A Survey on Selective Immunoglobulin A Deficiency Among Asthmatic Adults with Variable Total Immunoglobulin E levels in Tehran: An Office-Base Study

Khosrow Agin*

Department of Clinical Toxicology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Corresponding author:
Khosrow Agin,
Department of Clinical Toxicology,
School of Medicine, Shahid Beheshti
University of Medical Sciences, Tehran,
Iran,
Tel: +98 21 55413424, Fax: +98 21 55418914;
E-mail: khosrow.agin@yahoo.com

Abstract

Background: Selective IgA deficiency (SIgAD) is one of the most common primary antibody immunodeficiency diseases. The prevalence in Asia is lower than other areas. Asthma and allergic diseases are common among the SIgAD population. The aim of this study was to evaluate the prevalence of SIgAD among the adult asthmatic patients with variable immunoglobulin E (IgE) levels in serum. **Patients and methods:** 507 asthmatic patients of various age and sex who sequentially enrolled in the outpatient respiratory clinic were selected. Asthma diagnosis was based on the pulmonologist's diagnostic and ATS criteria. IgA and total IgE levels in serum were measured according to manufacturer's recommended kits. **Results:** 64 (13%) subjects detected as SIgAD. Mean age recorded 34.5 ± 13.9 SD years. The patient included 57% male and 43% female, respectively. Allergic asthma recorded 40% (205) of the study population. **Conclusion:** The SIgAD was remarkably found among Iranian adults with asthma. However, its frequency was lower in allergic asthma in comparison to the non-allergic subset. Additionally, the number of SIgAD subjects declined with increasing age. Detection of SIgAD among the asthmatic population may be effective in reducing complications.

Keywords: IgA deficiency; Selective IgA deficiency; Total IgE level; Allergy; Asthma; Adults Iranian

Introduction

Secretion of immunoglobulins A (IgA) is necessary for the defense mechanism of mucosal surfaces against infections and plays a significant role in the cleaning of foreign antigens. Individuals who are most frequented Selective Immunoglobulin A Deficiency (SIgAD), have been clinically healthy and who have had mild symptoms usually have been remained permanent in the adult population for their lifetime.

SIgAD is a universal primary immunodeficiency disease. [1] Its prevalence in Caucasians is up to (1:700). [2] While it is lower among Asia's population. In Iran, it is up to (7.5%) [3] among adults. Prevalence distribution of SIgAD is different among social groups which suggest a genetic base for such disorder. [4]

The SIgAD subjects can be clinically associated with atopy, [5] allergic diseases, [6] asthma, [7] different autoimmune diseases and sinopulmonary infections. Its deficiency may lead to chronic inflammation of the airway in Chronic Obstructive Pulmonary Disease, [8] (COPD) and have a significant role in eosinophilic activation in asthma disease. [9] Moreover, it may be progressive to the most common variable immunodeficiency disease and lead to increased production of immunoglobulin E (IgE) in serum. [10]

Asthma is one of the most common diseases in the world that can be triggered with SIgAD, [11] with an estimated 300 million affected people [12] worldwide. Asthmatic patient is more prone to the risk of infections. It may be due to impaired innate and adaptive immune system that predisposes individuals to microbial infections or may be related to the presence of one type of primary immune deficiency such as; SIgAD. [13] Likewise, asthmatic patients are susceptible to the hypogammaglobinemia [14] caused by application of corticosteroids.

The objective of the study was to assess the status of SIgAD prevalence among the adult asthmatic patients with variable immunoglobulin E levels.

Patients and Methods

This study was cross-sectional and conducted in Shahid Beheshti University of Medical Sciences (SBMUS), Tehran-Iran. The study was designed based on the outpatient clinic's asthmatic patients. Before starting at the study a consent form was received from all volunteers. Subjects sequentially enrolled and serum IgA and total IgE levels were initially evaluated. The entrance criteria consisted of asthmatic, adults of all age and both sexes with a recurrence of sinopulmonary infections and allergic symptoms in their medical history.

Asthma was defined based on an instruction of the American Thoracic Society (ATS) [15] and physician-diagnosed asthma. Accepted airway reversibility response to bronchodilator was improved up to 12% of FEV1 baseline or 200 ml of FEV1. The SIgAD was defined based on the following criteria; IgA level less than 70 mg /dl, normal IgM and IgG levels and age of diagnosis up to 14 years. The IgA was assayed in serum by an Immunoturbidimetry method with Biosystem kit (made in France) and Hitachi device measuring system. The total IgE (TIgE) also was measured by Elisa method of Pishtaz Co (Iran). The cutoff point which identifies allergy state was up to 200 Iu/ml.

