Research Article

Association of IL4 gene polymorphism with severity of asthma among Egyptian patients

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Abstract

Introduction: Asthma is a chronic inflammatory disorder characterized by airway inflammation caused by many cells and cellular elements. **Aim of the work:** To find association between IL-4, IL-6 and IL-18 polymorphism and asthma in Egyptian patients. To find the effect of IL-4, IL-6 and IL-18 polymorphism on severity of asthma. **Subjects and method:** The asthmatic patients participating in this study were from Asthma and Allergy Clinic, Minia chest hospital. Seventy five of asthmatic patients were enrolled in this study. **Results:** This study was carried on 75 asthmatic patients from Minia chest hospital and 75 healthy controls in the period between May 2017 & January 2018. Future studies should include more patients for more reliable assessment. Considering that bronchial asthma is a complex disease, the hetero-genecity of disease may cause research results to be in consistent. And the statistical power of a small sample associated analysis, there for, there is a need for larger studies to suggest any role of this cytokine gene polymorphism in bronchial asthma and cytokine role in asthma severity.

Keywords: Asthma, chronic inflammatory,

Introduction

Asthma is a chronic inflammatory disorder characterized by airway inflammation caused by many cells and cellular elements. Mast cells, eosinophils, T-lymphocytes, macrophages, neutronphils and epithelial cells play an important role in asthma (Elias et al., 1999). This inflammation is associated with variable airflow obstruction that is often reversible either spontaneously or with treatment.

The inflammation and airflow obstruction are responsible for the manifestation of asthma symptoms like recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or early in the morning in susceptible individuals.

The inflammation is also responsible for associated increase in the existing bronchial responsiveness to a variety of stimuli (Hasnain, 2008). Asthma is considered to be the result of allergic inflammation leading to the production of immunoglobulin E (IgE).

Allergens that enter the airway are presented by antigen presenting cells (APC) to the T cell which differentiates into T helper type 2 cells (TH2) in the presence of certain cytokines. TH2 cells secrete a number of cytokines including interleukin (IL)-4 and IL-13 acting on different target cells such as mast cells, eosinophils, epithelial cells, smooth muscle cells and lymphocytes (Elias et al., 1999).

The stimulated B cells start synthesizing IgE. *(Busse and Lemanske, 2001).* All these changes in the airways in the form of inflammation lead to the airflow Obstruction and thus asthmatic symptoms.

The prevalence of asthma worldwide is around 200 million with a mortality of around 0.2 million per year. Asthma can occur at any age, but children and young adults are commonly affected (Cukic et al., 2012).

IL-4 can be described as the main cytokine involved in the pathogenesis of allergic disorders. Effects that seem of particular importance for asthma include stimulation of mucus producing cells and fibroblast, thus also implicating IL-4 in the pathogenesis of airway remodeling.

Another potentially important activity of IL-4 in allergic inflammation is its ability to induce the expression of vascular cell adhesion molecule-1 on endothelial cells. This will produced enhanced adhesiveness of the endothelium for T-cells, eosinophils, basophils and monocytes, which are characteristics of allergic reactions.
Because of these properties IL-4 has long been considered as a potential target in allergies and asthma.(Mehta and Mahajan, 2006).

IL-6 has been accepted that it is released from alveolar macrophages from asthmatic patients after allergen challenge and increased basal release, compared with non-asthmatic subjects (Rincon and Irvin, 2012).
IL-18 augments eosinophil recruitment. IL-18 is high in allergic patients and elevated levels of IL-18 suggest its role in the expression of persistence and exacerbation of allergic inflammation.

IL-18 plays a potential role to activate immunologic responses and may reflect disease activity in mild and moderate asthma exacerbation (Zhang et al., 2018).

Aim of the work

- To find association between IL-4, IL-6 and IL-18 polymorphism and asthma in Egyptian patients.
- To find the effect of IL-4, IL-6 and IL-18 polymorphism on severity of asthma.

Subjects and method

Subject Sample size: The asthmatic patients participating in this study were from Asthma and Allergy Clinic, Minia chest hospital. Seventy five of asthmatic patients were enrolled in this study. Seventy five non asthmatic controls belonging to the same age group and living conditions as patients were enrolled for the study.

