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INTERFERON GAMMA GENE POLYMORPHISM AS A MARKER OF SOME ALLERGIC DISEASES (ALLERGIC SKIN DISEASES AND ALLERGIC CONJUNCTIVITIS) IN A SAMPLE OF EGYPTIAN POPULATION

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Abstract
Introduction: Allergy is a hypersensitivity disorder of the immune system. Allergic reactions occur to normally harmless environmental substances known as allergens; these reactions are acquired, predictable, and rapid. Allergy is one of four forms of hypersensitivity and is called type I (or immediate) hypersensitivity.
Aim: To Analyze the allelic distribution of interferon gamma gene polymorphism 874A>T in some allergic skin diseases and allergic conjunctivitis.
Material and Methods: This study included 300 Egyptian individual, divided into 100 patients with allergic skin diseases, 100 patients with allergic conjunctivitis and 100 healthy individual were taken as controls. Eosinophil count was estimated, Total IgE level was measured by ELISA technique, Nuclear DNA extracted from peripheral leukocytes and interferon gamma gene polymorphism 874A>T detected by Amplification Refractory Mutation system (ARMS-PCR).
Results: In the Skin allergic group, the (AT) genotype and the (TT) genotype were the most common (both are 45%), while in the Conjunctivitis group and the normal control groups the (TT) genotype was the most common (60% and 90% respectively). Moreover, there was statistically significant difference in the distribution of the IFN-γ genotypes at position 874 among the studied groups as compared all together.
Conclusions: The IFN-ɤ gene polymorphism at position +874 increases susceptibility to atopic diseases, and the identification of variants of the IFN-ɤ gene and their role in the development of atopic diseases provides a focus for the development of novel diagnostic and therapeutic strategies.

Key words: allergic skin diseases; allergic conjunctivitis; interferon gamma; gene polymorphism

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Introduction

Allergy is a hypersensitivity disorder of the immune system [1,2]. Allergic reactions occur to normally harmless environmental substances known as allergens; these reactions are acquired, predictable, and rapid [2,3]. Strictly, allergy is one of four forms of hypersensitivity and is called type I (or immediate) hypersensitivity [1,4]. It is characterized by excessive activation of certain white blood cells called mast cells and basophiles by a type of antibodies known as IgE, resulting in an extreme inflammatory response [3,5]. Common allergic reactions include eczema, hives, hay fever, asthma attacks, food allergies, and reactions to the venom of stinging insects such as wasps and bees [6,7].

Interferons (IFNs) are proteins made and released by the cells of most vertebrates in response to the presence of pathogens - such as viruses, bacteria, or parasites or tumor cells [8,9]. They allow communication between cells to trigger the protective defenses of the immune system that eradicate pathogens or tumors [10-15].

IFNs belong to the large class of glycoproteins known as cytokines [16,17].

Although they are named after their ability to „interfere" with viral replication within host cells, IFNs have other functions: they activate immune cells, such as natural killer cells (NK) and macrophages, they increase recognition of infection or tumor cells by up-regulating antigen presentation to T lymphocytes; and they increase the ability of uninfected host cells to resist new infection by virus [18-20]. Certain host symptoms, such as aching muscles and fever, are related to the production of IFNs during infection [21-26].

The aim of the work is to Analyze the allelic distribution of interferon gamma gene polymorphism 874A>T in some allergic diseases (allergic skin diseases and allergic conjunctivitis) and to study the relationship of the allele with markers of allergy (serum IgE level and absolute Eosinophil count).

This study included 300 Egyptian individual, divided into 100 patients with allergic skin diseases, 100 patients with allergic conjunctivitis and 100 healthy individual were taken as controls. The patients selected from the ophthalmology and dermatology outpatient clinic of the main University Hospital, Faculty of Medicine, University of Alexandria.

Informed consent was taken from all patients participating in the study; The study was approved by the Alexandria Faculty of Medicine, Research Ethics Committee.

