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Estimation the concentration of IL- 23, and IL-17A in the sera of patients with psoriasis in Baghdad city

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Abstract: Psoriasis is a common, chronic, disfiguring, inflammatory, hyperproliferation, and abnormal differentiation of keratinocyte, in which both genetic and environmental influences have a critical role. The study was designed to detection the levels of IL-23 and IL-17A among psoriatic patients compared with healthy group, also studied the correlation between them and some parameter such as:-age of onset and severity of psoriatic patients. Fifty psoriatic patients were selected randomly from both sexes with ages from (10-70) years. Patients were diagnosed clinically by dermatologist. Sera samples of both groups were collected from all individuals for the estimation levels of IL-23 and IL-17A by ELISA technique. All mean values sera levels (IL-23 96.74 pg/mL and 6.56 pg/mL for IL-17A) of patients were significantly higher than those of controls (18.74 and 3.01 pg/mL for IL-23and IL-17A respectively). There was a high significant in levels of patients sera of IL-23 and IL-17A, in compared with healthy control group according to these normal values. Furthermore, there was a significant correlation between the levels of IL-23, and age of disease onset among psoriatic patients. In contrast there was no significant association between the severity & interleukins (Il-23 and Il-17A). Emerging data in humans reveals a critical contribution of IL-23 and IL-17A in the pathogenesis of psoriasis. The IL-23 and IL-17A pathways were atherapeutic targets for biologic agents and systemic therapies in psoriasis treatment.

Key words : Psoriasis, IL-23, IL17A

تقدير تركيز الانترليوكين-23 والانترليوكين-17أ في مصول مرضى الصدفية في مدينة بغداد

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الخلاصة:الصدفية مرض جلدي شائع مزمن والتهابي يزداد فيه التكاثر والتمايز غير الطبيعي للخلايا المتقرنه التي يؤثر فيها العوامل الوراثية والبيئية على حد سواء بدور حاسم. صممت هذه الدراسه لكشف مستوى الانترلوكين23 والنترلوكين17أ بين مرضى الصدفية ومقارنتهم بمجموعة الاصحاء وكذالك دراسة الارتباط بينهم وبعض المتغيرات مثل عمر بداية ظهور المرض وشدة المرض لدى مرضى الصدفية. ضمت الدراسة خمسين مريضا بداء الصدفية تم اختيارهم بشكل عشوائي لكلا الجنسين وكانت اعمارهم تتراوح من (10-70) سنة. شخص المرضى سريريا بواسطة اخصائي الجلدية. وقد تم جمع العينات المصلية لكلتا المجموعتين ولكل الافراد وذلك لتقدير مستويات الانترلوكين 23 والانترلوكين 17أ بتقنية اليزا. اظهرت نتائج الدراسة اختلافات معنوية عالية في متوسطات المستويات المصلية لكل من انترلوكين 23 (74و96 بيكوغرام/مل) وانترلوكين 17أ (56و6 بيكوغرام/مل) لدى جميع مرضى الصدفية مقارنة بالاصحاء (74 و18 و 01 و3 بيكوغرام/مل) للانترلوكين 23و17أ على التوالي. كمااظهرت الدراسة وجود فروقات معنوية عالية في مستويات مصول المرضى للانترلوكينات 23 و17أ عند مقارنتها بمجموعة الاصحاء بحسب مستوياتها الطبيعية. ومن ناحية اخرى هناك ترابط معنوي بين مستويات الانترلوكين 23 وعمر بداية ظهور المرض لدى مرضى الصدفية . وهناك نتيجة مغايره بعدم وجود ارتباط معنوي بين شدة المرض ومستويات الانترلوكينات (23 و17أ). الحقائق المنبثقه من الانسان كشفت مساهمة حاسمة للانترلوكينات 23 و17أ في امراضية

داء الصدفية وان الانترلوكينات(23 و17أ) لها مسارات في الاهداف العلاجية فيما يتعلق بالعوامل الحيوية والعلاجات الجهازية في معالجة داء الصدفية.

Introduction

Psoriasis is characterized by hyperproliferation and abnormal differentiation of keratinocytes as well as vascular expansion, leukocyte infiltration, and alteration in cytokine production within the skin and systemically (1). The eruption is usually symmetrical (2). Also psoriasis affects about 1% to 3% of the general population (3,4). Two peaks of age of onset have been described; the largest is between 20 - 30 years and a smaller peak occurs between 50 - 60 years, this finding proposes that two different forms of psoriasis exist: type I psoriasis, with early disease onset before the age 40 years tend to have a positive family history of psoriasis, frequent association with histocompatibility antigen (HLA), and more severe disease. And type II psoriasis, with age of onset after 40 years usually have a negative family history, and lacking HLA association, although many patients do not fit into this classification (5).

