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Incidence of Toxoplasmosis in Psoriasis Patients and Possible Correlation with Tumor Necrosis Factor-α

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Abstract:

Toxoplasma gondii is an opportunistic parasite in immune-compromised persons. The prevalence of toxoplasmosis in psoriasis patients is investigated. In addition, the treatment effect on psoriasis patients infected with toxoplasmosis through evaluating Tumor Necrosis Factor-α (TNF-α) cytokine levels is studied. Blood samples were collected from 130 individuals who involved 60 control samples and 70 samples with psoriasis. They attended Medical City Hospital in Baghdad province from October 2017 - February 2018. Then, the anti- *T. gondii* antibodies (IgM and IgG) and TNF- α in the sera were determined via the enzyme linked immune-sorbent assay. The highest rate of anti-*Toxoplasma* IgG was in psoriasis patients before treatment, it was 45 (64.29%) compared with the control which was 33 (55.00%), while the highest sero-positive rate of *T. gondii* IgM in the control group was 14 (23.33%) compared with patients with psoriasis 10 (14.29%). The highest rate of toxoplasmosis was in the age group (21-30) years in psoriasis patients which was 14 (31.82%). In addition, the TNF- α levels in psoriatic patients before treatment were 180.2±2.2 µg/ml, and after treatment were 223.3±41.1 µg/ml compared with the healthy control group 90.5±1.9 µg/ml. These findings suggest that incidental rate of toxoplasmosis is higher in psoriasis patients. Thus, the incidental rate of toxoplasmosis could be considered as an indication to the high risk of psoriasis.

Key words: Psoriasis, Toxoplasmosis, Tumor Necrosis Factor - alpha.

Introduction:

Toxoplasma gondii is a protozoan parasite that infects one-third of human worldwide (1). *T. gondii* in humans is usually acquired through the ingestion of tissue cysts when the undercooked meat infected with *T. gondii* is eaten; though, the infection could also occur by eating the parasite's oocysts that spread from the cat feces or through unclean water (2). This parasite grows as a cyst particularly in muscle and brain tissue throughout life, causing a chronic infection (3). The pathology of toxoplasmosis can range from an asymptomatic in immune-competent individuals to severe symptom present in immune-compromised hosts (4). The incidence of reactivated toxoplasmosis relies on the prevalence and concentration of IgG antibodies. It is necessary to obtain information concerning the prevalence of *T. gondii* infection in different populations worldwide (5).

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Psoriasis is a chronic skin infections affecting 2–3% of the population. Up to now, there is no treatment known against this disease, but there are many cures that can reduce the consequences of this disease (6). This disease is caused by a complex interaction of the genetic and environmental factors. Psoriasis could also involve the joints inflammation in psoriasis arthritis, increased cardiovascular risk thus, increasing the risk of mortality (7). Psoriasis clinically symptom presented as an erythematous plaques with irregular margins and silvery scales. This disease equally affects the upper and lower extremities, but it commonly occurs in the elbows, knees, scalp, and trunk (8). Psoriasis can be triggered by some parasites and bacteria. A research finding revealed that the prevalence of *Helicobacter pylori* was significantly higher in psoriasis patients. Some of the worms like *Asacris*, hookworm, flat worms, liver flukes established in the gut produce toxins that cause psoriasis. Yeast, fungi and chronic bacterial infections also contribute to the skin disease like psoriasis (9).

Psoriasis occurs as a result of the deregulated interactions of the non-specific and

specific immune system and the main site for this deregulation is connective tissue and skin epithelium (10). Cytokines, consisting of T helper1-related Tumor Necrosis Factor- alpha (TNF- α), interferon gamma (IFN-γ) and interleukin-2 (IL-2); all these cytokines are elevated in psoriatic patients sera (11). TNF-α is a dynamic pro-inflammatory cytokine having pleiotropic actions on numerous cell kinds and an important role in the chronic disease pathogenicity. TNF-α is secreted by different cell kinds including immune cells like (B cells and T cells, natural killer cells, basophils, dendritic cells, eosinophil, neutrophil and mast cells), non-immune cells (astrocytes, granuloma cells, fibroblasts, glial cells, and keratinocytes) (12). TNF-α expand inflammation through numerous distinct pathways. The entrance of inflammatory cells to the lesional skin occurs through stimulating the adhesion molecules on endothelial cells of blood vessels (13) and finally dendritic cells and dermal macrophages cells activated by its action. Recent research has revealed that the inhibition effect of TNF-α in healing psoriasis has been reefed to the inhibitory effect of Th17 T cells (14). On the other hand, the innate immune response to *T. gondii* has the capability to sense the pathogen and secrete the IL-12, which motivates natural killer (NK) cells and T cells to secrete the interferon-gamma (IFN-γ) (14, 15). IFN- γ and TNF-α are acted to facilitate the killing of tachyzoites by macrophages.