Methods

All the studied individuals (allergic skin diseases, allergic conjunctivitis and control groups) were subjected to the following:

I. Full history of:

- Onset of symptoms.
- Previous history of the same symptoms.
- Aggravation of symptoms by some types of food.
- Past history of other allergic conditions as atopic asthma, eczema and rhinitis.
- Drug history.
- Family history of allergic diseases.

II. Clinical examination:

Symptom of allergy:

a. Ophthalmologic examination

b. Dermatological examination

III. Laboratory investigations:

- Eosinophil count was estimated.
-Total IgE level was measured by ELISA technique.
- Nuclear DNA extracted from peripheral leukocytes and interferon gamma gene polymorphism 874A>T was detected by Amplification Refractory Mutation system (ARMS-PCR).

1. Absolute Eosinophil Count.

Complete blood count (CBC) were performed on a 3 differential automated cell counter sysmex KX-2IN (Sysmex, Kobe, Japan) and Absolute Eosinophil Count was estimated.

2. Total IgE level by ELISA technique.

Total IgE level was assayed using DRG International Inc., [27] USA ELISA kit.

3. Detection Of Interferon Gamma Gene Polymorphism 874a>T

- Genomic DNA extraction

Genomic DNA was extracted from peripheral blood leucocytes. Venous blood was collected from each subject into EDTA tubes withdrawn under complete aseptic technique. Genomic DNA was isolated using illustra blood genomicPrep Mini Spin Kit (GE Healthcare, United Kingdom) using column extraction technique.

Gamma interferon gene polymorphism detection using polymerase chain reaction - Amplification Refractory Mutation system [28]

Genotyping for 874AT polymorphisms in IFN-γ was performed and genes were typed using the refractory mutation system-polymerase chain reaction (ARMS-PCR). To assess the success of PCR amplification in both reactions, an internal control was amplified using a pair of primers designed from the nucleotide sequence of the human growth hormone (HGH).

- Primers used:

a. Common primer (antisense) of IFN- γ 5'-TCA ACA AAG CTG ATA CTC CA-3'

b. Allele-specific sense primer T 5'-TTC TTA CAA CAC AAA ATC AAA TCT-3'

c. Allele-specific sense primer A 5'-TTC TTA CAA CAC AAA ATC AAA TCA-3'

d. Control primer (HGH) (sense), 5'-CCTTCCAAC CAT TCC CTT A-3'

e. Control primer (HGH) (antisense), 5'-TCA CGG ATTTCT GTT GTG TTTC-3'

Results

The results of the present study showed that in the Skin allergic group, the (AT) genotype and the (TT) genotype were the most common (both are 45%), while in the Conjunctivitis group and the normal control groups the (TT) genotype was the most common (60% and 90% respectively). Moreover, there was statistically significant difference in the distribution of the IFN-γ genotypes at position 874 among the studied groups as compared all together.

The results also revealed statistically significant association between genotype and the allele frequencies of the +874T/A gene polymorphism in patients with skin allergy compared with controls and show the A allele frequency was 32.5% and the T allele frequency was 67.5%, also revealed statistically significant association between genotype and the alleles frequencies of the +874T/A gene polymorphism in patients with Conjunctivitis group compared with controls and show the A allele frequency was 27.5% and the T allele frequency was 72.5%, and showed that there was statistically significant difference in the serum IgE level and absolute Eosinophil count among the studied groups with elevated values of both parameters in allergic groups compared to control group, but higher values in Skin allergic group than in the Conjunctivitis group.

We found that the relation between genotype with absolute eosinophil count and serum IgE level in skin allergy group show that there was no statistically significant relation

between AA and each other genotypes but there was statistically significant relation between AT and TT genotype, in conjunctivitis group show that there was no statistically significant between AA and AT genotype as regarding to the absolute eosinophil count of, but there was statistically significant between AA and AT genotypes as regarding to the Serum IgE level, and also there was statistically significant between AA and TT genotypes and when we compared AT and TT genotypes we founded that there was statistically significant between this two genotypes, when we compared AT and TT genotypes in control group we founded that there was statistically significant between this two genotypes.

