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Seroprevalence of *Toxoplasma Gondii* in Parkinson's Disease Iraqi Patients

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Abstract

Several studies have addressed the prevalence of *Toxoplasma gondii* (*T. gondii*), among Parkinson's disease (PD) patients in different countries, and the potential association between the infection and PD; the results of these studies were conflicting. The study aims to investigate the prevalence of *Toxoplasma* infection among sample of Iraqi PD patients. Also, to examine the potential association of age, PD duration, gender, smoking habit, zone of residence and family history of PD, with the prevalence of *Toxoplasma* infection in PD patients.

Seventy-four PD patients attaining Dr. Saad Al-Witry Neuroscience Hospital in Baghdad/ Iraq for routine follow up, from different Iraqi governorates, were enrolled in this cross-sectional study. Detection of *T. gondii* was performed by detection of anti-*Toxoplasma* IgG and IgM antibodies in serum by ELISA method.

The frequency rate of anti-*Toxoplasma* IgG antibodies in Iraqi PD patients was 43.2% (32/74); while, none of the participants was seropositive for anti-*Toxoplasma* IgM antibody. Age, PD duration, smoking habit and zone of residences were not shown to be risk factors for *Toxoplasma* infection in PD patients (P>0.05); meanwhile, female gender and positive family history of PD were shown to have a protective effect; (OR, 0.309; 95% CI, 0.099-0.966; P= 0.043) and (OR, 0.162; 95% CI, 0.037-0.705; P=0.015); respectively.

The prevalence rate of Toxoplasma infection in Iraqi PD patients is 43.2%, female gender and positive family history of PD might protect against *Toxoplasma* infection in PD patients.

Key words: Iraq, Neurodegeneration, Parkinson's disease, Prevalence, *Toxoplasma gondii*

انتشار المقوسة الغوندية في مرضى داء باركنسون العراقيين

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الخلاصة

تناولت العديد من الدراسات انتشار *التوكسوبلازما* أو المقوسة الغوندية ، بين مرضى داء باركنسون في بلدان مختلفة، والعلاقة المحتملة بين عدوى التوكسوبلازما وداء باركنسون. كانت نتائج هذه الدراسات متضاربة. تهدف الدراسة الحالية إلى معرفة مدى انتشار عدوى التوكسوبلازما بين عينة من مرضى داء باركنسون في العراق بالإضافة لفحص الارتباط المحتمل بين العمر ومدة مرض باركنسون والجنس والتدخين ومنطقة الإقامة والتاريخ العائلي لمرض باركنسون، مع ايجابية المصل للتوكسوبلازما في مرضى داء باركنسون.

تم تسجيل أربعة وسبعين مريضاً من مرضى داء باركنسون في هذه الدراسة المقطعية المستعرضة من مراجعي مستشفى الدكتور سعد الوتري للعلوم العصبية في بغداد / العراق الحاضرين للمتابعة الروتينية ، من مختلف المحافظات العراقية. تم إجراء الكشف عن اصابة *التوكسوبلازما* عن طريق الكشف عن الأجسام المضادة IgG و IgM المضادة للتوكسوبلازما في مصل الدم بطريقة الامتزاز المناعي المرتبط بالانزيم.

بلغ معدل تواتر الأجسام المضادة IgG المضادة للتوكسوبلازما في مرضى داء باركنسون العراقيين ٤٣,٢٪ (٣٢/٧٤). بينما، لم يكن أي من المشاركين إيجابي المصل للأجسام المضادة IgM المضادة للتوكسوبلازما. لم يُظهر العمر ومدة الاصابة بداء باركنسون والتدخين ومنطقة الإقامة كعوامل خطر لعدوى التوكسوبلازما في مرضى داء باركنسون (P> 0.05) ؛ بينما تبين أن للجنس الأنثوي والتاريخ العائلي الإيجابي لداء باركنسون تأثير وقائي (OR, 0.162; 95% CI, 0.037-0.705; P=0.015) و (OR, 0.309; 95% CI, 0.099-0.966; P= 0.043) على التوالي.

معدل انتشار عدوى التوكسوبلازما في مرضى داء باركنسون العراقيين هو ٤٣,٢٪ ، والجنس الأنثوي والتاريخ العائلي الإيجابي لمرض باركنسون قد يحميان من عدوى التوكسوبلازما في مرضى داء باركنسون.

