ATOPIC DERMATITIS AND ASTHMA IN CORELLATION WITH CYTOKINES LEVEL

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Rezumat

Context: *Există dovezi pentru reducerea producției de IFN-γ (interferon-gama) de către celulele T la pacienții astmatici și cu DA (dermatită atopică) și că aceasta se corelează cu activitatea bolii. Aceasta pare a fi o caracteristică a bolilor atopice și nu este specifică pentru astm. Acest lucru sugerează faptul că producția deficitară de IFN-γ poate fi importantă în astm.*

Obiectiv: *Acest studiu are obiectiv evaluarea nivelului serologic de interferon gamma la astmatici, pacienți cu DA și astmatici cu DA, compararea rezultatelor cu martori aparent sănătoși și verificarea asocierii între astm și DA.*

Pacienți și metode*: Studiul a fost realizat în Tikrit, Spitalul de Predare, în perioada martie-septembrie 2009. Un total de 85 pacienți au fost luați în studiu. Au fost incluși 40 pacienți cu astm bronșic, 23 pacienți cu DA, 22 pacienți atât cu astm cât și cu DA și 15 indivizi aparent sănătosi ca lot de control. O probă de sânge (5 ml) a fost colectată de la fiecare pacient și control. Eșantionul a fost împărțit în două părți, 3 ml pentru determinarea IFN-γ și 2 ml pentru determinarea numerică a leucocitelor și eozinofilelor.*

Rezultate: *Studiul a demonstrat că DA este cea mai frecventă la pacienții cu grupa de vârstă mai mică de 9 ani, astmul este mai des întâlnit la 20-29 de ani și 30-39 de ani, în timp ce preponderența apariției, la grupul cu ambele afecțiuni a fost la 20-29 ani. Eozinofilele au fost mai crescute la cei cu astm și DA iar IFN-γ seric a fost mai crescut la cei cu astm. Totalul numărului de leucocite nu arată nicio diferență semnificativă între grupurile studiate.*

Concluzii: *Studiul nostru extinde cunoștințele acumulate despre astm și DA și sugerează că eliberarea deficientă a IFN-γ este caracteristica generală a acestei boli, de asemenea studiul indică faptul că gradul deficienței în eliberarea IFN-γ ar putea fi legat de activitatea bolii.*

Summary

Background: *There is evidence for reduced production of IFN-γ by T cells in asthmatic and AD (atopic dermatitis) patients, and this correlates with disease activity. This appears to be a feature of atopic diseases and is not specific to asthma. This suggests that IFN-γ production may be important asthma.*

Objective: *The objective of the study is to evaluate the level of serological IFN-γ in asthmatic, AD and both asthmatic and AD patients, compare the results with healthy control lot and verify the association between AD and asthma.*

Patients and methods: *The study was performed in Tikrit Teaching Hospital during March till the end of september 2009. A total of eighty-five patients were taken into study. This included 40 patients with asthma, 23 patients with AD, 22 patients with asthma and 15 apparently healthy individuals as control group. A blood sample (5 ml) was collected from each patient and control. The sample was divided into two parts: 3 ml to determine IFN-γ and 2 ml to determine total WBC and eosinophils.*

Results: *The results of the study demonstrated that AD is more common in patients with less than 9 years old, asthma is more common in 20-29 and 29-30 years while both AD asthma, more common in 30-39 years old. Eosinophil count was higher in those with AD asthma and serum IFN-γ was higher in those with asthma. Total WBC did not show significant difference between the studied groups.*

Conclusions: *Our study extend the findings observed for asthma and AD and suggests that deficient IFN-γ release is a general feature of the disease, also the study indicates that the degree of the deficiency in IFN-γ release might be related to disease activity.*

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Introduction

Under atopy (a-topos-Greek-wrongly-placed), Coca and Cooke (1923) included the tendency to specific allergic disorders, namely atopic eczema, allergic bronchial asthma, and allergic reactions due to pollen, such as hay fever, rhinitis, conjunctivitis (1).

