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The Role of IL-6 and IL-17 in Patients with Toxoplasmosis in Baghdad, Iraq

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A B S T R A C T

Toxoplasma gondii is one of the most frequent human zoonosis, infecting around a third of the world's population. Aim of the study: The present study was carried out to evaluate the role of serum level of IL-6 and IL-17 in aborted women infection with *Toxoplasma gondii*. Sixty aborted women (patients) and also thirty apparently healthy women as a control group were involved in present study. The women were between 20 to 43 years of age, all were attend Medical Centers in Baghdad city, during the period from 1st October 2021 till 15th August 2022. The interleukins that were measured by ELISA test were Interleukin-6(IL6), and Interleukin-17(IL17). The study showed a high significant increase in serum level of IL-6 and IL-17 in patients (27.45 ±3.19,218.02 ±23.97Pg/ml) respectively, when compared with serum levels in control group (9.52 ±0.96pg/ml, 24.31 ±2.35pg/ml) respectively, The role of IL-6 and IL-17 in the immune response against toxoplasmosis was studied, it was found that there was a concomitant increase of IL-6 with the increase of IL-17. A significant elevation levels of IL-6 and IL-17 in aborted women with toxoplasmosis in comparison with healthy women. That demonstrates the significance of these interleukins in stimulating or impressing immune response and resistance to toxoplasmosis.

Introduction

Toxoplasma gondii (*T. gondii*), an obligate intracellular protozoan related to phylum Apicomplexa, is a zoonotic protozoan capable to infect different animals and humans, causing widespread disease called toxoplasmosis (Riyadh A. Alzaheb, 2018). Dietary habits, geographical environments of the country and the immunity of the host play important roles in the seroprevalence of toxoplasmosis in human (Samaneh Abdolahi Khabisi *et al.*, 2022).

Toxoplasmosis globally widespread is likely to be due to its multiple methods of transmission and protozoan developed with different hosts (Lamberton *et al.*, 2008). Humans obtain toxoplasmosis through, ingestion of oocysts in soil, contaminated vegetables and fruits or drinking contaminated water, and through eating of undercooked or raw meat containing viable tissue cysts (Flegr *et al.*, 2014; Jitender P. Dubey, 2021). Although infection with *T. gondii* is commonly asymptomatic, it can resulting in chorioretinitis and cervical lymphadenopathy in immunocompetent

persons. However, in immunocompromised persons, this infection can potentially cause death in high-risk groups, including immunodeficient individuals and pregnant women (LID, 2012).

In immunocompetent humans, most primary infections with *T. gondii* are asymptomatic or cause moderate signs including fever, swelling of lymph nodes and malaise. Toxoplasmosis of severe complications, such as encephalitis, can occur in immune-compromised patients. Moreover, other complications such as ocular toxoplasmosis, particularly retinochoroiditis, and fatal multivisceral sequels related with atypical genotypes can develop regardless of the immune condition of the host. In pregnant women primary toxoplasmosis can cause heavy damages to the foetus and may cause in irreversible conditions like abortion and severe neurodevelopmental malformations such as microcephalyand hydrocephaly (Aref Teimouri *et al.,* 2022). Acute infections in immune-competent pregnant women are usually asymptomatic, but 10% of women may also present different symptoms like headache, fever, flu-like illness, lymphadenopathy, chorioretinitis and myositis (Abdlhadi, 2005).

Toxoplasmosis promote cell mediated immune response and humeral immunity like antibody production, which contains IgM and IgG antibodies. Acute toxoplasmosis is suspected if the *Toxoplasma* IgM antibody is positive. Chronic toxoplasmosis is suspected by IgG positivity (Su *et al.,* 2010). Cytokines are essential for the normal development of pregnancy, any imbalance in the amount or position of expression can effect on trophoblastic and endometrial reactions leading to pregnancy complications (Stebegg *et al.,* 2018). The early stimulation of neutrophil production during toxoplasmosis is dependent on IL-17-mediated signaling. The neutrophils has been recorded to be critical for successful in the innate immune response (Yisong and Richard, 2009). It's clear the protozoans during early stages of toxoplasmosis for thus adaptive immune response, which is induce later, is not effective (Kelly *et al.,* 2005). Protozoan load is not efficiently reduced, when the presence of neutrophils levels were low, for thus adaptive immune response is cant to handle this high burden, which finally cause mortality (Kareem G. Mohammed *et al.,* 2012). Different researchers found that neutrophils play an necessary role in innate immune response to *T. gondii* infection (Bennouna *et al.,* 2003; Bliss *et al.,* 2001), many studies were performed to describe the initial cellular sources of IL-17 during *T. gondii* infection. The T and B cells, revealed that natural killer(NK) cells were main sources to the induction of IL-17. This result led to other experiments that established that many of the events that induce T cell secretion of IL-17 also stimulate the secretion of this interleukin from NK cells. As well as, these findings highlight the notable role of IL-6 in this regulatory passage and characterize a new role for this pleotropic interleukin during innate immune responses to *T. gondii* protozoan (Sara T. Passos, 2010).