Psoriasis is characterized by main pathogenic changes:- 1- Epidermal hyperproliferation with loss of differentiation, with up regulate of keratin 6 and keratin 16 type. 2- Dilatation and proliferation of dermal blood vessels. 3- Accumulation of inflammatory cells, particularly neutrophils and T-lymphocytes. In addition to the growth factors, cytokines, inflammatory mediator sand other biological markers which have been shown to be altered in lesional psoriatic skin (6).

Interleukin 23 together with IL-12 belongs to the IL-12 family and are both structurally related; IL-12 is formed by the p40 and p35 subunits; IL-23 consists of p40 and p19 subunits (7). Although both IL-12 and IL-23 are present in psoriasis, studies support that IL-23, rather than IL-12, is crucial in psoriasis pathogenesis (8). Interaction of IL-23-IL23R augments the proliferation of the differentiated Th17 cells characterized by the production of IL-17A and other related proinflammatory cytokines, activates NK cells, and regulates antibody production (9).

The interleukin-17 is part of a family of cytokines consisting of the prototypical ligand, IL-17 (IL-17A) and 5 other IL-17 ligands (IL-17B through IL-17F) (10). IL-17A and IL-17F are known to act as homodimers or as IL-17A/F heterodimers. Thus, these two molecules are likely to have similar biological activities (11). IL-17A and IL-17F act directly on keratinocytes to stimulate the production of a number of molecules known to be elevated in psoriasis lesional tissue such as cytokines; β-defensins; antimicrobial peptides (AMPs); and neutrophil-, macrophage-, and lymphocyte-attracting chemokines such as IL-8, CCL20 (also called macrophage inflammatory protein-3 α) and CCL2 (also called monocyte chemotactic protein 1) (12).

There is no consensus about how to classify the severity of psoriasis. Mild psoriasis has been defined as a percentage of body surface area (BSA)≤10, a Psoriasis Area Severity Index (PASI) score ≤10, and a dermatology life quality index (DLQI) score ≤10. Moderate to severe psoriasis

was defined by the same group as BSA >10 or PASI score >10 and a DLQI score >10. The Psoriasis Area Severity Index is the most widely used measurement tool for psoriasis (13).
A diagnosis of psoriasis is usually based on the appearance of the skin. Skin characteristics typical for psoriasis are scaly, red, plaques, papules, or patches of skin that may be painful and itch. There are no special blood tests or diagnostic procedures needed to make the diagnosis (14).

Aims of the Study

The study was designed to detect the levels of IL-23 and IL-17A among psoriatic patients compared with healthy group, also studied the correlation between them and some parameter such as:-age of onset and severity of psoriatic patients.

Materials and Methods

Five mL of venous blood were collected from 50 patients with plaque psoriasis. These patients attended Imamein Kadhimein medical city, outpatient clinic of Dermatology in Baghdad city (Iraq) during the period from November 2013 to May2014. The included patients had not received any treatment, topical or systemic for at least 4 months. Patients were diagnosed clinically and the disease severity was evaluated using the Psoriasis Area and Severity Index (PASI). The study also included 38 healthy individuals as a control group. Blood samples allowed for few minutes to form appropriate clot. Serum was separated by centrifuged at 1500 rpm and divided into two Eppendorf tubes for each aliquots and stored at freeze (-20°C) to be used for serological studies. Serum levels of IL-23, and IL-17A were measured by enzyme linked immunosorbent assay (ELISA) applies a technique called a quantitative sandwich immunoassay using CUSABIO (Germany) kit that contains the key components required for the quantitative measurement of natural and/or recombinant human IL-23,and IL-17A within the normal value of 6-25 pg/mL, and □3pg/mL, respectively.

Statistical Analysis

Analysis of data was carried out using the available statistical package of SPSS-20 (Statistical Packages for Social Sciences- version 20). Data were presented in simple measures of mean, standard deviation, Using independent student-t-test for difference between two means, while different percentages (qualitative data from different groups and from control group) were tested using chi-square test (χ2-test). Statistical significance was considered whenever the P value equal or was less than 0.05 (15).

Results and Discussions

The patients comprised 16 (48.6%) males and 34 (51.4%) females with males: females ration of 1:1.4. The demographic picture of the studied groups showed that the mean age of onset in psoriatic patients was 32.50±2.30 (SE) years. Family history revealed that (0.26%) of psoriatic with a previous family history for psoriatic as shown in Table (1).