Recent immunological advances render that definition simplistic and imprecise (2).

Atopic dermatitis (AD) is a chronic, pruritic eczematous disease that nearly always begins in childhood and follows a remitting/flaring course, that may continue throughout life (3).

Asthma (Greek. panting) a condition marked by recurrent attacks of paroxysmal dyspnea, with wheezing due to spasmodic contraction of the bronchi (4). Asthma is a chronic disease of the respiratory system in which the airways occasionally constricts, becomes inflamed, and is lined with excessive amounts of mucus, often in response to one or more triggers (5).

Cytokines are small peptides secreted mainly by activated leukocytes. Different cytokines may trigger the same biological responses, a characteristic "functional redundancy". Additionally, cytokines are pleiotropic, with each cytokine mediating numerous seemingly unrelated biological effects (6). IFN-γ was one of these cytokines was involved in the regulation of nearly all phases of the immune response system, including the activation, growth and differentiation of T-cells, B-cells, macrophages, natural killer cells and other cells types such as endothelial cells and fibroblasts. Defects in the IFN-γ activation pathway are associated with susceptibility to severe micro-allergic infections and allergic diseases. IFN-γ is hence regarded as a key immune-regulator (7).

In asthma is reduced by IFN-γ by T-cells from asthmatic patients and this correlates with disease activity. IFN-γ receptor develop a prolonged airway eosinophilia in response to the allergen. IFN-γ inhibits alergic eosinophilia and allergic airway hyperresponsiveness, probably by inducing the formation of IL-10. These indicate that IFN-γ has a potential modulating effect on allergen responses. Allergen immuno-therapy of asthmatic patients results in increased production of IFN-γ by circulating T-cells and increased IFN-γ producing T-cells in nasal biopsy samples (8).

Atopic dermatitis is a type of IgE-mediated hypersensitivity, but the exact etiology is unknown. The pathogenesis is multifactorial and involves a complex immunological cascade. The major elements in immune disregulation are Langerhans' cells, inflammatory dendritic epidermal cells, monocytes, macrophages, lymphocytes, mast cells, and keratinocytes, all of which interact through a complex cascade of cytokines leading to a predominance of Th2 over Th1 cells. The Th2 Cytokines, IL-4, IL-5, IL-10 and IL-13 are increased in the skin, and there is a corresponding decrease in Th1 cytokines, mainly IFN-γ and IL-2 (9).

The newly discovered family of molecules, the chemokines molecules are involved in muliple facets of immunity, beyond their role in cell chemotaxis. Current clinical interest has focused on the role chemokines antagonists, which might play in regulating inflammation (10).The vast majority of asthmatics has an atopic background, in which the inflammatory process of asthma may be driven following sensitization and exposure of common **aeroallergens** to which they become sensitized (11). The majority of infants with atopic dermatitis also develop asthma and/or allergic rhinitis later in life (12).

Patients and Methods

The study was conducted in the Tikrit Teaching Hospital during the period from March 2009 to the end of September 2009. A total of eighty five patients (46 males and 39 females), their age range 3-80 (37.4 ± 15.7) and fifteen used as controls in this study (10 males and 5 females). All patients were examined clinically, then interviewed and detailed questionnaires were completed for each patient.

The patients were divided into three groups according to their clinical presentation and history. The first group consists of (40) patients presented with asthma (22 males and 18 females), the second group of (23) patients presented with atopic dermatitis (16 males and 7 females), and the third group consist of (22) patients presented with both asthma and atopic dermatitis (11 males and 11 females).

A blood sample (5 ml) was collected from each patient and control group. The collected sample was divided into two parts, three ml

immediately transferred into a plain tube. The blood in the tube was allowed to clot at room temperature (for 30 minutes), then centrifuged at 3000 revolution per minute (r.p.m.) for 15 minutes and serum was then moved to another plain tube, and stored at - 20 until the time of analysis for determination of IFN-γ (13), while 2 ml was used to determine total W.B.C. and eosinophils count.