Materials and Methods

Patients and Control

The study contained ninety women: Sixty aborted women (patients) and thirty women with close ages who had no abortion were considered as a control group. All were attended Medical Centers in Baghdad City, during the period from 1st October 2021 till 15th August 2022. Their age ranged between (20-43) years.

Sample collection and Examination

Five milliliters (ml) of venous blood sample was collected from the ninety women under sterile condition, put in gel tube and left at room temperature then undergone centrifugation at 1000 rpm for 15 minutes. The serum was collected in plain tubes and stored at -20 ^{o}C until be used to detect IgM, and IgG by Enzyme linked immunosorbent assay (ELISA) test: Antibodies of *T. gondii* finding by ELISA kits (ToxoIgMDiaSino, catalog No. 180602, ToxoIgGDiaSino, catalog No. 180601), are a qualitative detection of human

serum/plasma of Toxoplasma antibodies. Then (Interleukin-6 and Interleukine-17) measurement by using ELISA kits (IL-6 China, catalog No. E0090Hu, IL-17 China, catalog No.E0142Hu). These tests were completed according to the manufacturer's specifications.

Statistical Analysis

The data for the studied characteristics were analyzed according to the analysis of variance of a factor experiment that was applied. T- test was used to significant compare between means and chi-square test was used to significant compare between percentage (0.05 and 0.01 probability in this study) (SAS, 2011).

Results and Discussion

The present study included 90 women, who included: Patients (60 aborted) women and (30 healthy) women as control groups. Patients and control are identical with regard to age and differ in mean of abortion (1.63 ±0.11-0.00 ±0.00) respectively, as shown in (Table 1). The seroprevalence data obtained are shown in Tables (2 and 3). It had been found that the positive anti-*Toxoplasma* antibodies IgM only presented in 13 aborted women (21.67%) and IgG in 39 aborted women (65%), these findings recorded an overall 52 positive toxoplasmosis for IgM and IgG antibodies in aborted women. While the control group were 0% for IgM and IgG antibodies. Table (4) showed high significant differences ($P<0.01$) in mean ofIL-6 and IL-17 in toxoplasmosis aborted women were (27.45 ±3.19, 218.02 ±23.97Pg/ml) respectively, when compared with mean of IL-6 and IL-17 in control group (9.52 ±0.96, 24.31 ±2.35Pg/ml).

Toxoplasmosis is the infection and disease in human and animal, it is responsible for congenital birth defects and toxoplasmic encephalitis (18), at birth retinochoroiditis, or central nervous system involvement, with a risk of late present of ocular infections (Wallon and François, 2018). In present study patients and control are identical with age and healthy control with no abortion. The ELISA test for the presented of IgM and IgG anti-*Toxoplasma* antibodies was selected in this study, due to the realty that in early infections, IgM antibody level mostly elevated within seven to fourteen days of infection. Then the presence of increased levels of *T. gondii* specific IgG antibody detect that toxoplasmosis has found but does not differentiate between acute and chronic infections (Sensini, 2006). The results of present study were agreement with a study done by Aziz and Drueish, in (2011) among patients recorded, 25 (59.5%) women were IgG positive, and 17 (40.5%) women were IgM positive (Aziz and Drueish, 2011), and in other study showed high infection of positive IgM, and IgG56.2% in abortion women (Baqer and Alhadi, 2022). As well as Anwar and Nuha, in (2017) recorded a low rate of positive *T.gondii* IgG and IgM antibodies in sera of aborted women (38.15%) in Samara city (Anwar and Nuha, 2017). *Toxoplasma gondii* is an opportunistic protozoan with cosmopolitan in distribution that stimulates an innate immunity characterized by immediate induction of neutrophils to the site of infection, followed by production of proinflammatory cytokines related with a strong Th1 protective response (Rachel Guiton *et al.,* 2010). In present study, patients women had a higher level of IL-6 as compared to healthy women, which appear to confirm the finding of an inflammatory status. The main role of IL-6 is the included in the immunity through the action on lymphocytes B. It is a mediator responsible for the induction of early proteins and increased cytotoxic activity of NK cells. IL-6 is an acute and nonspecific, as well as sensitive marker of inflammatory states (Jonathan S Silver *et al.,* 2011). Previous study have recorded a major role for IL-6 in immune response to *T. gondii* (Jebbari *et al.,* 1998), and these findings are consistent with its role as a pro-inflammatory factor. Other studies have recorded the major role of IL-6 and IL-27 signaling in stimulating the generation of IL-10-producing CD4+ T cells that are main for resisting infection-induced pathology (Awasthi et al., 2007; Anderson *et al.,* 2009). The trans membrane protein gp130 is a signal transducing