The council of the faculty of medicine, Minia University, approved the study protocol ethically. All the asthmatic subjects had specialist physician-diagnosed asthma according to European Community Respiratory Health Survey (ECRHS) (Eur respir, 1996) which considered a person asthmatic if he had an attack in the previous 12 months or recurrent use of asthmatic drugs. For control, unrelated subjects without history of asthma and atopy, matched for age and sex with asthmatic patients, were randomly selected from general population.

History and physical examination

For the assessment of the severity of asthma and their symptoms a detailed history was taken based on a questionnaire designed. Asthma severity was diagnosed according to Canadian consensus *(D Ukena et al., 2008)* which consider patient very mild if he had mild infrequent symptoms and use short acting beta agonist rarely.

Mild if symptoms well controlled and use short acting beta agonist occasionally with low doses of inhaled corticosteroids.
Moderate with well controlled symptoms and short acting beta agonist use with low to moderate doses of inhaled corticosteroids.
Severe with will controlled symptoms and short acting beta agonist use with high doses of inhaled corticosteroids.
Very severe if symptoms controlled or not well controlled with short acting beta agonist use, high doses of inhaled corticosteroids and oral corticosteroids.

Exclusion criteria

Patients with a history of smoking or any illness involving lungs e.g., chronic bronchitis, emphysema, tuberculosis, pneumonia etc. were excluded from this study. The participants in control group were healthy individuals and exclusion criteria included asthma-like symptoms, known allergies, history of smoking and a positive family history of asthma and allergy.

Results

This study was carried on 75 asthmatic patients from Minia chest hospital and 75 healthy controls in the period between May 2017 & January 2018. Patients approved to be asthmatic by (ECRHS).Patients were divided into mild, moderate and sever according to the Canadian consensus. The aim of the study was to find the association between IL-4, IL-6 and IL-18 polymorphism and asthma development in Egyptian patients and to find the effect of IL-4,

IL-6 and IL-18 polymorphism on severity of asthma.

Patient characteristics

Data of this study showed that asthmatic patients had positive family history more than control which is statistically significant. Regarding age and sex there was no statistical difference between asthmatic patients and control group **(Table 1).**

Table (1): Distribution of the studied participants according to their characters

Data		Patients n-75	Controls n-75	P
Age	**Range**	18-60	18-60	0.08
	Mean ±SD	43.2±10.8	39.7±13.4	
Sex	**Male**	41(54.7%)	31(41.3%)	0.05
	Female	34(45.3%)	44(58.7%)	0.05
Family history	**Positive**	20(26.7%)	0	0.001*
	Negative	55(73.3%)	75(100%)	0.006*

Asthma and atopy are closely interrelated. Frequency of atopic disorders as allergic rhinitis and dermatitis were studied in association with asthma. Frequency of DM, hypertension and HCV which are common in Egypt were studied in association with asthma. It was observed that 9.3% of asthmatic patients had hypertension, 8% had DM, 5.3% had allergic rhinitis, 4% had HCV, and 2.7% had hypertension and DM. **(figure 1) .**

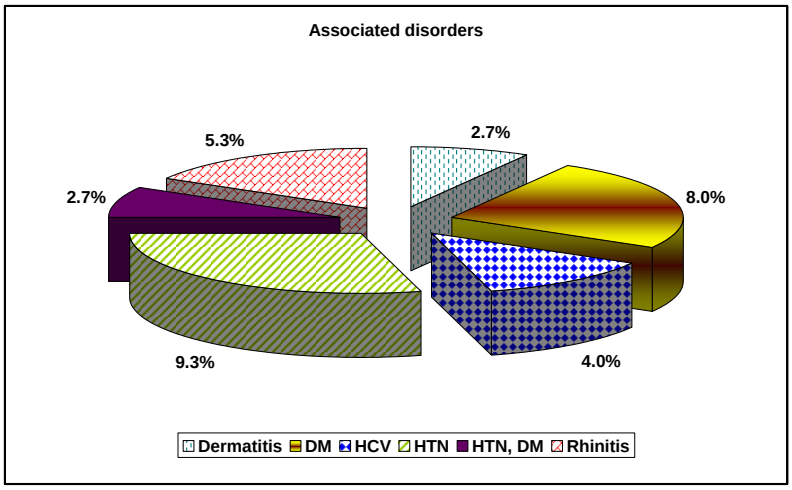

Figure (1): Disorders associated with asthma.