The treatment of psoriasis depends on disease severity; it includes topical therapies for slighter disease, phototherapy for moderate disease and biological agents for patients with severe skin disease. Etanercept (ETN) (Enbrel trade name) is one of the biological therapies of psoriasis (16). It was the first TNF-α inhibitor to be used for psoriasis treatment. ETN is a soluble, Dim Eric, fusion protein composed of the extra-cellular ligand binding part of the TNF-α receptor attached to the Fc part of human IgG1. ETN has a capacity to binding, neutralizing, and inhibit soluble TNF-α (17). This study investigates the possible relationship between psoriasis and *T. gondii* infection via evaluating the sero-positivity rate of anti *T. gondii* antibodies. In addition, the treatment effect on psoriasis patients infected with toxoplasmosis through evaluating Tumor Necrosis Factor-α (TNF-α) cytokine levels is studied.

Material and Methods:

One hundred and thirty individuals were enrolled in this study (60 control samples and 70 psoriasis patients). The psoriasis samples included treated patients with 8mg/week of Etanercept and untreated patients. The patients attended from different provinces in Iraq to Teaching Hospital in the Medical City Hospital, Dermatology and Venereology Department in Baghdad during October, 2017- February, 2018.

Five ml of blood samples were collected from patients and control groups. The blood was retained in Gel Clot tubes and allowed to clot at 25 ºC. For serum aspiration, the samples were centrifuged at 3000 round per minute for 10 minutes and distributed into three eppendorf tubes by using micropipette. For future immunological analysis, the samples were stored at -20 ºC.

Different laboratory kits were used in this study, the level of anti-*T. gondii* IgG and IgM antibodies were read through the ELISA technique using the obtainable kits (The human Infected *Toxoplasma* IgG EIA (I231-1091), the human *Toxoplasma* IgM EIA (I231-1101) and Toxo- latex (Spin react. Spain) were used according to the manufactures instructions. Moreover, TNF-α was evaluated using TNF-α Human ELISA Kit, Demeditec, Germany.

Data Analysis

The Statistical Analysis System- SAS (2012) program was used for data analysis. Chi-square test was used to significantly compare between percentages. P value <0.05 was considered statistically significant (18).

Results and Discussion:

During the three months of the study period, 60 samples of blood were collected as control group and 70 psoriasis patients. Using latex agglutination test, the current study showed that the higher percentage of toxoplasmosis was in psoriasis patients which was (74.29%) compared with the control group which was (68.33%) (Table 1).

Table 1. Comparison between control and psoriasis group in results of toxoplasmosis infection using Latex test.

Studying groups	Toxo (-)		Toxo (+)		P-value
	No	%	No	%	
Control (No. 60)	19	31.67	41	68.33	0.0001 **
Psoriasis (No. 70)	18	25.71	52	74.29	0.0001 **
P-value	0.0934 NS		0.0934 NS		---

** (P<0.01), NS: Non-Significant.

The presence of acute toxoplasmosis is characterized by the presence of positive anti- *T. gondii* IgM antibodies while the chronic infection is characterized by the presence of anti- *T. gondii* IgG. Chronic infection in psoriatic patients treated

with ETN recorded 25 (71.43%) sero-positive, 10 (28.57%) sero-negative anti-*Toxoplasma* IgG antibodies comparing with 20 (57.14%) sero-positive, 15 (42.86%) sero-negative anti-*Toxoplasma* IgG antibodies in untreated patients, 33 (55.00%) sero-positive, and 27 (45.00%) sero-negative anti-*Toxoplasma* IgG, in healthy control (Table 2). The results revealed that the psoriatic patients cured with ETN had a higher percentage of toxoplasmosis IgG.

Table 2. Comparison between studying groups in results of anti-*Toxoplasma* IgG using ELISA test

Studying groups	IgG (-)		IgG (+)		P-value
	No.	%	No.	%	
Control	27	45.00	33	55.00	0.0472 **
Psoriasis before treatment	15	42.86	20	57.14	0.0086 **
Psoriasis after treatment	10	28.57	25	71.43	0.0001 **
P-value	0.0097 **		0.0097 **		---
* (P<0.05), ** (P<0.01)					

The current study showed the psoriatic patients treated with ETN have (8.57%) seropositive anti-*Toxoplasma* IgM antibodies compared with the untreated patients who have (20.00%) seropositive anti- *Toxoplasma* IgM antibodies (Table 3).