Table 1:Demographic picture of the studied groups

Demographic Variables	Psoriatic patients	Healthy control
Age (Mean±SE)	36.62±2.12	34.05±1.98
Age of onset(Mean±SE)	32.50±2.30	-
Males :Females Ratio	16:34=1.43	19:19=1.1
Positivity of family history No. (%)	13(0.26)	-

Several researchers reported that psoriasis occurs in any gender or race with equal male to female ratio (16). The results showed slightly the more in females than males are similar to (17). Nowadays, it is believed that psoriasis is most likely a T helper Th1/Th17 induced inflammatory disease. Stressful life situations are known to cause flare-ups and psoriasis activity may be linked to stress from major life events. We know that stress greatly affects both the hormone and immune systems and that there are many different hormonal phases throughout a woman's life time. The severity of psoriasis may fluctuate or be influenced by each phase and this relationship can be seen as disease frequency seems to peak during puberty, postpartum, and menopause when hormone levels fall, while symptoms improve during pregnancy, a state when hormone levels are increased (18). The result of present study in the mean age of onset are similar to (19) and the age of onset was earlier in females than in males this finding is in agreement with other Iraqi studies (20).

Levels of IL-23 & IL-17A among the Studied Groups

The levels of both IL-23 and IL-17A were highly significantly (HS) ($P \leq 0.0001$) altered among the patients' group in comparison with control group as shown in Table (2).

Table 2: Levels of IL-23 and IL-17A among psoriatic and control group

Groups	IL-23 (pg/mL)		IL-17A (pg/mL)	
	Patients	Healthy Control	Patients	Healthy Control
No.	50	38	50	38
Mean	96.74	18.74	6.56	3.01
Minimum	2.70	6.80	0.50	1.08
Maximum	245.51	154.27	16.31	8.04
Standard Deviation	79.63	24.08	4.18	1.46

Standard Error	11.26	3.91	0.59	0.24
	t=5.832, p<0.0001(HS)		t=5.001, p<0.0001(HS)	

Emerging data in humans reveals a critical contribution of Th17-associated cytokines, particularly IL-23 and IL-17A in the pathogenesis of psoriasis. Considerable progress and new insights into the immunopathogenesis of psoriasis has been made over the past decade. The IL-23/Th17 pathway and its associated proinflammatory molecules, cytokines, and antimicrobial peptides stimulate the amplification of the immune response, leading to the clinical features of psoriasis. IL-23 and IL-17 are two of the key cytokines elevated in psoriatic lesions. This realization has led to the development of strategies to target these specifically as therapeutic options (21). The T helper (Th) cells -Th1, Th17 and Th22- play an important role in the pathogenesis of psoriasis. Th1 cytokines IFN-γ, IL-2, as well as Th17 cytokines IL-17A, IL-17F, IL-22, IL-26, and IL-23 are increased in serum and lesional skin (22).

Determination of human IL-23 in the Sera of psoriatic Patients and Control Group

Quantitative of IL-23 level in the sera of the studied groups revealed that there was highly significant difference between its level among patients (96.74±11.26 pg/ mL) in comparison to control group (18.74± 3.91 pg/ mL) (P≤0.0001). These data are represented in Table (2), to table (3) showed, that there was significant elevation in the level of IL-23 (94.6%) abnormal value VS (5.4%) abnormal value for control group according to its normal value was (6-25 pg/mL) .

Table 3: Distribution of IL-23 level among the studied groups

Studied Groups	IL-23pg/mL					
	Normal		Abnormal		Total	
	No.	%	No.	%	No.	%
Psoriatic patients	15	29.4	35	94.6	50	56.8
Healthy control	36	70.6	2	5.4	38	43.2
Total	51	100.0	37	100.0	88	100.0

χ^2=37.134 df= 1 p= 0.0001(HS)**

The above mentioned results were in concord with abroad studies (23, 24). More recent, Michalak-Stoma study that there was statistical analyses of the conducted study results revealed significantly higher serum levels of IL-6, IL-20, and IL-23 in psoriatic patients comparing to healthy controls (25). (Kagami; *et al.*,2010) described an increase in IL-23 expression on CD4+ T cell in peripheral blood of psoriatic patients as compared with healthy control (22). This puts the spotlight on IL-23, which is secreted by skin dendritic cells (DCs), and induces production of proinflammatory mediators by Th17 cells such as IL-17A, IL-17F, and IL-22. These

mediators will act on keratinocytes (KCs) leading to their activation and hyperproliferation (7).