Results

This study included 40 patients with bronchial asthma, 23 patients with atopic dermatitis, 22 patients with both atopic dermatitis and asthma, and 15 apparently healthy individuals as control group. The number and percentage of patients with AD, patients with age groups less than 9 years and 10-19 years were higher when compared with the remaining age groups. While the number and percentage of patients with asthma by age groups 20-29 years and 30-39 years were higher than in other age group. While the number and percentage of patients with AD and asthma by age group 20-29 years and 30-39 years were higher than in other age groups. The age distribution of all groups presented is Table (1).

Severe asthma was significantly higher in those with positive family history than those with negative family history of atopy, as shown in Table (2).

There was no statistically significant difference among all groups in the distribution of patients who had both asthma and atopy according to the family history and the severity of the disease as shown in Table (3).

There was no significant difference in gender distribution and severity of asthma as shown in Table (4).

There was no significant difference in gender distribution and severity of atopic asthma as in Table (5).

As shown in Table (6), atopic dermatitis was significantly higher in those with a family history of atopy.

Table 1. Age distribution of the patients and control group

Age	Smple distribution								Total	
	AD		Asthma		Both		Control group			
	No	%	No	%	No	%	No	%	No	%
<9	13	56.52			6	27.27			19	19
10-19	5	21.74	2	5	7	31.82	2	13.33	16	16
20-29	2	8.70	11	27.5	3	13.64	5	33.33	21	21
30-39	3	13.04	9	22.5	4	18.18	6	40	22	22
40-49			3	7.5	1	4.55	1	6.70	5	5
50-59			9	22.5	1	4.55	1	6.70	11	11
>60			6	15					6	6
Total	23	100	40	100	22	100	15	100	100	100

Table 2. Asthmatic patients according to the family history and severity of disease

Disease severity	Family history				Total	
	Positive		Negative			
	No.	%	No.	%	No.	%
Light intermittent	5	17.86	4	33.33	9	22.5
Light persistent	5	17.86	2	16.70	7	17.5
Moderate	3	10.71	4	33.33	7	17.5
Severe	15	53.57	2	16.70	17	42.5
Total	28	100	12	100	40	100

Table 3. Distribution of the patients had both asthma and atopy according to the family history and severity of disease

Disease severity	Family history				Total	
	Positive		Negative			
	No.	%	No.	%	No.	%
Light intermittent	5	27.78	0	0	5	22.73
Light persistent	2	11.11	1	25	3	13.63
Moderate	4	22.22	0	0	4	18.18
Severe	7	38.89	3	75	10	45.46
Total	18	100	4	100	22	100

Table 4. Gender distribution of the asthmatics patients according to severity of disease

Disease severity	Family history				Total	
	Positive		Negative			
	No.	%	No.	%	No.	%
Light intermittent	3	15.79	6	28.57	9	22.5
Light persistent	2	10.53	5	23.81	7	17.5
Moderate	5	26.32	2	9.52	7	17.5
Severe	9	47.37	8	38.10	17	42.5
Total	19	100	21	100	40	100

Table 5. Gender distribution of he asthmatic patients according to severity of disease

Disease severity	Family history				Total	
	Positive		Negative			
	No.	%	No.	%	No.	%
Light intermittent	1	9.09	4	36.36	5	22.73
Light persistent	1	9.09	2	18.18	3	13.64
Moderate	3	27.27	1	9.10	4	18.18
Severe	6	54.55	4	36.36	10	45.45
Total	11	100	11	100	22	100

Table 6.The relationship between atopic dermatitis and a family history of atopy

Family history	Atopic dermatitis	
	No	%
Positive	20	87
Negative	3	13
Total	23	100

Eosinophils were significantly higher in those with bronchial asthma and atopic dermatitis is compared with the control group, but there was no significantly difference among other groups as shown in Table (7). IFN-γ was significantly higher in those with bronchial asthma compared with control group, but there was no significant difference among other groups, this mean decrease of IFN-γ decrease in all study group, but less decrease in asthmatic patients compared with control group. There was no significant difference in total WBC count among all groups, as shown in Table (7).