Table 3. Comparison between studying groups in results of anti-*Toxoplasma* IgM using ELISA test.

Studying groups	IgM (-)		IgM (+)		P-value
	No.	%	No.	%	
Control	46	76.67	14	23 .33	0.0001 **
Psoriasis before treatment	28	80.00	7	20.00	0.0001 **
Psoriasis after treatment	32	91.43	3	8.57	0.0001 **
P-value	0.0287 *		0.0287 *		---
* (P<0.05), ** (P<0.01)					

In addition, the results showed that the psoriatic patients have a high percentage (64 .29%) of seropositive anti-*Toxoplasma* IgG antibodies compared with the control group who have (55.00%) seropositive anti- *Toxoplasma* IgG antibodies. On the other hand, a high percentage (14%) of seropositive anti-*Toxoplasma* IgM antibodies in the control group was found compared with the psoriatic patients who have (10%) seropositive anti- *Toxoplasma* IgM antibodies (Table 4).

Table 4. Comparison between anti-*Toxoplasma* IgG and IgM antibodies in the control and psoriasis groups.

Antibody	Control		Psoriasis		P-value
	No.	%	No.	%	
Anti- *T. gondii* IgG (+)	33	55.00	45	64 .29	0.0437 *
Anti- *T. gondii* IgM (+)	14	23.33	10	14.29	0.0448 *
P-value	0.0095 **		0.0001 **		---
* (P<0.05), ** (P<0.01).					

Considering the age of the studied group, a significantly higher percentage of toxopalsmosis (IgG) was noted in psoriatic patients aged between 21-30 years (31.82%), (9.09%) respectively when compared with the other age groups (Table 5).

Table 5. Distribution of the sample study according to age groups in control and psoriasis pateints.

Age group (year)	Control IgG (+) (No. =33)	Psoriasis patients IgG (+) (No. =45)	P-value
0-10	1 (3.03%)	0 (0.00%)	0.319 NS
11-20	3 (9.09%)	8 (18.18%)	0.0426 *
21-30	18 (54.55%)	15 (31.82%)	0.0072 **
31-40	8 (24.24%)	6 (13.64%)	0.0398 *
41-50	2 (6.06%)	9 (20.45%)	0.0251 *
51-60	1 (3.03%)	7 (15.91%)	0.0294 *
P-value	0.0001 **	0.0001 **	---
* (P<0.05), ** (P<0.01), NS: Non-Significant.			

The results documented that serum TNF-α levels elevated significantly (P<0.01) in sera of psoriatic patients (before treatment) which was 180.2±2.2 µg/ml while it was 223.3±41.1 µg/ml in sera of psoriatic patients (after treatment) in comparison with healthy control group 90.5±1.9 µg/ml. Also the results revealed a significant difference (P<0.05) between psoriatic patients before and after and after treatment (Table 6).

Table 6. The mean concentration of TNF-α in serum of the studied groups.

Studying groups	TNF-α mean concentration (µg/ml)	P-value
Healthy control	90.5±1.9	0.01 **
Patients with toxoplasmosis	98.09±1.3	0.05*
Psoriasis patients infected with toxoplasmosis before treatment	180.2±2.2	0.01 **
Psoriasis patients infected with toxoplasmosis after treatment	223.3±41.1	0.01 **

* (P<0.05), ** (P<0.01)

Infection with *T. gondii* is usually asymptomatic, but it can be life threatening in immune-deficient patients. It is generally assumed that 25-30% of the world's human population is infected by *T. gondii*. Toxoplasmosis was raised up after Iraq occupation with more than 40% compared to the eighties, when the incidental rate of toxoplasmosis was 2% of the women tested at that time (19).

Psoriasis is chronic and wide spread disease all over the world that mediated the immune response in the skin with systemic pro-inflammatory activation. The environmental and genetic factors are responsible for its pathogenesis (20). Several researches declared a probable relationship between the infection of parasites and psoriasis. High levels of IgG antibodies in comparison with the levels of IgM antibodies are steady with chronic latent infection that usually develops in previous time. *T. gondii* was higher in a population with psoriasis compared with population without psoriasis disease. This result may be due to the fact that the susceptibility to infect with parasites increased in psoriasis patients (9, 21).