Estimation of IL-17A in the Sera of psoriasis Patients and Healthy Control Groups

Estimation of IL-17A level in the sera of the studied groups revealed that there was highly significant difference between its level among patients (6.56±0.59 pg/ mL) in comparison with control group (3.01±0.24 pg/ mL) (P≤0.0001). These data are represented in Table (2).

In table (4) showed that there was a highly significant (p≤0.0001) elevation in the level of abnormal IL-17A (93%) VS (6.1% for control group) according to its normal value (□3pg/mL).

Table 4: Distribution of IL-17A among psoriatic patients and control Group

Studied Groups	IL-17A pg/mL					
	Normal		Abnormal		Total	
	No.	%	No.	%	No.	%
Psoriatic	19	34.5	31	93.9	50	56.8
Healthy control	36	65.5	2	6.1	38	43.2
Total	55	100.0	33	100.0	88	100.0

χ^2=29. 624 df=1 p= 0.0001*(HS)

Psoriatic KCs are also an important source of IL-17. Increased levels were observed in both the psoriatic skin and serum of psoriatic patients (26). Thus, level of IL-17A in patients group was elevated in comparison with healthy group, which is compatible with other Iraqi study, The study reveals that the level of IL-17 was higher in patients with psoriatic than that of control group (17). This observation supports the hypothesis that the high level of IL-17 may be critical mediators of the persistently altered epidermal growth and differentiation and local inflammation that was characteristic of psoriasis and Th17 cells may be proximal regulators of psoriatic skin inflammation (27). However, many other studies were support this result, they found that the IL-17 level was increased in lesional tissue and serum of psoriatic patients (28). The current result was supported by the facts mentioned by Bovenschen; *et al.* (2011), have been reported to have increased circulating IL-17A producing cells in patients with psoriasis (29). The central role of IL-17 in psoriasis pathogenesis this inflammatory elements that establish a self-reinforcing cycle, including Th17 skewing of naive T cells in the presence of IL-23 leading to the local production of IL-17 ligands. Keratinocytes in turn are stimulated by these IL-17 ligands leading to an

aberrant differentiation program and elevated production of proinflammatory factors including AMPs and chemokines (including CCL20, which attracts both Th17 cells and DCs). These keratinocyte-derived factors in turn stimulate further recruitment of inflammatory cells, including IL-17 producing cells, and establish a self-sustaining inflammatory feedback loop (30).

Distribution the Severity of Psoriatic Patients

In this study the majority (31) of the psoriatic patients (62%) presented with mild disease, while the (15) patients (30%) presented with moderate disease, and the remainder were severe disease group consist of (4) patients (8%) according to Psoriasis Area Severity Index (PASI) score that showed in figure (1).

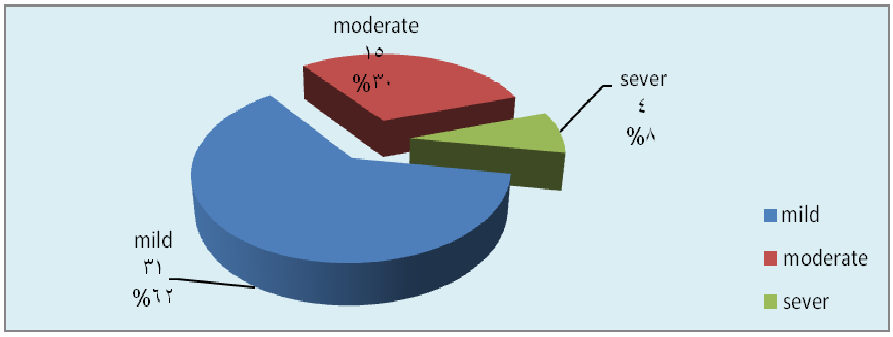

Figure 1: Severity distribution among psoriatic patients

The severity yielded from studied sample was compared with a recent study of psoriatic patients selected from Iraqi patients in Mosul city by AL-Ashow; *et al*. (2012), which show the following : 74 (48.1%) of cases had mild psoriasis, 54 (35.1%) had moderate, and the 26 (16.8%) were considered as severe cases (31). The present study to some extent is in agreement with US study. Minor difference may be due to variation in the severity assessment between researchers (due to lack of standardized severity assessment method) and variation in the course of disease (due to the nature of psoriasis to wax and wane) (32).