The exclusion criteria were as based on the medical history, the SIgAD, malignancy, systemic diseases (losing protein enteropathy), infections (AIDS), consumption of immunosuppressant drugs, high –dose of corticosteroid, and known genetic diseases. [16]

The data included in the study were obtained using statistical program SPSS; version 22. The frequency and the mean of data were presented with percentage and mean ± SD. The normality was not detected by Kolmogorov-Smirnov test (P_{age}, p_{IgA} and P_{IgE}= <0.001). Comparison of means was performed by non-parametric test; Kruskal-Wallis Test, Mann-Whitney Test, and Chi-Square Tests. The statistical significant value was set at P<0.05 throughout the study.

Results

A total of 507 subjects participated in the study. Characteristics of the sample population were defined based on the mean age of 34.5 ± 13.9 SD years. (Range 16-74, Median age 33 and Mode 16) The frequency of age was divided into several groups of classes as following: I (16-24) 31%, II (25-34) 23%, III (35-44) 23%, IV (45-54) 15% and V (>55) 8% . All of asthmatic patients sample population included 57% male and 43% female. The study shows that the distribution of genders was approximately equal in all decades, but its frequency gradually decreases between 20s to 50s.

Figure 1 shows the distribution of age classes to mean global IgA in serum and among different sexes. Global of SIgAD frequency was 13% in asthmatic subjects. The frequency of SIgAD distribution was 33 (52%) in females and 31 (48%) in males. The mean of global IgA levels in the serum of asthmatic patients was 162.6 ± 81.5 mg/dl. The Minimum and the maximum values were 10 and 430 mg/dl, respectively, (with median 150mg/dl and Mode 100). Table 1 shows the characteristic of SIgAD and normal range IgA subsets. The frequency distribution of SIgAD was 29 within allergic asthma (6% sample study and 14% class) and 35 Non-allergic subsets (7% sample and 12% class). There were no significant differences between global serum IgA and TIgE levels in sample study (P=0.3).

The highest values of the SIgAD subjects were obtained in the 20s and 50s, respectively. Despite a difference in age and sex, the same frequency pattern was detected about global IgA level. A comparison of means was performed between serum TIgE, global IgA, and age with sex groups. Significant differences

were detected between sex variable with serum TIgE, and age of study population (P_{IgE}=0.03 and p_{Age}=0.01). The frequency of SIgAD decreased along with increasing the age classes of asthmatic patients (older age).
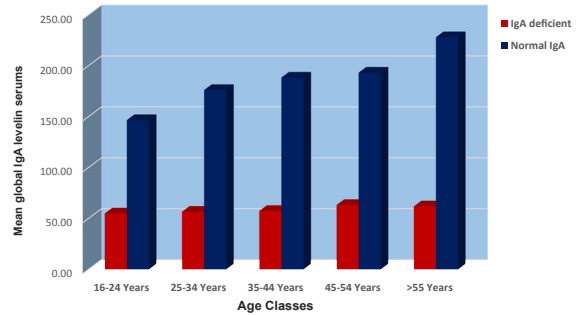

Figure 1: Discloses age classes distribution respect to mean global IgA in serum and variable sexes.

Table 1: Reveals statistical characteristics of Selective IgAD and normal IgA subsets.

Subsets of asthmatic patients	Sex Male/ Female	Age Mean ± SD Year	Serum IgE Mean ± SD Iu/ml	Serum IgA Mean ± SD mg/dl	Total number %
IgA deficient subclass	31/33	30.8 ± 12.3	222.8 ± 240.9	57.3 ± 12.2	64 (13%)
Normal serum IgA	259/184	35 ± 14	259.8 ± 247.4	178 ± 0.78	443 (87%)

Figure 2 represents the relation between the age classes and the mean of TIgE level in serum, in sample study. In the population study, the mean of TIgE was 255, 02 ± 335.89 Iu/ml, (with median 137 and Mode 500). 40% (205) of sample study were allergic asthma. Allergic condition recorded more in 52% of the males. Moreover, the number of allergic individuals associated with raising the age decreased. Figure 3 displays the age classes related to the number of SIgAD and status of mean serum TIgE levels.
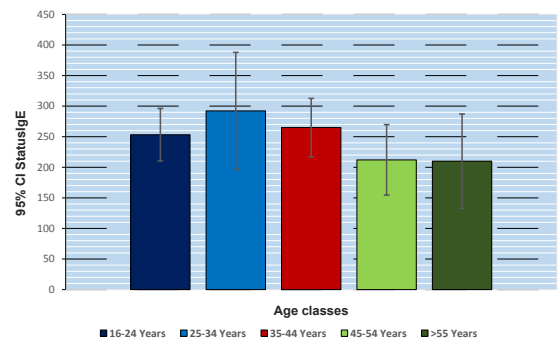

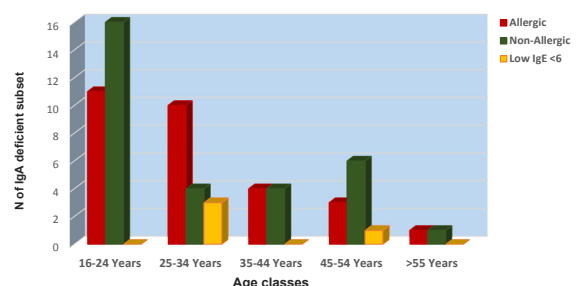**Figure 2:** The age classes to the mean of total IgE level in serum in focus population.

