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Evaluation Of Some Immunological Biomarkers Of Allergic Rhinitis Patients In Wasit Province \ Iraq

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Abstract:

Background: Allergic rhinitis (AR) is an inflammation of the nasal mucous membranes, and IgE-mediated type 1 hypersensitivity reaction induced by exposure to allergens.

Aim of the study: To measure the serum levels of total immunoglobulin E (tIgE), interleukin-13 (IL-13) and eosinophil cationic protein (ECP), and toestimate whether the determination of C-reactive protein would be used as a marker of inflammation in AR patients, also assessment of corticosteroid resistance and finding the effects of neutrophil serine proteases on AR patients.

Materials and Methods: Thisstudy involved 60patients with allergic rhinitis and 30controls,all biomarkerswere measured by use ELISA technique.

Results: The results of this study showed a significant increased (P≤0.05) in serum levels of tIgE, IL-13, ECP and hs-CRP, in male and female patients with allergic rhinitis disease compared with the control in both age groups.In AR patients, the serumlevels of HGR-β and NEwere found to be increased significantly.

Conclusion: Depending on our study results, serum levels of tIgE, IL-13, ECP and hs-CRP have a rule in the immune response and can be used as a marker of inflammation in patients with AR in absence of other atopic diseases. Most of patients have resistance or insensitivity to corticosteroid treatment. For the first time, the present study demonstrates the role of serum neutrophil elastase (NE) in the immune response of AR.

Keywords: Allergic Rhinitis, IL-13, ECP, hs-CRP, HGR-β, Neutrophil Elastase.

Introduction:

Rhinitis is a common disorder that affects up to 40% of the population, and defined as an inflammation of the nasal mucosa (1). Allergic rhinitis is the most common form and a prototype of IgE-mediated disease, induced by exposure to allergens in sensitized individuals (2), it is characterized by rhinorrhea, sneezing, itching and nasal obstruction with presence of inflammatory cells in the mucosa and submucosa (3). AR process is triggered by exposure to allergens such as pollen, house dust mites, animal dander, and molds that penetrating the nasal epithelium (4). The

development of AR requires an interaction between the environment, immune system, and genetic susceptibility (5).Allergens are taken up by antigen-presenting cells, processed, and presented to helper T lymphocytes. Thereafter, activated helper T lymphocytes release some cytokines such as IL-13, interact with B lymphocytes to induce the synthesis of allergen-specific IgE, whichbinds to the high-affinity receptor for IgE on the surface of mast cells (6),IL-13 has an important role in the pathophysiology of AR (7). ECP is important mediators of allergic inflammation in respiratory tract mucosa and a cationic granular protein released from activated eosinophils during allergic diseases(8).Neutrophil elastase is one of the physiologic proteolytic enzymes secreted by neutrophils in response to inflammation and pathogen invasion (9), its biological roles include acting as proinflammatory, stimulates the secretion of cytokines, glycosaminoglycans and mucus (10).

Materials and Methods:

Study design:

This study was done in Wasit province / Iraq, during the period from August 2020 to March 2021, 90 samples were involves, age between 5 to 45 years, 60 patients with AR (38 males and 22 females) compared with 30 healthy individual (16 males and 14 females).

Diagnosis and excluded criteria:

The clinical diagnosis of AR patient was carried out by an ear, nose, and throat specialist physician based on history, clinical examination and nasal endoscopy; also this diagnosis was confirmed by using complete blood count (CBC) and total serum IgE levels. The excluded criteria were smoking patients, and patients with other atopic diseases such as asthma, dermatitis, food allergies, conjunctivitis and any other respiratory disease, or rheumatoid arthritis, coronary artery disease and others.The healthy control in this study were without any past or present history of systemic diseases or pathological states like allergic, chronic inflamed, atopic or other pulmonary diseases.

Blood samples:

Four ml of blood was put in gel and clot activator tube,left to clot at room temperature (20-25 °C) for 15 minutes, then it was centrifuged for 10 minutes at 2500 - 3000 run per minute, the serum was isolated and divided into several parts, each part of was kept in the eppendorff tube, labeled and freeze at (-20 °C) until use.The data was taken from patients and control as well as their divided into two groups according to gender, each group was divided into two age groups less than 18 years and older or equal to 18 years (<18 and ≥18)for all the studied parameters. SerumtIgE, IL-13, ECP, hs-CRP, HGR-β and NE were evaluationby use enzyme linked immunosorbent assay technique, ELISA kits according to the manufacturer's instructions (Bioassay Technology Laboratory, China).

Statistical Analysis

The data were statistically analyzed by IBM SPSS 25 statistics program (Statistical Package for the Social Sciences) using independent-Sample T Test analyze, the data described as mean ± significant difference (mean ± SD) and taking P≤0.05 as the lowest limit of significance value to evaluate differences between allergic rhinitis patients and the control, as well as between age

groups of both subjects.

