IgE antibody in serum detection and diagnostic significance as a biomarker in patients with uncontrolled asthma

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Abstract:
Background: The presence of atopy increases the probability that a patient with respiratory symptoms has allergic asthma but this is not specific for asthma nor is it present in all asthma phenotypes. Atopic status can be identified by skin prick testing or level of serum IgE. IgE is a tissue bound molecule found in serum in equilibrium with that bound to mast cells and basophils. The aim of this study was to evaluate the levels of serum total IgE in patients with uncontrolled asthma and test the significance of serum IgE as a biomarker/predictor of severity for uncontrolled asthma.

Materials and Methods: A simple random sampling of 55 patients in the age group of 5 to 63 years with 19 males and 36 females over two groups of 45 cases with uncontrolled asthma and 10 controls of controlled asthma were included in the study. Clinical examination, spirometry and serum IgE levels were measured.

Results: The level of serum IgE was high in 80% of the total study population with as high as 88.8% in the uncontrolled asthma group and 40% in the controlled group. The mean serum IgE level in uncontrolled asthma patients was 2222 IU/L, while in the control group it was 1224 IU/L.

Conclusions: The high levels of serum IgE in uncontrolled asthma patients clearly indicates the definite correlation between higher IgE levels and uncontrolled asthma and demonstrates an inverse relationship with serum IgE levels and FEV1 %.

Keywords: Allergy; Asthma; Atopy; GINA; Serum IgE.

Introduction:
The central role of IgE in allergic inflammation has been well established after the advent of anti-IgE therapy and its therapeutic response in allergic asthma patients [1]. Allergen specific IgE has been established as one of the most important bio marker in allergic asthma patients [2-4]. Serum IgE is also used as a clinical guide for disease diagnosis, environmental modification, and therapy. The predictive value of Serum IgE in the management of asthma has been evaluated in the past with very good association between the two [5]. But some investigators propose that Serum total IgE level has limited utility as a biomarker in allergy, especially in a tropical country like India. It has been observed that serum levels of total IgE are very high in people living in tropics despite being non-atopic [6,7]. Infect the levels are so high when compared to the atopic western counterparts. There are some studies some studies which suggest that total IgE levels are associated with asthma even in subjects negative for specific IgE to common aeroallergens [8]. The paradox of high total and low specific IgE needs further exploration. We undertook this study to investigate the serum levels of total IgE in controlled and uncontrolled asthma and test its significance as a biomarker in difficult to treat asthma.

Materials and Methods:
A cross-sectional study with simple random sampling in the urban population of Chennai was conducted at The Institute of Thoracic Medicine, Madras Medical College, Chennai. An ethical committee approval was obtained and all the subjects were explained the detailed procedure and a written consent were obtained. A total of 55 patients were enrolled in the study of which 45 had uncontrolled asthma symptoms (CASES) in spite of adequate medications and 10 had controlled symptoms (CONTROLS). The control of asthma was decided based on GINA (global initiative for asthma) symptom control tool and risk assessment.

Patients of more than 5 years of age, diagnosed as asthmatic according to GINA and with documented variable airway outflow obstruction within one year were included in the study. Pregnant women, lactating women, smokers and individuals with other proven diagnosis were excluded from the study. The study was approved by the institution’s ethics committee.

The forced expiratory volume in first second (FEV1%) percentage and total serum IgE levels were measured for all the patients enrolled in the study. The pulmonary function testing was done using computerized spirometer (Easypro One, NDD) and patients were classified as having mild, moderate, severe and very severe obstruction based on GINA guidelines. Two ml of venous blood sample was collected under strict aseptic precautions and centrifuged after clot formation to separate the serum. IgE levels were measured using chemi-luminescence two step sandwich immunoassay. Statistical analysis was done and p-value of <0.05 was taken to indicate statistical significance.
Results:
The study population included a wide range of age. The lowest person’s age included was 5 yrs and the highest was 63 yrs. The average was 34.6 yrs. The range was 58 years (5-63). Most of the study population was clustered around the age group 25-49 years of age (40 subjects) out of which 30 showed elevated levels of serum IgE (75%) (>158 IU/mL). Out of 55 subjects included in the study, 19 were males (34.55%) and 36 were females (65.45%). In that 16 of the 19 males had significant elevation of serum IgE and 28 of the 36 females had elevated serum IgE. The overall mean serum IgE level in the study was 2041 IU/L, 2222 IU/L in the cases and 1224 IU/L in the control group. Chi square test value of 2.99 was derived for the males subgroup which was >2.71 implying a p value of <0.1 which is significant. In females the Chi square test value was 11.28 which was >3.84 implying a p value of <0.05 which is highly significant.

Females show a declining IgE levels with age in contrast to males who show a raising trend. The duration of the symptoms had an impact on the levels of serum IgE. The study population included subjects ranging from recently first time diagnosed to long time symptomatic patients. The longest symptomatic individual had duration of 57 years. 6 of the individuals had been symptomatic since their childhood. The mean duration of symptoms was 11.74 yrs.

