ORIGINAL ARTICLE

IMMUNOGLOBULIN IGE LEVELS AND CLINICAL DYNAMICS OF ASTHMA IN CHILDREN AND ADOLESCENTS

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Background: The involvement of IgE in type 1 hypersensitivity reactions, including asthma and allergic rhinitis, is widely recognized, and established. However, within this region, there exists a dearth of research exploring the relationship between serum IgE levels and the severity of asthma within the pediatric population. Consequently, the primary objective of this study was to compare the IgE status among children and adolescents diagnosed with asthma, and to examine its association with asthma exacerbations and hospitalizations. By investigating these parameters, we aimed to shed light on the potential role of IgE in influencing disease outcomes in this specific population. **Methods:** A retrospective study was conducted at The Aga Khan University Hospital from January 2015 to December 2020. Children and adolescents aged 6–18 years who were diagnosed and admitted with asthma, and who had measurement of IgE levels during asthma exacerbation were included in the study. The participants were stratified into two groups based on their IgE levels: normal IgE levels and high IgE levels. Various parameters, including the number of asthma exacerbations, emergency room (ER) visits, hospitalizations, average length of stay, as well as other clinical characteristics such as the presence of allergic rhinitis in the past and a family history of asthma were assessed. **Results:** A total of 122 patients were included in the study. Of them 57 patients (46.72%) were found to have high IgE levels, and 65 patients (53.28%) had normal IgE levels based on their age group. The average number of exacerbations per year was significantly greater the in high IgE group (3.6±1.09), in comparison to the normal IgE group (2.49±1.22). **Conclusion:** Higher serum IgE levels correlated with increased asthma exacerbations, emergency room visits, hospitalizations, and a positive family history of asthma, suggesting a potential link between IgE and asthma severity in the pediatric population of Pakistan.

Keyword: Allergens; Immunoglobulin E; Asthma exacerbation; Childhood Asthma

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INTRODUCTION

Asthma has a high incidence and prevalence in the paediatric population worldwide.[1] The aetiology of asthma is predominantly multifactorial, with contributions from both genetic susceptibility and environmental influences that significantly impact its underlying pathophysiological mechanisms. Atopy stands as the foremost crucial identifiable predisposing factor in the development of asthma. Atopy is the genetic predisposition for developing an immunoglobulin E (IgE)-mediated response to common aeroallergens.[2]

Immunoglobulin E (IgE) represents a specific subclass of antibodies within the immune system.[3] While its primary role is to confer immunity, it assumes a pivotal role in type 1 hypersensitivity reactions[3,4], thereby serving as a hallmark for such reactions. Consequently, its involvement extends to the realm of airway inflammation and allergic responses.[3] These reactions encompass a range of conditions, including but not limited to asthma, allergic rhinitis, and food allergies. Nevertheless, the precise mechanisms governing IgE production and its intricate relationship with asthma remain inadequately comprehended.

Associations between asthma severity[3,7] and high levels of IgE have been previously established. V Siroux *et al*. reported a positive relationship between severe childhood asthma and a high level of serum IgE.[8] High IgE levels have also been implicated in developing airway remodeling[4] and hyperresponsiveness[6]. Also, elevated levels of IgE at six months of age are a strong predictor of the onset of asthma.[16]

The exploration of serum IgE levels and their impact on asthma within the paediatric and adolescent population remains relatively limited in this particular region. Given the increasing incidence of asthma[5] and the increase in mortality in the paediatric population associated with asthma exacerbations[19], it is imperative to understand the underlying mechanisms contributing to exacerbations and hospitalizations in the paediatric population. Moreover, a deeper understanding of the mechanisms underlying IgE

production and its relationship with asthma can lead the way for the development of novel therapeutic approaches allowing for more personalized and effective treatments for paediatric asthma.

In addition to its clinical implications, studying serum IgE levels about asthma severity can contribute to our broader understanding of the disease. Asthma is a complex condition influenced by a multitude of factors, including genetics, environmental triggers, and immune responses. Hence, the primary objective of this study is to conduct a thorough comparative analysis of the clinical dynamics between patients exhibiting elevated IgE levels and those with normal levels, aiming to establish a robust and definitive association between serum IgE levels and the severity of asthma. By exploring the intricate relationship between heightened IgE levels and asthma exacerbations, hospitalizations, and markers of disease severity, such as pulmonary function tests and quality of life assessments, we can gain an understanding of the impact of IgE-mediated immune responses on the pathogenesis and clinical outcomes of paediatric asthma.

