skin prick test or serum levels of allergen specific IgE. As there is an association between serum tIgE levels and the degree of airflow obstruction, serum tIgE levels can provide useful information regarding the severity of asthma and persistence of bronchial hyperresponsiveness in later adulthood. Its main restriction as a biomarker is its low specificity for asthma, as high levels of serum IgE may be present in other allergic, parasitic, viral and immune diseases.⁶ However, low serum tIgE levels can help to exclude the diagnosis of allergic asthma.²⁷ Quantitative measurement of tIgE, when integrated with other clinical indicators can be used to predict development of asthma and for risk stratification. It can help in the choice of treatment modalities including the use of anti IgE therapy with omalizumab. Omalizumab is a recombinant anti IgE monoclonal antibody developed for the treatment of allergic diseases associated with high circulating tIgE levels and is a valuable option in patients with high serum tIgE levels with severe asthma who remain symptomatic despite high doses of standard therapy. The efficacy of monoclonal antibody developed against tIgE used in the treatment of severe asthma indicates that tIgE plays a major role in the pathogenesis of asthma.²⁸

Eosinophils have been considered important pro-inflammatory and epithelial-damaging cells in asthma.⁵ Eosinophils contain intracellular granules which are sources of inflammatory proteins (major basic protein, peroxidase and cationic protein), prostaglandins, leukotrienes and cytokines which enhance tissue inflammation and lead to airway hyperresponsiveness.¹⁰

Chaudhary et al, have noted that the AEC levels were higher in patients with asthma compared to normal children.¹⁶ In this study, AEC was found to be raised in 56% cases of asthma. Also, AEC increased with increasing severity of asthma. These observations are consistent with those noted in other studies.^{12,13,16,21} Tran et al, observed that asthmatic patients with higher blood eosinophil counts (>300 cells/ μ l), experienced more

asthmatic attacks than those with lower eosinophil counts.²⁹ Carr et al, concluded that asthmatic patients with significant eosinophilia are at higher risk of more severe disease.³⁰ Elevated blood eosinophils is a good predictor of asthma development.⁶ A recent systematic review has confirmed that blood eosinophilia is a significant risk factor predicting the persistence of early wheezing in school aged children.³¹ Blood eosinophilia ($\geq 4\%$) has been included as one of the criteria in the Asthma Predictive Index and its modifications.³²

Anti IL5 therapy (mepolizumab and benralizumab) decreases the production and maturation of eosinophils and helps reduce exacerbations. Its utility in severe asthma indicates that eosinophils play an important role in the pathogenesis of asthma.³³ Peripheral blood eosinophil counts are widely used to demonstrate the allergic etiology of disease, to monitor its clinical spectrum and in the choice of therapy.¹⁸

In this study 48.6% patients had a family history of asthma. Also, patients with a family history of asthma had higher levels of serum tIgE compared to those without a family history of asthma. Similar observations have been made by Gurjar et al, and Chaudhary et al.^{13,16} Also, asthma prevalence has been found to be higher in children whose parents presented with increased levels of tIgE.⁶ These observations suggest that family history of asthma is an important risk factor for asthma in children especially in allergic asthma.

Other atopy related disorders like allergic rhinitis and atopic dermatitis are frequently associated with asthma. Allergic rhinitis was noted in 25.7% and atopic dermatitis in 5.5% of patients with asthma in this study. Snehalatha et al, noted 38% and 9.8% patients of asthma to have allergic rhinitis and atopic dermatitis respectively.¹²

Atopic or allergic asthma is a phenotype of asthma which is genetically determined and is characterized by allergic sensitization. Children with atopic asthma typically have the onset of the disease early in life, have a positive family history of asthma or allergy and may have other coexistent diseases (allergic dermatitis and allergic rhinitis), produce IgE antibodies specific to identifiable allergens and have asthma exacerbations triggered by these allergens. Children with allergen sensitization are likely to have severe asthma, poorer lung function and severe exacerbations due to these allergens.¹⁵

In this study, 57(52.3%) patients had increased levels of both serum tIgE and AEC. The levels of both were found to increase with increasing severity of asthma. Devi et al, and Gurjar et al, made similar observations in their studies and noted that serum tIgE level was a better marker for predicting severity of asthma compared to AEC.^{13,21} Satwani et al, concluded that peripheral eosinophilia along with raised serum tIgE levels is a significant allergic marker.³⁴ While IgE is involved early in the inflammatory cascade and can be considered as a

cause of allergic asthma, eosinophilia can be considered a consequence of the whole process.⁵

Limitations of the study was it was a small study on hospitalized children at a single centre. Normal age matched controls from the general population were not included in the study. Larger multicentric studies are required. As serum tIgE is nonspecific, the role of specific IgE antibodies against commonly prevalent allergens requires to be studied.

CONCLUSION

Serum tIgE is a suggestive and supportive indicator of atopy in children with asthma. Blood eosinophilia is useful to demonstrate the allergic aetiology of the disease, as a predictor of asthma development and as an indicator of increased risk of severe disease in children. Serum tIgE and AEC can therefore be considered as markers for predicting asthma activity and severity in patients with allergic asthma. While an isolated measurement of tIgE or AEC may be insufficient, the combination of these atopic markers, along with medical history and lung function tests, improves the diagnosis, helps to identify children with high risk phenotypes and in the choice of treatment and follow-up of an asthmatic child.

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