Results:

The results of thestatistical analysis in tables (1) and (2) showed the mean value of immunological biomarkers of males and females with allergic rhinitis compared to control subjects according to age groups.

Table (1): The mean value ofimmunological biomarkers of males with allergic rhinitis compared to control subjects according to age groups.

Age groups (years) / Parameters & Subjects		< 18	≥ 18
Total serum immunoglobulin E (tIgE)	Patients	A,a 467.07±214.19	A,a 471.04±224.49
	Control	B,a 137.28±47.68	B,a 114.22±31.38
	Sig. value	0.021	0.022
Interleukin-13 (IL-13)	Patients	A,a 13.21±4.83	A,a 13.41±2.41
	Control	B,a 3.28±1.11	B,a 3.33±1.118
	Sig. value	0.026	0.016
Eosinophil cationic protein (ECP)	Patients	A,a 13.076 ± 2.286	A,a 13.074 ± 2.787
	Control	B,a 7.842 ± 0.446	B,a 7.611 ± 0.711
	Sig. value	0.0003	0.002
High sensitivity C - reactive protein (hs-CRP)	Patients	A,a 7.200 ± 1.725	A,a 7.483 ± 2.814
	Control	B,a 2.085 ± 0.638	B,a 2.444 ± 0.938
	Sig. value	0.012	0.004
Glucocorticoid receptor β (GR-β)	Patients	A,a 5.571 ± 4.070	A,a 5.254 ± 1.763
	Control	B,a 3.185 ± 0.744	B,a 2.933 ± 0.540
	Sig. value	0.020	0.017
Neutrophil elastase (NE)	Patients	A,a 13.184 ± 4.550	A,a 13.633 ± 3.693
	Control	B,a 5.472 ± 3.686	B,a 8.144 ± 1.632
	Sig. value	0.034	0.001

- Mean ± SD: Mean ± significant difference.

- The different capital letter refers to significant differences at (P≤0.05) vertically between patients and control to same age groups.
- The different small letter refers to significant differences at (P≤0.05) horizontally between age groups of patients and control.

Table (2): The mean value ofimmunological biomarkers of females with allergic rhinitis compared to control subjects according to age groups.

Age groups (years) / Parameters & Subjects		< 18	≥ 18
Total serum immunoglobulin E (tIgE)	Patients	A,a 457.22±121.52	A,a 427.61±128.95
	Control	B,a 119.16±39.57	B,a 136.25±37.51
	Sig. value	0.021	0.002
Interleukin-13 (IL-13)	Patients	A,a 16.22±9.69	A,a 13.15±9.23
	Control	B,a 3.16±1.32	B,a 3.75±1.58
	Sig. value	0.022	0.011
Eosinophil cationic protein (ECP)	Patients	A,a 13.433 ± 1.872	A,a 13.163 ± 3.043
	Control	B,a 7.016 ± 0.483	B,a 7.075 ± 0.967
	Sig. value	0.037	0.0001
High sensitivity C - reactive protein (hs-CRP)	Patients	A,a 7.353 ± 1.473	A,a 7.230 ± 3.139
	Control	B,a 2.366 ± 0.531	B,a 2.375 ± 0.700
	Sig. value	0.027	0.016
Glucocorticoid receptor β (GR-β)	Patients	A,a 5.422 ± 3.647	A,a 5.192 ± 4.604
	Control	B,a 2.883 ± 0.444	B,a 2.875 ± 0.494
	Sig. value	0.017	0.028
Neutrophil elastase (NE)	Patients	A,a 12.335 ± 4.082	A,a 12.515 ± 3.910
	Control	B,a 7.061 ± 2.063	B,a 7.312 ± 1.573
	Sig. value	0.043	0.018

- Mean ± SD: Mean ± significant difference.
- The different capital letter refers to significant differences at (P≤0.05) vertically between patients and control to same age groups.

- The different small letter refers to significant differences at (P≤0.05) horizontally between age groups of patients and control.

Discussion:

This study showed a significant increased (P≤0.05) in serum levels of tIgE, IL-13, ECP, hs-CRP, HGR-β and NE in male and female patients with allergic rhinitis disease compared with the control in both age groups.Total serum IgE level is a unique immunoglobulin that plays a central role in the pathophysiology of acute and chronic allergic reactions (11), increase the production of IgE antibodies against environmental allergens is the first immune response requires in AR and the interaction between them is an essential pathogenesis mechanism triggering the symptoms of AR (12). This result agreed with (13), which found total IgE levels were high in AR patients, these results were especially valuable because this study excluded patients with atopic diseases such as asthma, dermatitis, food allergies, and other diseases related to tIgE level elevated, that confirms its significant role in the pathogenesis of AR. In Iraq, tIgE is frequently used in the diagnosis of AR (14).