Discussion

Asthma is defined as a chronic inflammatory disease of the airways that is characterized by increased responsiveness of the tracheobronchial tree to a variety of stimuli (14).

In 1925, Coke introduced the concept of atopy, meaning ”out of place” or ”strange” to

Table 7. The mean level of eosinophils, IFN-γ, and WBC count among different study groups

Simple distibution	Number	Eosinophils	IFN-γ	WBC
		Mean ±SD	Mean ±SD	Mean ±SD
AD	23	3.3±1.8	0.2±0.1	6464.5±1944.2
Asthma	40	3.2±1.7	1.1±1.3	6668.7±1856.4
Both	22	4.6±1.5	0.2±0.5	6072.3±1402.6
Control	15	2.4±1.4	0.2±0.6	6350.2±1731.1

identify the hereditary tendency to develop allergies to foods and inhalant substances. Affected families may manifest eczema, asthma, and have fever in any combination. In 1933, Wise and Sulzberger introduced the concept of atopic dermatitis, emphasizing cutaneous manifestation of the atopic diathesis (15). AD is characterized principally by dry skin and pruritus consequent rubbing leads to increased inflammation and lichenification, and to further itching and scratching; itch-scratch cycle (16).

AD is frequently the first manifestation of an atopic diathesis, which occurs in genetically predisposed individuals and also includes, asthma and allergic rhinitis. Up to 80% of children with AD will eventually develop allergic rhinitis or asthma later in childhood. This classic "atopic Triad" has numerous pathophysiologic elements in common, including cyclic nucleotide regulatory abnormalities, immune cell alteration and inflammatory mediators and allergic triggers (17). Asthma and eczema may fluctuate together, perhaps suggesting an allergic cause for both, or alternatively, usually quite independent (18).

The patern of cytokines secretion is particularly important because of the known effects of cytokines, namely IL-4 is critical for in vitro IgE synthesis, and IFN-γ inhibits IL-4 induced IgE synthesis in vitro. Moreover IFN-γ is **down-regulated** by IL-4. Induction of IgE synthesis by IL-4 may be influenced not only by IL-4 production, but also simultaneous suppression of IFN-γ (19).

The result of this study, demonstrated that AD were higher with age group less than 9 years, while asthma with age group 20-29 years, and patients with both AD and asthma, were between 10-19 years. These observations are in agreement with the finding of other investigators as Wurthrich (20), who shows that 60% of patients develop AD within the first year of life and 85% by age 5 years. However other studies by Drazen J (21) showed that asthma approximately affects 5% of adult population, most cases begin before age 25 years, but it may develop at any time through life.

These data demonstrated that severe asthma was significantly higher in those with positive family history than those with negative family history of atopy. These observations agree with the finding of other investigators.

The results of this study show that AD and severe asthma were significantly higher in those with positive family history.

The results demonstrated non-significant difference in gender distribution and severity of disease. The severity of asthma was similar in men and women.

The data demonstrated a non-significant difference among all groups who had both asthma and atopy according to the family history and severity disease. These observations are agreement with finding of other investigators as Bergmann et al. (22), who stated the AD is a risk factor for childhood asthma.

According to our study, eosinophil count was significantly higher in those with both AD and bronchial asthma as compared with the control group, but there were no significant differences among other groups. IFN-γ was significantly higher in those with bronchial asthma, but there were no significant difference among other groups, this mean IFN-γ decrease in all study groups, but less decrease in asthmatic patients, compared with group control.

Our study extends the finding observed for asthma and AD, and suggest that defect IFN-γ release is generalized feature of these diseases, also, this study indicates that the extent of defect in IFN-γ release might be related to activity disease. This finding agreement establishes that the result of the Parish and Luckhurst (23), who reported that T-cells from airways, but not from peripheral blood were obtained from asthmatic subjects release mediators that promoted eosinophil chemokinesis and chemotaxis but not chemokinesis and chemotaxis.

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