الكلمات المفتاحية: العراق، التنكس العصبي، مرض باركنسون، الانتشار، التوكسوبلازما جوندي

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Introduction

Toxoplasma gondii (*T. gondii*) is an obligate intracellular parasitic protozoan that causes a zoonotic disease known as toxoplasmosis. *T. gondii* can infect most worm-blooded mammals including human [1]. The infection is transmitted to the humans by consumption of raw or undercooked meat comprising the parasites' cysts, ingestion of oocysts, and from the infected mother to the fetus [2]. Moreover, *T. gondii* is transmitted through blood transfusion and organ or stem cell transplantation [3]. It is estimated that over one third of the world population is infected with *T. gondii*, thus, it is considered the etiological cause of the most prevalent infection in humans [4]. The infection is mostly asymptomatic in individuals with competent immune responses, and tissue cysts of the parasite are formed principally in the brain and skeletal muscles [5]. The infection remains latent until when the hosts' immune responses are challenged where tissue cysts rupture causes release of the quiescent parasite that rapidly divide [6]. The reactivated infections might result in neurological damage and inflammation [7, 8].

Parkinson's disease (PD) is the second most common progressive neurodegenerative disorder, just preceded by Alzheimer's disease. PD affects about 1% of the world population aged 60 years or older [9, 10]. The pathological hallmarks in PD involve dopaminergic and non-dopaminergic neurodegeneration and cytoplasmic accumulation of misfolded proteins known as Lewy bodies. Many pathological mechanisms have been proposed to explain these events [11-17].

The prevalence of *T. gondii* infection in Parkinson's disease patients has been studied in many epidemiological studies in an attempt to investigate whether *T. gondii* infection is associated with increased risk for Parkinson's disease; and the results have been very inconsistent. Ramezani *et al.* has reported a significantly higher frequency rate of anti-toxoplasmosis seropositivity in the idiopathic PD patients compared to healthy individuals and patients with other neurological disorders; and has suggested that *T. gondii* infection contributed to an increased risk of idiopathic PD [18]. Similarly, *Miman et al*. has considered toxoplasma infection might contribute to the pathogenesis of PD [19]. Contrariwise, other studies have reported no association between *Toxoplasma* infection and PD [2,20, 21]. Actually, Fallahi *et al.* has suggested that *T. gondii* infection could not be a risk factor for PD and that patients with PD are at more risk to acquire *Toxoplasma* infection [2]. To date, the prevalence of *Toxoplasma* in Iraqi PD patients is not documented. Thus, this study aims to investigate the prevalence of anti-*Toxoplasma* antibodies in a sample of Iraqi PD patients; and to examine the potential association of age, PD duration, gender, smoking habits, zone of residence and family history of PD, with the prevalence of *Toxoplasma* infection in PD patients.

Patients and Methods

This cross-sectional study was conducted at Dr. Saad Al-Witry Neuroscience Hospital in Baghdad/ Iraq, during the period extending from May to December 2019. The study was approved by the Research Committee and by the Ethics Committee of the College of Pharmacy/University of Baghdad. Seventy-four patients with an established diagnosis of PD, according to *The United Kingdom Parkinson's Disease Society Brain Bank* Clinical Diagnostic *Criteria* for idiopathic PD [22]; who were attending the hospital for routine follow up, were enrolled in the study. Patients with other neurological diseases and people with a history of brain surgery were excluded from the study. Sociodemographic data regarding patients' age, gender, zone of residence, and smoking habits; in addition to PD duration and family history of PD were collected by one of the researchers. A consent was obtained from each patient after being informed about all aspects of the study.

A five millilitres venous blood samples were collected from the patients and left at room temperature to clot, then the samples were centrifuged at 3000 rpm for 15 minutes to obtain sera. Sera were separated and kept frozen at (-20 °C) until assayed. Anti-*Toxoplasma* IgM and IgG levels were assayed using a readily available enzyme-linked immunosorbent assay (ELISA) kit purchased from (ACON laboratories, San Diego, USA). Calibration curve was drawn to obtain serum anti-*Toxoplasma* IgG and IgM levels from their absorbance. For qualitative assessment of anti-*Toxoplasma* IgG and IgM seropositivity, Index value >1.1was interpreted as positive, also according to the manufacturer recommendations.

Statistical analysis

Statistical analyses were performed using SPSS, version 22 (SPSS Inc., Chicago, IL, USA), software for windows. Descriptive statistics, mainly mean values and standard deviation (SD), were presented for numerical variables, and frequencies and percentages were used for categorical variables. Independent student t-test was conducted to examine the significance of the difference in the means of numerical variables between anti-*Toxoplasma* IgG -positive and -negative groups.

While, chi-square test was used to check the significance of the difference in the frequencies of the categorical variables between anti-*Toxoplasma* IgG-positive and -negative groups.