Discussion

Asthma and other atopic diseases are considered to be multifactorial, with environmental and genetic factors all contributing towards disease manifestation and progression (Micheal et al., 2013).Since no data was available on the association of IL-4, IL-6 and IL-18 polymorphisms and asthma for adult Egyptian population, this study was done. The randomly selected asthmatic patient visiting asthma clinic for the follow up of their treatment were recruited for this study .Asthmatic patients were classified on the basis of their symptoms to mild, moderate and sever group. A considerable number of patients reported a positive family history of asthma with or without other allergic conditions.

IL-4 has a well-established role in the pathogenesis of asthma and has been associated with the severity of asthma and other atopic disease as dermatitis and allergic rhinitis

(Mehta and Mahajan, 2006). Several polymorphisms in IL-4 gene were described to be associated with the development of asthma.

In the present study, the association between IL-4 gene polymorphism 590 C >T and bronchial asthma in Egyptian patients and control group was studied. Our data showed no significant association between IL-4 590 C >T polymorphism and asthma.

The frequency of the CC, TC and TT genotypes among asthmatic were 32%, 42.7 % and 25.3 % while among control group, these frequencies were 36%, 42.7% and 21.3% respectively. The frequency of the "C "allele among asthmatic and control group were 53.3% and 57.3% respectively. On the other hand, the frequency of "T" allele among asthmatic and control group were 46.7 % and 42.7 % respectively. This is in agreement with different studies in different populations: Kuwaiti (Hijazi and Haider, 2000) , Australian (Elliott et al., 2001) , Jordanian (A Attab et al., 2008), United kingdom (Walley and Cookson, 1996) ,Chinese (Cui et al., 2003) , Brazilian (de Faria et al., 2008), Indian (Nagarkatti et al., 2004) and (Bijanzadeh et al., 2010).

Summary and conclusions

Bronchial asthma is one of the world's most common chronic diseases and it represents an important cost factor for health care system. It is a serious global health problem. Cytokines play a key role in the modulation of immune responses. There are inter-individual variations in cytokines production which may be attributed to SNPs in the DNA of these cytokines. These variations influence the balance between pro-inflammatory and anti-inflammatory cytokines and might affect the severity as well as the treatment outcome of the bronchial asthma.

IL-4, IL-6 and IL-18 play an important role in the pathogenesis of bronchial asthma. This study was carried out on seventy five asthmatic patients and seventy five healthy subjects were included as a control group. Patients were classified according to their severity into three groups, mild, moderate and sever. Venous blood samples were collected from all patients and healthy controls.

Genomic DNA from venous blood of subjects included in the study was extracted. SNPs in IL-4, and IL-18 were genotyped by (PCR-ssp).SNPs in IL-6 were genotyped by (RFLP - PCR).Subjects were older than 18 years old. The patients age range was 18-60 years (mean = 43.2) while that of the healthy controls was (mean = 39.7).The genotype distribution for IL-4 polymorphism (590 C >T) were not significantly different among healthy control subjects and asthmatic patients as the frequency of the CC, TC and TT among patients were 32%, 42.7% and 25.3% while among healthy control subjects, the frequency were 36%, 42.7% and 21.3 % respectively. The genotype distribution for IL-6 (572 G >C) polymorphism were not significantly different among the asthmatic and control group as the frequency of CC, GC, and GG among patients were 1.3%, 33.3% and 65.4% while among control subjects, the frequency were 0%, 26.7% and 73.3% respectively. The genotype distributions for the IL-18 (137 G >C) polymorphism were significantly different among healthy and control subjects as the frequency of CC, GC and GG were 4% , 0% and 96% while among control subjects , the frequency were 0% , 10.7 % and 89.3% respectively.

No significant different was found in genotype distribution of different asthmatic group, mild, moderate and sever in IL-4 (590 C >T), IL-6 (572 G >C) and IL-18 (137 G >C) SNP. In conclusion, IL-4 (590 C >T) SNP and IL-6 (572 G >C) SNP didn't affect bronchial asthma in Egyptian patients included in our study.IL-18 (137 G >C) SNP is a risk factor of asthma in Egyptian patients.

Future studies should include more patients for more reliable assessment. Considering that bronchial asthma is a complex disease, the heterogenecity of disease may cause research results to be in consistent. And the statistical power of a small sample associated analysis, there for, there is a need for larger studies to suggest any role of this cytokine gene polymorphism in bronchial asthma and cytokine role in asthma severity.

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