Frequencies of severity & some parameters among psoriatic patients

However, there was no significant relationship between the severity and different parameters except for family history revealed that there was a significant difference between its and the severity of disease (p□0.05) in psoriatic patients. Also there was no significant difference between the

disease severity and the levels of IL23 & IL-17A according to these normal values of IL-23 (6-25pg/mL) and IL-17A (□3pg/mL) in patients group were occur was listed in table (5).

Table 5: The relationship between the severity and different parameters in psoriatic patients

Parameters		SEVERITY								
		Mild		Moderate		Sever		Total		P.Value
		No.	%	No.	%	No.	%	No.	%	
Gender	males	10.0	32.3	5.0	33.3	1.0	25.0	16.0	32.0	0.950
	females	21.0	67.7	10.0	66.7	3.0	75.0	34.0	68.0	
	Total	31	100	15	100	4	100	50	100	
Family history	yes	4.0	12.9	7.0	46.7	2.0	50.0	13.0	26.0	0.026*
	No	27.0	87.1	8.0	53.3	2.0	50.0	37.0	74.0	
Age of onset	<40	14.0	45.2	9.0	60.0	3.0	75.0	26.0	52.0	0.404
	≥40	17.0	54.8	6.0	40.0	1.0	25.0	24.0	48.0	
	Total	31	100	15	100	4	100	50	100	
IL23pg/mL	Normal	10.0	32.3	4.0	26.7	1.0	25.0	15.0	30.0	0.904
	Abnormal	21.0	67.7	11.0	73.3	3.0	75.0	35.0	70.0	
IL17pg/mL	Normal	12.0	38.7	6.0	40.0	1.0	25.0	19.0	38.0	0.853
	Abnormal	19.0	61.3	9.0	60.0	3.0	75.0	31.0	62.0	
	Total	31	100	15	100	4	100	50	100	

Although, the levels of IL-23 and IL-17A were increase but there was no significant association between them and severity of disease. However there was a significant difference between family history and the disease severity. The present results was agreement with (33,34). On the contrary, some studied showed the evaluated association with serum levels of some proinflammatory cytokines and their correlation with severity of psoriasis in Turkish population (35). The variations between the present results comparing with recent studies may be related to the differences in sample size, to the specific morphological structure of their skin, or the specific Iraqi nature which increased the stress in the subjective nature and that related to adverse life events. The diagnostic features may not all be present at the same time in every case and are some times obscured or evanescent (36).

Pearson General Correlations of the studied parameters

The association study of the different parameters was listed in Table (6). This table revealed that there was a highly significant correlation between age of onset and the age of patients (P≤0.0001) and significant association between age of onset and IL-23 level (P □0.05).
Also the relationship between the levels of IL-23, and IL-17A among the studied groups revealed that there were highly significant difference (p≤0.0001).

Table 6: Correlation Coefficients among the studied Parameters in the Study sample

Studied parameters	Pearson Correlation	Age of onset	IL-23	IL-17A
Age	Pearson Correlation	0.906(**)	0.172	0.129
	Sig. (2-tailed)	0.0001	0.108	0.231
Age of onset	Pearson Correlation	1	0.290(*)	0.224
	Sig. (2-tailed)	.	0.041	0.118
IL-23pg/mL	Pearson Correlation		1	0.607(**)
	Sig. (2-tailed)		.	0.0001

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

The current result was supported by the facts mentioned by Di-Meglio; *et al.* (2013), spearman□s correlation was used to correlate IL-23 levels with those of IL-17A,IL-22,IL-F,and IFN-γ. Values of p□0.05 were considered significant (37). Also Michalak-Stoma; *et al.* (2013), found a significant positive correlation between the IL-23 and IL-17 values was p□0.05 (25). An increase in the IL-23 concentration was accompanied by an increase in the IL-17 concentration. In previous studies, it was found that interaction of IL-23 with its receptor on Th17 cells stimulates the production of IL-17 and other related proinflammatory cytokines activates NK cells and regulates antibody production (7). It is difficult to draw conclusions and very difficult to compare data obtained in different laboratory conditions. It could be argued that plasma levels of examined cytokines were already performed and published a few times but one has to bear in mind also the fact that cytokine evaluation results may vary due to different assays, individual variation in the stage of disease, demographic differences, and coexisting pathologies (36). The discovery of the IL23/Th17 pathway and the subsequent development of new treatments have been major breakhrough and better insight into psoriasis immunopathogenesis does not only lead to improved treatments for psoriasis but may also provide better understanding of pathological mechanisms behind other autoimmune diseases such as Crohn's disease and better therapeutic treatments for these diseases (38).

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