FEV 1 and Serum IgE had an inverse correlation. In all, 60% (3 of 5) of mild, 83.33% (25 of 30) of moderate, 83.33% (15 of 18) of severe and 50% (1 of 2) of very severe obstruction had raised IgE. Table 1 and Fig. 1

Table 1: Showing level of serum IgE with their corresponding FEV1%

<table>
<thead>
<tr>
<th>FEV1%</th>
<th>Cases-high</th>
<th>Cases-normal</th>
<th>Controls-high</th>
<th>Controls-normal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>21-30</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>31-40</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>41-50</td>
<td>9</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>51-60</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>61-70</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>71-80</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>81-90</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>44</td>
<td>11</td>
<td>5</td>
<td>5</td>
<td>55</td>
</tr>
</tbody>
</table>

Fig. 1: Shows the solid violet line represented by IgE going up with the solid green line showing a downslope, which is being represented by FEV1%

Table 2: Shows the level of serum IgE in the cases and control group

<table>
<thead>
<tr>
<th></th>
<th>IgE High</th>
<th>IgE Normal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>40</td>
<td>5</td>
<td>45</td>
</tr>
<tr>
<td>Controls</td>
<td>4</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>44</td>
<td>11</td>
<td>55</td>
</tr>
</tbody>
</table>

Total serum IgE positivity in the study population is 44 out of 55 subjects, which was 80% of the study population. Serum IgE positivity among the cases of uncontrolled bronchial asthma are 40 out of 45 which is 88.8%. Serum IgE positivity among the controls of well controlled bronchial asthma are 4 out of 10 subjects, which is 40 %. Table 2. With the odds ratio of 12, elevated Serum IgE levels were 12 times more associated with the uncontrolled asthma patients than the well-controlled asthma patients.

Discussion:
We found that serum total IgE level was raised in Uncontrolled Asthma patients than controlled Asthma patients. Severe asthma is defined as asthma which requires treatment with high dose inhaled corticosteroids plus a second controller (and or systemic corticosteroids) to prevent it from becoming uncontrolled or which remains uncontrolled despite this therapy [9]. Around 50% of patients are not well controlled and 5-10% suffers from severe disease that is refractory to usual treatment. Although various bio markers like Neutrophils, Eosinophils, Fractional Exhaled Nitric oxide (FeNO), exhaled breath condensate, Galectins, Periostin has been tested in Asthma, the ideal bio marker has not been a reality [10].

IgE level and Age- Most of the study group has been clustered around the age group 25-49.this has been reflected in other studies as well. Females show a declining IgE levels with age in contrast to males who show a raising trend in our study. This is interesting
because males have been found to have increased serum levels of IgE when compared to females at any given age [11]. Total and specific serum IgE decreases with age in allergic rhinitis, asthma and insect allergy but not in patients with atopic dermatitis [12].

IgE level and gender: The females outnumbered males in this study. It has been observed males have a higher serum IgE level than females. Smokers have raised serum IgE level when compared to non-smokers. There is a disparity in serum IgE level between male and female smokers. Female smokers have low serum IgE levels when compared to their male counterparts [13]. Whether biomass exposure which is prevalent in Indian women has any role to play has not been well studied.

IgE level in uncontrolled asthmatics - Amina et al made an attempt to find the relationship between Serum IgE level and asthma [5]. The study indicated that the mean serum IgE level was much higher in asthmatics than controls which were statistically significant. Around 6% of asthmatics had normal levels of IgE. Our study subjects were Uncontrolled asthmatics while in most of the studies a mixture of controlled, partially controlled and uncontrolled asthmatics were recruited. The mean Serum IgE level of 2222 IU/L in uncontrolled asthmatics and 1224 IU/L in controls in our study is much higher when compared to other studies. There was wide variability in the range of Serum IgE levels, from 7 to 4000 IU/L. In all, 88.8% of uncontrolled asthma patients had raised total serum IgE levels in our study. Among the controls 40% had raised serum IgE level. With the odds ratio of 12, elevated Serum IgE level was 12 times more associated with the uncontrolled asthmatics than well controlled asthmatics. Immunoglobulins have been found to be more concentrated in people who have evolved in tropics than in people who have evolved in temperate climate [14]. The mean IgE levels in Indian patients in asthma, and allergic rhinitis and allergic rhinitis were found to be significantly increased as compared with control and first degree relatives of asthma patients [15].

Correlation of FEV1 and IgE level: Spiro metric FEV1% had an inverse correlation with Serum IgE level. As the level of obstruction increased there was a corresponding increase in IgE level. This has been demonstrated in other studies as well [5].

Limitations:
Severe asthma with fungal sensitization and Allergic Bronchopulmonary aspergillosis has not been ruled out in our study, since very high Serum IgE levels can occur in these conditions as well.

Conclusion:
The results of the study clearly shows the definite correlation between higher IgE levels and uncontrolled asthma with the chi square value of 12.22 (p<0.05) which is highly significant. Anti IgE therapy as a part of bronchial asthma management (recently included in GINA guidelines) may be vital for uncontrolled bronchial asthma management. The presently available IgE antibody therapy has to be evaluated in the background of the findings of present study. Anti IgE therapy has an important role to play in the management of uncontrolled bronchial asthma.

Conflicts of Interest: None declared
Acknowledgements: None

References:

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