The diagnosis of toxoplasmosis generally depends on the clinical and laboratory records. In clinical records, the serological essays are routinely detected IgM and IgG specific antibodies using ELISA test that shows a high sensitivity and specificity. Serological essays are helpful because the lack of anti-*T. gondii* IgM practically excludes recent infection in immune-competent patients (22).

Several studies have verified an association between the sero-prevalence rates of toxoplasmosis with age. This study revealed that the highest positive levels were found in age 21-30 years patients group. The increase in quantitative titers with age could be due to the increasing disclosure years as the humans get older. Several insignificant infections could yield low antibody rates at first and higher rates later (23).

The current study showed that the serum levels of TNF-α in psoriatic patient were significantly increased comparing with healthy control group. Recent studies have denoted that TNF-α has a role in the pathogenesis of the psoriasis disease (24, 25, 26). Patients with active skin disorder have increased concentrations of TNF-α in both skin lesion and blood (13). Also the levels of TNF-α interestingly elevated in psoriatic patients treated with ETN compared with the concentration of TNF-α to patients before treatment (Table 6). Cells provisionally produce TNF-α in their plasma membrane that is bearing the cells by antibody dependent cell cytotoxicity (ADCC) (27, 28). ETN has the Fc part of IgG1 which can trigger ADCC (28). On the other hand, *Toxoplasma* infection suppresses the production of TNF-α in order to initiate the infection (29).

Conclusion:

In the present study, high serum concentrations of TNF-α in psoriatic patient after treatment could result from the accumulation of TNF-α in serum patients due to the role of ETN drug in the blocking TNF-α receptors on skin cells. On the other hand, when an individual is infected with psoriasis disease and treated with ENT, he will be under risk of toxoplasmosis. Thus, due to the immunodeficiency and opportunistic toxoplasmosis infections, psoriatic patients have to sporadically test for toxoplasmosis to avoid the potential consequences of this infection.

Conflicts of Interest: None.

The author has signed on animal welfare statement.

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الاصابة بداء المقوسات في مرضى الصدفية وعلاقته مع عامل نخر الورم- α

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الخلاصة:

المقوسات الكوندية هي طفيليلت اجبارية داخل خلوية وتعتبر طفيليًا غازيا في الأفراد الذين يعانون من نقص المناعة. تهدف هذه الدراسة تحديد مدى انتشار داء المقوسات في مرضى الصدفية. بالإضافة إلى ذلك ، دراسة دور العقاقير البيولوجية ETN في نشاط الصدفية وداء المقوسات من خلال تقييم عامل نخر الورم - ألفا (TNF- α) قبل وبعد العلاج في المرضى من مختلف الأعمار والاجناس. تم جمع عينات الدم من 130 شخصا من بينهم 60 عينة كمجموعة سيطرة و 70 عينة لاشخاص مصابين بالصدفية يراجعون مستشفى مدينة الطب في محافظة بغداد من شهرأكتوبر 2017 إلى شهريناير 2018. تم اختبار الأمصال لتحديد الأجسام المضادة لداء المقوسات (IgM و IgG) وعامل نخر الأورام - ألفا (TNF- α) باستخدام الإنزيم المرتبط وقد لوحظ أعلى معدل إيجابي للاجسام المضادة لداء المقوسات (IgG) في المرضى الذين يعانون من الصدفية قبل المعالجة والتي كانت 45 (64 .29٪) مقارنة مع السيطرة التي كانت 33 (55.00٪) ، في حين كان أعلى معدل إيجابي للمصل ولوحظ للاجسام المضادة لداء المقوسات (IgM) في مجموعة السيطرة 14 (23.33 ٪) مقارنة مع المرضى الذين يعانون من الصدفية 10 (14.29 ٪). وفقا للفئات العمرية ، كان معدل الانتشار المصلي لمرض المقوسات الكوندية الأعلى في الفئة العمرية (21-30) سنة في مرضى الصدفية التي كانت 14 (31.82٪). بالإضافة إلى ذلك ، كانت مستويات الـ TNF- α في مرضى الصدفية قبل المعالجة 180.2 ± 2.2 ميكروغرام / مل ، وبعد المعالجة كانت 223.3 ± 41.1 ميكرغرام / مل مقارنة مع مجموعة السيطرة الصحية 90.5 ± 1.9 ميكروغرام / مل. هذه النتائج تشير إلى أن معدل داء المقوسات هو أعلى في مرضى الصدفية. وبالتالي ، يمكن اعتبار الاصابة بداء المقوسات مؤشرا على ارتفاع مخاطر الإصابة بالصدفية.

الكلمات المفتاحية: الصدفية، داء المقوسات، عامل نخر الورم - ألفا.