Univariate and multivariate logistic regression were used to identify risk factors associated with the seropositivity of anti-*Toxoplasma* IgG in PD patients. Variables with *P*-values less than 0.05 in the univariate logistic model were included in the multivariate logistic model. The confidence interval was set to 95%, and the default level of statistical significance was based on $P < 0.05$

Results

In this study, the mean age of PD patients was 60.65 ± 10.67. Forty-three patients (58.1 %) were males and 31 (41.9%) were females. In terms of zone of residence, 60 patients (81.1%) were living rural areas and 14 (18.9%) were living in urban areas. The mean duration of disease was 6.41 ± 3.75 years; only 17 patients (23%) have a family history of PD and only 16 patients (21.6%) were smokers; (Table 1).

The overall prevalence of *Toxoplasma* in PD patients was 32/74 (43.2%); *Toxoplasma* positive patients were found positive for anti-*Toxoplasma* IgG antibody, which reflects chronic *Toxoplasma* infections. All PD patients were found as negative for anti-*Toxoplasma* IgM antibody. None of the samples was in the equivocal range for anti-*Toxoplasma* IgG or IgM antibody. The mean serum levels of anti-*Toxoplasma* IgG antibody in seropositive PD patients was 3.538 ± 2.164 (Table 2).

Table 1. Characteristics of 74 Parkinson's disease patients

Age (year)	60.65 ± 10.67
PD duration (year)	6.41 ± 3.75
Gender [n (%)]	
Male	43 (58.1%)
Female	31 (41.9%)
Smoking [n (%)]	
No	58 (78.4%)
Yes	16 (21.6%)
Zone of residence [n (%)]	
Rural	60 (81.1%)
Urban	14 (18.9%)
Family history of Parkinson's disease [n (%)]	
No	57 (77%)
Yes	17 (23%)

Table 2. Frequency and serum levels of anti *T. gondii* antibodies in Parkinson's disease patients

	Serum *anti-Toxoplasma IgG antibody*			**Serum *anti-Toxoplasma IgM antibody***		
	Frequency	**Level**	**Range**	**Frequency**	**Level**	**Range**
***Toxoplasma* Positive**	32 (43.2%)	3.538 ± 2.164	1.30-7.54	0 (0%)	-------	-------
***Toxoplasma* Negative**	42 (56.8%)	0.473 ± 0.134	0.31-0.79	100 (100%)	0.232 ± 0.048	0.18-0.36

The means of age and PD duration were significantly different between anti-*Toxoplasma* IgG antibody seropositive and seronegative patients ($P<0.001$). Moreover, there was a significant difference between the frequency of *Toxoplasma* between male and female PD patients and between those with positive and negative family history of PD ($P = 0.036$ and 0.015; respectively); (Table 3).

Table 3. Patients' characteristics by prevalence of toxoplasmosis

Variable	***Toxoplasma* positive n=32**	***Toxoplasma* negative n=42**	**P value**
Age (year)	64.31 ± 10.17	57.86 ± 9.87	**0.000**
PD duration (year)	7.16 ± 4.89	5.83 ± 2.49	**0.000**
Gender			
Male	23 (71.9%)	20 (47.6%)	**0.036**
Female	9 (28.1%)	22 (52.4%)	
Smoking			
No	23 (71.9%)	35 (83.3%)	0.236
Yes	9 (28.1%)	7 (16.7)	
Zone of residence			
Rural	28 (87.5%)	32 (76.2%)	0.218
Urban	4 (12.5%)	10 (23.8%)	
Family history of PD			
No	29 (90.6%)	28 (66.7%)	**0.015**
Yes	3 (9.4%)	14 (33.3%)	

Univariate logistic regression analysis showed that the older age, female gender and positive family history of PD are significantly related to anti-*Toxoplasma* IgG antibody seropositivity; (Table 4). Multivariate logistic regression analysis of these variables showed that female gender and positive family history of PD reduce the risk of anti-*Toxoplasma* IgG antibody seropositivity in PD patients; (OR 0.309, 95% CI: 0.99-0.966, P = 0.043) and (OR 0.162, 95% CI: 0.037-0.705, P = 0.015); respectively; (Table 4).

Table 4.Multiple logistic regression analysis to predict potential independent risk factors for prevalence of toxoplasmosis in Pakinson's disease patients

Variable	Unadjusted		Adjusted	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.069 (1.014-1.127)	**0.014**	1.041 (0.983-1.102)	0.169
PD duration	1.103 (0.968-1.257)	0.141	--------	------
Gender				
Male	*(Reference group)*			
Female	0.356 (0.134-0.948)	**0.039**	0.309 (0.099-0.966)	**0.043**
Smoking				
No	*(Reference group)*			
Yes	1.957 (0.637-5.991)	0. 240	--------	------
Zone of residence				
Rural	*(Reference group)*			
Urban	0.457 (0.129-1.621)	0.225	--------	------
Family history of PD				
No	*(Reference group)*			
Yes	1.036 (0.054-0.799)	**0.022**	0.162 (0.037-0.705)	**0.015**

Discussion

Latent *Toxoplasma* infection has been shown to be associated with neurodegeneration [23]. The exact mechanism by which *Toxoplasma* infection results in neurodegeneration is not well elucidated; however, neuroinflammation has been proposed to be a major contributor [24]. In chronic *Toxoplasma* infection, the cysts tend to concentrate in the neurons [25], where they are subjected to persistent local cellular immune reactions [26]. Neuroinflammation might continue for years if *Toxoplasma* infection is not eradicated [23].