Discussion

Allergic diseases are common illnesses that have been increasing in prevalence in our surroundings which could be due to increased environmental exposure to allergens or genetic predisposition [1,2].

Studies of allergic diseases have traditionally used allergy skin test reactivity, serum IgE levels or peripheral blood eosinophilia to identify atopic subjects. Although the diagnostic value of specific IgE levels against definite allergens is well accepted, there are conflicting results about predictive value of total serum IgE levels [10,11]. Population studies have shown an association between prevalence of different allergies and serum total IgE levels independent of specific reactivity to common allergies or symptoms of allergy [29,30].

This study was undertaken to Analyze the allelic distribution of interferon gamma gene polymorphism 874A>T in some allergic diseases (allergic skin diseases and allergic conjunctivitis).

In the current study we found that, the frequency of allele A874 of INF- ɤ gene was greater in allergic patients than in control subjects [31]. This is consistent with the finding of other studies; Hussein et al. [31] who found the same results. Grewe et al. [32] stated that IFN-ɤ gene polymorphism is correlated with the allergic skin diseases (his study was conducted in allergic skin diseases only), he mentioned that the correlation may be related to the capacity of IFN-ɤ to enhance Eosinophil viability and activate vascular endothelial molecules, which in turn increases infiltration by eosinophils and induces allergic diseases.

However Hoffmann et al. [33] who conducted his study in 329 normal volunteers and patients he reported that there is no association between allergic disease and IFN-ɤ alleles.

This discrepancy could be due to differences in population and age groups; in other words, each analysis may identify the allele or haplotype responsible for the phenotype in that specifi c population.

In our study there was a significant increase in eosinophil count in both allergic skin and allergic. Conjunctivitis groups compared with the control group. Other authors have found similar results [34,35]. When we compared between allergic skin and allergic conjunctivitis groups as regards peripheral blood eosinophil count we found statistically significant differences which mismatch with Winther et al. [36], who found no statistically significant differences between the two groups as regards peripheral blood eosinophil count, this mismatch may be due difference in environment, population or season in which both studies were conducted.

In clinical practice, peripheral blood Eosinophil counts are widely used to demonstrate the allergic etiology of disease, to monitor its clinical course and to address the choice of therapy [37]. Therefore, peripheral blood eosinophil count can be useful for observing the association of host factors and environmental determinants as indicators of allergy prevalence [38].

In the current study we found that, the frequency of allele A874 of INF- ɤ gene was greater in allergic patients than in control subjects, and that is correlates with markers of atopy (increased IgE levels and eosinophil count). This agreed with Hussein et al. [31] who reported significant association between genotype and the frequency of the A allele of the +874T/A polymorphism in atopic patients. However, Ohly [39] revealed that there was no significant association between the +874T/A polymorphism and IgE level in atopic German newborns. Also in a study conducted in a Chinese population by Chang et al. [40], there was no association between short tandem repeats at the first intron of IFN-ɤ gene and allergic diseases.

In our study we also found that total IgE was higher in allergic patients (allergic skin diseases and allergic conjunctivitis) than in control patients. These results matching with Hussein et al. [41] and Kawai et al. [42] who reported a significant correlation between the allergic diseases and total IgE levels. Johansson et al. [43] found that the total serum IgE in allergic conjunctivitis was higher than that of the control patients in addition to Staikuniene et al. [44] who reported an elevation of serum IgE level by a more than 2-fold in allergic skin patients.

However, other studies question the role of total IgE as a useful indicator of allergic skin diseases. Kaliner et al. [45] found that 40% of allergic patients had normal total IgE levels. Wüthrich and Schmid-Grendelmeier [46] mentioned that the overlap IgE levels made it suggestive but not diagnostic of allergic diseases and explained it by the presence of non–IgE mediated inflammatory mechanisms which may play a significant role in the mechanism of allergic diseases.