component of the receptors used by various closely associated cytokines that include IL-6. IL-6 and gp130 are essential for the development of a protective immunity that allows the host to control protozoan multiplication. For thus, IL-6 contribute to the control of pathogen multiplication or limit pathology (Murtada Hafedh Hussein and Moslim Mohsin Khalaf, 2022).

Table.1 Comparison between patients and control groups in Age and Abortion

Group	Mean ± SE	
	Age (year)	Abortion
Patients	31.98 ±0.78	1.63 ±0.11
Control	31.73 ±1.20	0.00 ±0.00
LSD value	2.786 NS	0.307 **
P-value	0.858	0.0001
** (P≤0.01), NS: Non-Significant.		

P: Probability, **NS:** Not significant.**= highly significant

Table.2 Seroprevalence of anti- *Toxoplasma gondii* antibody IgM in patients and control

ToxoIgM		No	Percentage (%)
Patients	Positive (+)	13	21.67
	Negative (-)	47	78.33
	Total	60	100
Control	Positive (+)	0	0
	Negative (-)	30	100
	Total	30	100

Table.3 Seroprevalence of anti- *Toxoplasma gondii* antibody IgG in patients and control

ToxoIgG		No	Percentage (%)
Patients	Positive (+)	39	65.00
	Negative (-)	21	35.00
	Total	60	100
Control	Positive (+)	0	0
	Negative (-)	30	100
	Total	30	100

Table.4 Comparison between toxoplasmosis patients and control groups in IL-6 and IL-17

Positive cases (count)	Mean ± SD	
	IL-6 (Conc. Pg/ml)	IL-17 (Conc. Pg/ml)
Toxoplasmosis patients (IgM+IgG positive)	27.45 ±3.19	218.02 ±23.97
control	9.52 ±0.96	24.31 ±2.35
T-test	7.062 **	58.711 **
P-value	0.0018	0.0001
**** (P≤0.01).**		

SD: Standard Deviation

While the role of IL-17 in different infectious diseases is an emerging region of interest. Using IL-17RA–deficient mice, its provide strong proof for a harmful role of the IL-17 receptor signaling pathway during toxoplasmosis (Rachel Guiton *et al.,* 2010). In present study, patients women had a higher level of IL-17 as compared to healthy women, which appear to confirm the finding in other study, who found that an early increase in IL-17 had been reported in infection with *T. gondii* (Gazzinelli *et al.*, 1993). Ye *et al.,* found that IL-17 was implicated in the development and acute recruitment of neutrophils, which are the main to clear the protozoan during acute toxoplasmosis, in case of animals without IL-17 gene are more liable to oral toxoplasmosis (Kelly *et al.,* 2005). T-helper-17cells are a recently detected class of effector T cells that attracting much attention newly, while it was accepted that Th17 is a T cell lineage distinct from Th1 and Th2, and its evolution in relation to Th1 and Th2 is under discussion. Interleukin-17 is secreted by Th-17cells. In addition to its role in resistance and clearance of many parasites, IL-17 expression has been also presented to be related with many autoimmune diseases such as multiple sclerosis and psoriasis (Nurieva *et al.,* 2007).

A significant elevation levels of IL-6 and IL-17 in aborted women with toxoplasmosis in comparison with healthy women. That demonstrates the significance of these interleukins in stimulating or impressing immune response and resistance to toxoplasmosis.

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