Many studies have addressed the prevalence of Toxoplasma infection among PD patients in different countries, and the potential association between the infection and PD; the results of these studies were conflicting [2,18-21,27,28]. Except for Ramezani *et al.*[18] and Miman *et al.*[19] who have reported significant difference in seroprevalence of *Toxoplasma* infection between PD patients and healthy control, other studies did not report such finding. In a recent meta-analysis, Zhou *et al*. reported no correlation between PD and anti-*Toxoplasma* IgG antibody seropositivity [29]. This meta-analysis has attributed the positive correlation that has been reported in some studies [18, 19], to the small sample sizes and sampling bias that these studies were conducted in a nearby geographical area.

To the best of our knowledge, this is the first study investigating the prevalence of *Toxoplasma* infection and PD in Iraq. In the present study, 43.2% of PD patients were seropositive for anti-*Toxoplasma* IgG antibody, indicating chronic latent infection. While, all PD patients were seronegative for anti-*Toxoplasma* IgM antibody, indicating no acute *Toxoplasma* infection among participants (Table 2). These results occur in agreement with studies that have reported seroprevalence, based on anti-*Toxoplasma* IgG antibody, in Turkey (42.3%)[19], Egypt (43.3%)[27], Iran (53%)[2]. Ramezani *et al.*[18] and Mahami et al.[21] have reported higher seroprevelance rates in Iran (82.5% and 85%; respectively). Low seroprevalence rates has been reported by Alvarado-Esquivel *et al.* (9.2%) in Mexico[20] and by Çelik *et al.* (18%) in Turkey[28].

In the present study, the age of seropositive PD patients was significantly higher than their seronegative counterparts (Table 3). Age has been reported to be a risk factor for *Toxoplasma* infection[30, 31]. The increase in *Toxoplasma* seroprevalence with age can be attributed to the increase in the likelihood of contact with the parasites' oocyts with time, due to occupational factors for example. Moreover, the improvement in the knowledge about *Toxoplasma* infection and its routes of transmission might reduce the prevalence

of *Toxoplasma* infection among younger individuals.

The duration of PD in *Toxoplasma* seropositive patients in the present study, was significantly higher than that of their seronegative counterparts (Table 3). However, PD duration was not a risk factor for the seroprevalence of *Toxoplasma* in PD patients (Table 4). Typically, onset and diagnosis of PD occur ages higher than 55 years, thus, the higher PD duration in *Toxoplasma* seropositive PD patients might reflects the higher age of those patients rather than of pointing a pathological significance.

Regarding gender, the results showed significant difference between males and females of *Toxoplasma* seropositive and seronegative PD patients (Table 3), and female PD patients were shown to be at lower risk for *Toxoplasma* infection (Table 4), which disagree with Mahami *et al.*[21] who reported no association between gender and *Toxoplasma* infection in PD patients.

Female gonadal sex hormones in rats have been shown to modulate the dopaminergic actions in the striatum and nucleus accumbens of the brain[32]. Dluzen *et al.* has showed that estrogen protects against neurodegeneration of the striatal dopaminergic system, probably by inhibiting the uptake of neurotoxins[33]. The *Toxoplasma*-induced dopamine manipulation, which has long been suggested[34], might be inhibited by estrogen, hence, contributing to the lower prevalence and risk of *Toxoplasma* infection in female PD patients reported in the study.

The results of the present study showed that PD patients with positive family history of the disease are at lower risk for *Toxoplasma* infection (Table 4). Up to our knowledge, this is the first study reporting such a relationship and further studies are required for confirmation. If confirmed, this finding may highlight a genetic role in protecting against, *Toxoplasma* infection in PD patients. It is worthy to mention that, several studies have linked genetic polymorphisms with increased[35, 36], or decreased[37] susceptibility to *Toxoplama* infection.

Finally, smoking and zone of residence were not associated with *Toxoplasma* infection in PD patients that occur in agreement with other studies[20, 21].

In conclusion, the study showed that the prevalence rate of *Toxoplasma* infection in Iraqi PD patients is 43.2%. Moreover, female gender and positive family history of PD are protective factors against Toxoplasma infection in PD patients. Further, large-scale studies are required to confirm these findings.

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