The present study revealed a significant correlation between peripheral blood eosinophil count, and total IgE levels in the all studied groups. This consistent with A Japanese study conducted by Yoshizawa et al. [47] to evaluate the role of eosinophils in allergic diseases, by correlating eosinophil count and IgE level and revealed a positive correlation between the number of peripheral blood eosinophils and IgE level [48], and matched with Hussein et al. [31] who reported a positive correlation between peripheral blood eosinophil count, and total IgE levels in his studied groups and finding that there was a negative correlation between peripheral blood eosinophil count, and total IgE levels with the serum level of IFN-ɤ ,and mentioned that his finding may simply reflect the fact that IFN- ɤ expression in this situation is a surrogate marker of TH1 cell activation and reflects its down regulation in blood eosinophilia and serum IgE levels and also mentioned that his data support the hypothesis that a normal level of IFN-ɤ synthesis regulates disease severity in allergic diseases, as activated B-cell clones could remain active (perhaps for years) and produce IgE.

Nevertheless, IgE-mediated local release of mast cells in atopic areas could lead to acute exacerbations of atopic manifestations after acute allergen exposure, although this does not imply an obligatory role for IFN- ɤ /IgE in the pathogenesis of chronic atopic diseases.

Cline et al. [49] reported the highest total IgE levels were seen in the age group 8-14 years. In the presented study no significant relationship of serum Total IgE levels with any age group was observed. Interestingly no association was found with either sex, however many studies have reported males to have raised IgE levels [49].

According to Toma et al. [50], infants suffering from severe allergic diseases have significantly higher number of eosinophils and eosinophilic nuclear lobes, platelets, and total serum IgE level.

Studies over the past 2 decades have shown that eosinophils play a major role in allergic diseases, characterized by activated eosinophils in the peripheral blood and in the lesional skin [51]. Interestingly, immunological response to allergens represents an important trigger for the increase of eosinophil counts in the peripheral blood and serum IgE level [52].

A Japanese study found that the eosinophil levels correlated with the allergic diseases, high blood eosinophil levels in atopic diseases [53]. They found that both the absolute eosinophil count and the IgE level showed significant increase with allergic diseases. The distribution of the absolute eosinophil count and the IgE level were reflected in the large range and higher standard deviation.

A study carried out in Egyptian atopic patients showed a significant association of IFN- ɤ gene polymorphism at position +874 A/T [31]. Study from China reported a significant association of IFN-ɤ +874 A/T gene polymorphism and severe acute respiratory syndrome [54,55].

A significant association was observed between interferon-ɤ gene polymorphisms and systemic lupus erythematosus suggesting that elevated interferon-ɤ is associated with increased systemic erythematosus susceptibility [56]. Lai et al. reported that genetic polymorphism of IFN-ɤ gene is associated with individual susceptibility to cervical carcinogenesis [57].

Feher et al could not find any association between IFN-γ +874 A/T gene polymorphism and Alzheimer disease [58]. Other study found a significant association of 'TT' genotype of IFN-γ +874 gene polymorphism and ischemic stroke in South Indian population [54].

In about 80% of adult patients with allergic skin diseases, the disease is associated with increased serum IgE levels (>150 IU/mL) [59,60]. In contrast, 20% of adult patients with allergic skin diseases have normal serum IgE levels. This subtype of allergic skin diseases often has a late onset (>20 years of life) and a lack of IgE sensitization against inhalant or food allergens [59,60]. However,some of these patients might have IgE sensitization against microbial antigens, such as *Staphylococcus aureus enterotoxins* and *Candida albicans*.

From this study it was concluded that:

The IFN-ɤ gene polymorphism at position +874 increases susceptibility to atopic diseases, and the identification of variants of the IFN-ɤ gene and their role in the development of atopic diseases provides a focus for the development of novel diagnostic and therapeutic strategies. Elevation of total IgE level and absolute eosinophil count in the atopic patients, and positive correlation between these parameters supports their effect, either directly or indirectly, in the atopic diseases and make them are strong predictors of atopic diseases.

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