Figure 3: Displays the age classes related to the number of SIgAD and status of mean serum IgE levels among IgA deficient subsets.

Low serum TIgE was detected in the sample study (1.8%). The SIgAD was more prevalent in recent finding 4 (6%).

Discussion

IgA is the most abundant antibody isotype produced by the body secretions. Its functions have not been clearly understood by the immune system. IgA has two subclasses; monomeric IgA1 in serum and dimeric IgA2 in mucosal secretions. IgA deficiency (IgAD) is a result of a mutation in B-cells types [17] which are able to neutralize the intracellular bacterial pathogen (virus), bind to antigen at lamina propria by immune complex, prevent of the bacterial colonization by inhibition of adhesion mechanism, diminish inflammatory responses, [18] prevent the release of inflammatory cytokine (TNF-6, IL6) [19] and induced IL10 expression. [20]

85-90% of SIgAD are asymptomatic. It may be associated with a number of diseases and conditions such as; recurrent sinopulmonary infections, autoimmunity diseases, [21,22] allergic disorders 8 [23] and tumors (1.5%). [24] The prevalence of IgAD has been reported to be about 7.5% in Iranian population 3, in Caucasian 1:700 and is the lowest in Asian countries. [25] The only report that did not support the latter finding was related to Saudi Arabia that was reported in 1998 (45%). [26]

Asthma is a global disease that its prevalence progressively increases by 50% every ten years, particularly in developing countries. The frequency of allergy is following asthma burden. [27] Additionally, the allergic frequency was reported up to 40% worldwide. Similarly, the allergic asthma frequency was 40% [28] in our sample study as well. In the sample study, the numbers of allergic condition decreased with increasing age but the mean of TIgE levels was higher in other age classes. Allergic disorders have a higher frequency in younger people compared to older age. [29] This finding correlates with the number of allergic individuals and distribution in different age classes. The aging process is associated with markedly remodeled immune system both adaptive and innate, which is called immunosenescence. This leads to changes that result in increased susceptibility to chronic inflammation, enhanced Th2 and allergic inflammation. However, the genetic, genetic-environmental interactions and external risk factors are play role in development of allergic reactions among elderly. [30,31]

The increased TIgE in our study is especially debated among older- age classes. The earlier cohort study disclosed the inverse ratio between TIgE and aging. [32] Tow issues can be suggested as follow. Highly immunoglobulin E levels may not be associated with age-related changes, and a few of studies have been supported it. [33,34] Alternatively, the findings from our research may reflect the effects of external causal factors as environmental conditions on this asthmatic community. [35]

The allergen exposure is not the only mechanism of IgE production through mast cell activation. The humoral immune responses can reactivate the allergic responses by IgG, [36] raised IgG4 [37] and low-level secretory IgA antibodies. [38] In addition, IgAD individuals are more prone to atopic diseases.

[39] Our endpoint results indicated that SIgAD consisted of 6% of the global study asthma population and 14% of the allergic asthmatic subset. It is an improvement with consideration of allergy prevalence within the primary IgAD.

Low–level IgE Patients are susceptible to more frequency presentation of autoimmune disease, multiple immunoglobulin deficiencies, and non-allergic airway bronchial hyper reactivity. [40] We found an undetectable level of TIgE among asthmatic samples (1.8%), in which, four subjects were SIgAD. The prevalence of IgE hypogammaglobinemia was reported in association with SIAD between 6, 4–32%. [41] The result of our study corroborated the recent investigations.

The IgA level in males was higher than females in normal condition. [42] It may be caused by gene control and environmental effects. [43] Sex differences distribution of SIgAD was higher in men than women. [44,45] The earlier finding was not in agreement with our results in the current study. However, the IgA level increased with increasing age. It was an improvement in our output and the number of SIgAD declined with increasing age classes.

Conclusion

In conclusion, the endpoint of the study relevantly represented the presence of SIgAD in the asthmatic population. SIgAD had more frequency in younger age class than older age. However, in the females, its frequency was lower in the allergic asthmatic subset with respect to the non-allergic subset and the number of SIgAD subjects declined with increasing age classes. The detection of SIgAD among the asthmatic population may be effective in reducing comorbid complications.

Acknowledgement

Conflict of Interest

All authors disclose that there was no conflict of interest.

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