MATERIAL AND METHODS

A retrospective study was conducted at The Aga Khan University Hospital, Karachi, Pakistan. The data was collected from January 2018 to December 2022. Children and adolescents aged 6–18 years admitted with asthma exacerbation and had serum measurement of immunoglobulin E (IgE) levels at the first asthma exacerbation during this time were included in the study.

Patients with asthma exacerbation were categorized into two groups. Patients with normal serum IgE concentrations as per defined ranges were categorized into the Normal IgE group, and those with serum concentrations above the upper level of defined ranges were categorized as the High IgE group. References levels were based on the Siemens Advia Centaur total IgE kit that was used to measure serum IgE levels in this study (Table 1).

Serum IgE levels were documented for every patient and after categorization into two groups, their demographic and clinical data were analyzed for age at presentation, gender distribution, body mass index (BMI), age at onset of asthma, family history (parents and siblings), eczema, allergic rhinitis and allergic conjunctivitis. Patients in these two groups were further compared for their use of controller medications for the past 6 months from their first documented exacerbation during the study period. This included the use of inhaled corticosteroids (inhalers or nebulization), inhaled steroids with inhaled long-acting beta-agonist (LABA), and oral Montelukast therapy. Patients in these two groups were followed for one year on outcome variables and compared for the number of asthma exacerbations with emergency visits, number of hospitalizations and average length of stay (LOS) for each admission.

Environment and food Allergens serum test was used to identify specific allergens in patients with high IgE (Table 1). The class number is an indication of the amount of endogenous IgE specific to the selected allergen. Class II and above reactivity of allergen was considered significant. (Table-3)

Diagnosis of asthma in this study was based on Global Initiative for Asthma (GINA) guidelines which include identifying a characteristic pattern of respiratory symptoms such as wheezing, shortness of breath, chest tightness or cough, and documented variable expiratory airflow limitation.[20] This includes positive bronchodilator responsiveness, in which there is an increase of FEV1 >12% after administration of salbutamol, indicative of asthma.[20] Patients admitted with bronchopneumonia, bronchiolitis, and upper airway obstruction and previously diagnosed with chronic lung disease, cystic fibrosis, tuberculosis, congenital cardiac diseases and immune deficiency syndrome were excluded from this study.

The definition of asthma exacerbation by the American Thoracic Society (ATS) and European Respiratory Society (ERS) was followed in this study. This is defined as a worsening in symptoms and/or lung function, and/or an increase in rescue bronchodilator use, for at least two days. This can be classified as moderate or severe exacerbation – moderate exacerbation involved no hospital admission or emergency department (ED) visit, whereas if the event resulted in an admission or ED visit, along with oral corticosteroid treatment for at least three days, it was severe exacerbation.[19]

The data were analyzed using IBM Corp. released 2020, IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp. Continuous variables were expressed as mean and standard deviation, while categorical variables were described as frequency and percentages. The t- test was used for means and the Chi-square test was used for categorical data to assess significant differences between the groups. The *p*-value of $\leq .05$ was considered significant, with a type I error of 5%.

RESULTS

A total of 122 patients admitted for asthma fulfilled the criteria for the study duration. Out of these patients, 57 (46.72%) were categorized in the high IgE group, and 65 (53.28%) patients were categorized under the normal IgE group.

Occurrence of eczema and allergic rhinitis were significantly higher in the high IgE group as compared to the normal IgE group ($p<0.05$), while there was no

significant difference in the occurrence of allergic conjunctivitis (p=0.07). Patients with High IgE levels have a significant family history of asthma (p<0.05). The use of controller medications was also compared, with no significant difference in findings, except inhaled LABA with inhaled steroids having greater usage among the high IgE group (p<0.05). Clinical and demographic details are presented in Table-4. Mean asthma exacerbations per year that resulted in an ER visit (3.6±1.09) and hospitalization (2.54±0.82) were significantly high in the high IgE group (p=0.001). However, the average length of stay (LOS) showed no significant difference between the groups. (p=0.86). These findings are presented in Table V and Figure 1. Common allergens were studied and their frequencies are presented in figure 2. The most common allergens found were dust mites namely *Dermatophagoides pteronyssinus* (84.21%) and *Dermatophagoides farinae* (80.7%) followed by Egg white allergy (28.07%).