The serum levels of IL-13 were higher in AR patients as compared to the control, this agreed with (15)who found a rise in IL-13 in nasal secretion samples after nasal allergen challenge. IL-13 has an important role in pathophysiological allergic reactions;it was responsible for driving the epithelial cells into a hyper-secretory phase which leads to increase allergic reactions in the airways, and in the contraction of the smooth airway muscles (16). IL-13 selectively produced by T_H2 cells and can mediate allergic inflammation and disease (17), it was bind specifically to its receptor on mast cells which may cause the release of mediators that may be accelerate the secretion of IgE and lead to induce inflammation (18). Other study found increased in IL-13 in patients with IAR and PAR (12).

The levels of ECP were higher in AR patients, this agreed with (19), the allergic inflammation of airways and exposure to allergen may be associated with a rise in levels of serum ECP (20), and it was an important mediator in the pathogenesis of AR in regardless of allergen sensitization species, it positively correlated with eosinophilia in AR patients (21). In allergic diseases and after contact with IgE through surface receptors, the eosinophil degranulation and releases of ECP occur, eosinophil cells influx into the inflammatory location, so the serum ECP level was rapidly increased (20). The levels of ECP were significantly increased in the moderate-severe HDM AR patients (19).The levels of hs-CRP were higher in AR patients(22), an increased in C-reactive protein concentration measured by high sensitivity assays may be associated with airway inflammation. CRP is a well-known serum systemic inflammatory marker and acute phase reactant that participates in the response to inflammation (13), levels are increased in response to inflammation, tissue injury or infection (23). One of the major features of AR is chronic airway inflammation, which involves many cell types that play the most important roles such as mast cells, eosinophils, and T-lymphocytes (24), in sensitive individuals, the inflammation induced by environmental allergens leads to symptoms of AR such as nasal congestion, rhinorrhea, sneezing, and nose itching, CRP is an inflammatory marker (25).

The present study found a high levels of HGR-β in AR patients compared to the control, GR-β has a low capacity to bind toglucocorticoids(GCs) and is considered to be an endogenous inhibitor of GR-α, because it was able to interact directly with GR-α within the nucleus and then inhibit GC action (26).The overexpression in the level of the GR, especially

the GR-β, is functionally involved in steroid resistance.In AR patients, the abnormal expression of GR-β serves as a predictor of corticosteroid resistance (27), this relationship was clarify by found the number of GR-β in the resistant patients was significantly higher than in the sensitive and control group (27). The mechanisms that induce the overexpression of GR-β remain poorly understood (26). In AR, the chemotaxisand accumulation of pro-inflammatory cytokines in the nasal mucosa can induce increase GR-β levels rather than GR-α in different types of cells, as well as the half-life of GR-β protein is twice that of GR-α, this can induce accumulation of GR-β leading to GCs resistance (28).(29)agreeed with our results by observed an increase in the expression of GR-β in the nasal epithelium and submucosal inflammatory cells of severe allergic rhinitis patients, and suggests GR-β might be used as a parameter indicating steroid resistance in AR. According to our results, most AR patients have resistance or insensitivity to corticosteroid treatment.

To our knowledge, this is the first study showing the levels of neutrophil elastase mediator in the serum of patients with AR, NE was higher in AR patients compared with controls. WBCs and neutrophil recruitment happen in response to IgE-mediated reactions, which are reflected in an increase in elastase in response to allergen exposure in sensitized individuals, elastase promotes the recruitment of neutrophils to the lung when inducing IL-8 secretion (30). The prolonged release of neutrophil elastase damages the epithelium and can be responsible for vasomotor symptoms that characterize AR (31). Neutrophil serine proteases activated eosinophils in vitro and enhanced airway inflammation through eosinophils activation and degranulation, causing releasing of ECP and the amount of it depending on the dose of elastase (32). NE activity comes to be implicated in the pathobiology of many lung diseases, it may result in pathologic states or intensify them (33), and significantly contributes to chronic inflammatory airway diseases by inducing mucin production in airway epithelial cells (34), the neutrophils in asthmatic patients are characterized by high concentrations of active neutrophil elastase (35). The effective inhibition of these proteases could be a future therapeutic target.

Conclusions:

In conclusion, AR patients have higher serum levels of tIgE, IL-13, ECP and hs-CRP than healthy controls, this indicatethe rule of these biomarkers in the immune response and they may be used as a marker of inflammation in patients with AR in absence of other atopic diseases, as well as most AR patients have resistance or insensitivity to corticosteroid treatment, and for the first time, the present study demonstrates the role of serum neutrophil elastase (NE) in the immune response of AR, and found that allergic rhinitis patients are characterized by high concentrations of neutrophil elastase in serum compared with the control, so the inhibition of NE could be exploited as a target for the development of new strategy of therapies for allergic rhinitis.

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