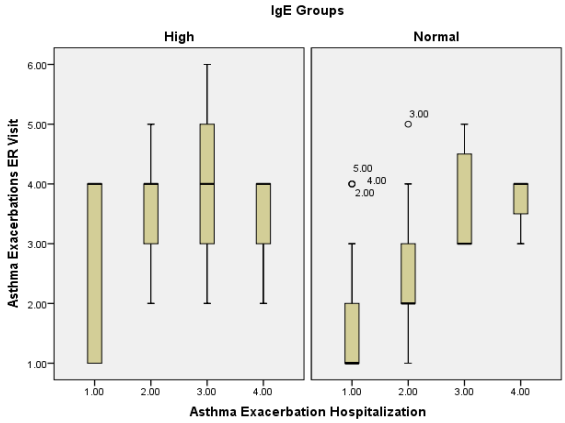

Figure-1: Comparison between Normal and High IgE groups, Patient demonstration in Boxplot in two groups.

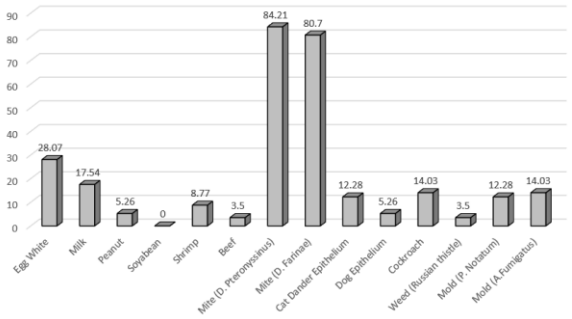

Figure-2: Allergen frequencies in High IgE group.

Table-1: Age Related Serum IgE Level Ranges

Age (years)	IgE Ranges (IU/ml)
6-10 Years	0.5-393.0
11-15 Years	1.9-170.0
≥16 years	150

Table-2: Food and environmental allergens

Food Allergens	Environmental Allergens
Egg White	Mite (*Dermatophagoides pteronyssinus*)
Milk	Mite (*Dermatophagoides farinae*)
Peanut	Cat Dander Epithelium
Soyabean	Dog Epithelium
Shrimp	Cockroach
Beef	Weed (*Russian thistle*)
	Mold (Penicillium *Notatum*)
	Mold (*Aspergillus Fumigatus*)

Table-3: Class and reactivity of allergen

Class	KU/L	Reactivity of Allergen
0	<0.10	Absent or not detected
0	0.10-0.34	Very Low
I	0.35–0.69	Low
II	0.70–3.49	Moderate
III	3.50–17.49	High
IV	17.5–52.49	Very High
V	52.5–99.99	Very High
VI	>100	Very High

Table-4: Clinical and demographic characteristics of groups

Variables	High IgE group 57	Normal IgE group 65	p-value
Age	11.4± 0.58	10.6± 0.82	0.08
Gender Ratio (M :F)	1.2:1	1.3: 1	
BMI	14.3±0.9	13.1±1.2	0.16
Age at onset of Asthma (Years)	3.68 ± 0.74	5.98±0.89	0.067
Eczema	18 (31.57%)	9 (13.84%)	<0.001
Allergic Rhinitis	48 (84.21%)	29 (44.61%)	<0.001
Allergic conjunctivitis	9 (15.78%)	7(10.76%)	0.07
Family History of asthma	38 (66.66%)	22(33.84%)	<0.001
Controller medications			
Inhalation Steroids	28 (49.12%)	26 (40%)	0.30
Inhaled LABA with Inhaled steroids	25 (43.85%)	19(29.23%)	<0.001
Montelukast	54 (94.73%)	52 (80%)	0.39

Table-5: Outcome variables comparison between the groups

Variables	High IgE group 57	Normal IgE group 65	p-value
Asthma Exacerbations with ER Visit	3.6± 1.09	2.49±1.22	0.001
Mean number of hospitalizations	2.54±0.82	1.86±0.88	0.001
Average Length of Stay (LOS)	3.21±1.23	3.1±1.42	0.86

DISCUSSION

Our findings report a positive correlation between elevated levels of serum IgE in paediatric patients with asthma and the occurrence of asthma exacerbations and hospitalizations. The average number of asthma exacerbations was significantly high (p<0.001) in the elevated IgE group (3.6±1.09) as compared to the standard IgE group (2.49±1.22). The average number of hospitalizations per year was also significantly different (p<0.001) between the groups, with the most significant number among patients with elevated IgE levels (2.54±0.82).

In the paediatric population, there is a common coexistence of atopic diseases, including asthma, allergic rhinitis, food allergies, and eczema. It is noteworthy that the presence of one atopic disease can render an individual predisposed to developing other atopic diseases throughout their lifetime. This phenomenon is described as the "atopic march".[15]

Acknowledging the influence of different atopic diseases on elevated serum IgE levels, the present study also incorporated an analysis of data about various atopic conditions.[9] Asthmatics with raised IgE levels had significantly more occurrence of eczema and allergic rhinitis (p<0.00) than those with normal levels. J Havnen et al. presented similar findings, where 47% of the children had raised serum IgE levels, and the incidence of high IgE levels was even higher (58%) when atopic dermatitis and other hypersensitivity diseases occurred with bronchial asthma.[10] In another study, hyper-IgE was independently associated with asthma, more severe atopy, and more severe eczema during childhood and adolescence.[11] In our study, it is evident that there exists a significant association between a family history of asthma and raised IgE levels (p<0.001). This feature distinguishes the findings of this study from previous research, as other studies have reported no significant association between a family history of asthma or allergies and elevated levels of total serum IgE.[12,13] However, our study did not identify a significant difference in the occurrence of allergic conjunctivitis between asthmatic individuals with high IgE levels and those with standard IgE levels.

Our study found a significant association (p<0.001) between environmental and food allergies and elevated IgE levels within the group exhibiting elevated IgE levels, a notable proportion of 73.68% tested positive for environmental allergies, while 29.82% tested positive for food allergies. These outcomes concur with previous research findings, indicating consistency in the observed patterns. Ru-Xin Foong *et al*. found an association between asthma and IgE-mediated allergies, these patients are at a higher risk of severe asthmatic attacks.[17]

Our study aligns with previous research[21], highlighting the house dust mite, *Dermatophagoides pteronyssinus* (84.21%) and *Dermatophagoides farinae* (80.7%), as the primary allergen associated with asthma. This consistency across studies reinforces the importance of this relationship and underscores its clinical relevance in guiding diagnostic and therapeutic strategies for asthma management.

Furthermore, our study also found a significant difference (p<0.001) between the use of inhaled LABA and steroids between the two groups, with the high IgE group utilizing those more (43.85%). These findings corroborate existing literature, in which elevated IgE levels increase asthma severity, leading to greater medication use. This may also suggest that higher IgE levels warrant the need for a management plan with inhaled LABA and inhaled steroids.

The findings of our study prompt further consideration regarding the potential use of anti-IgE therapy as a viable treatment option for these patients. The underlying pathophysiology of asthma can be attributed to an exaggerated hypersensitivity response, in which IgE plays a central role as a key mediator. This immune response leads to the activation and release of mast cells, eosinophils, and lymphocytes, contributing to the inflammatory cascade observed in asthma. The resultant airway inflammation eventually leads to significant airway remodeling.[15, 18] There has been some work done in this field, with studies showing a significant reduction in the use of corticosteroids, asthma exacerbations, and an improvement in quality of life after the use of Omalizumab, a monoclonal anti-IgE.[14,15]

The findings of this study necessitate further investigation into the potential utilization of IgE as a valuable diagnostic tool in discerning between allergic and non-allergic asthma. Moreover, it may serve as a predictive marker for future prognosis and the frequency of asthma exacerbations. These avenues of research hold promise in enhancing our understanding of asthma subtypes and refining personalized management approaches. These potential applications can equip clinicians with a vital means to facilitate early detection of allergic asthma. By utilizing IgE as a diagnostic tool, healthcare professionals can identify patients at an earlier stage, enabling them to initiate more proactive and targeted treatment strategies. This approach holds the potential to delay or prevent further decline in lung function, thus improving long-term outcomes for individuals with allergic asthma. Given the observed rise in mortality rates linked to heightened asthma exacerbations[19], the associations identified between elevated levels of IgE and such exacerbations warrant further comprehensive investigation.

Limitations of this study include the lack of a control group of non-asthmatics for serum IgE level comparison and the inability to conduct long-term follow-up to assess patient progression over time. Seasonal changes that may affect serum IgE levels were

also not evaluated. Further studies can employ a prospective design as well as compare lung function tests in individuals with high IgE levels versus normal IgE levels to deepen our understanding of the relationship between IgE and respiratory function.

CONCLUSION

This study supports the hypothesis that elevated IgE levels are associated with increased exacerbations and hospitalizations. It poses the question of using anti-IgE therapy as a treatment modality in these patients. Further prospective research can explore the effects of such therapy on reducing asthma exacerbations and hospitalizations.

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Conflicts of interest
There are no conflicts of interest.

AUTHORS' CONTRIBUTION

DA, RB and MO helped in the conception and design of the study, WV and MO did data collection, RB, MO and DA did analysis and interpretation of data; DA and RB contributed to drafting the work and revising it critically for important intellectual content. All authors approved the Final version for publication and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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