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Raad A. Kadhim, Abeer F. Al-Rubaye, and Mahdi T. S. AL-Hadad

Etiology of Parkinson's disease: *Toxoplasma* parasite as a model

Raad A. Kadhim[1,a)], Abeer F. Al-Rubaye[1,b)] and Mahdi T. S. AL-Hadad[2,c)]

[1] *Biology department, College of sciences for women, University of Babylon, Iraq*
[2] *Ministry of Health, AL-Najaf Health Directorate, Middle Al- Furat Hospital, Iraq*

[a)] Corresponding author: raadabbas21@yahoo.com
[b)] abeerbio15@gmail.com
[c)] mahditahermm@gmail.com

Abstract: Parkinson's disease is a chronic neuropsychiatric disease that affects the central nervous system, the main symptoms of which are tremors, the difficulty of movement and balance problems, as well as non- motor symptoms such as anxiety and depression. It is believed to be a multi-cause disease. Latent toxoplasmosis occurs when cystic or bradyzoite phases of the parasite Toxoplasma gondii reside into the brain cells and other tissues in host body, where the parasite begins to manipulate the behavior of the host and can cause neurological and psychological symptoms in some infected individuals. Therefore, this parasite is a dangerous source of many neurological diseases such as schizophrenia and dementia. A total of 80 samples were collected, 35 samples for individuals with Parkinson's (19 males and 16 females) and 45 samples for healthy control (33 males and 12 females). IgG antibodies, which had been detected against toxoplasma parasite indicate presence of chronic or latent infection. This had been done by using the ELISA test during the period from November 2017 to March 2018. The collected samples of the control group included volunteer donors from Najaf province, while samples with Parkinson's disease were collected from various provinces located in the middle of Iraq (Najaf, Babylon and Baghdad). The results showed that the percentage of chronic infection (Positive IgG antibodies) was significantly higher ($P < 0.05$) in patients with Parkinson's (65.71%) than in healthy control (37.77%) by using Chi square test (X2). There no significant differences in the percentage of infection between males and females in all study groups. In conclusion, the current study find that there is may be a close relationship between chronic toxoplasmosis and Parkinson's disease.

Keywords: Chronic toxoplasmosis**,** Parkinson's disease

INTRODUCTION

Parkinson's disease (PD) is a serious disease affecting the human nervous system, it is multi- origin disease. The incidence of this disease is estimated about 108 –257/100000 in Europe, and this percentage varies in different regions of the world, the fundamental motor signs of PD include tremor, stiffness, bradykinesia and postural instability, although the clinical picture involves other motor and non-motor signs (1). In the 1950s, Poskanzer and Schwab established their well-known hypothesis Poskanzer and Schwab hypothesis (PSH) in which they attributed Parkinson's disease to Influenza. Since that time, this hypothesis has led researchers to assume a relationship between the infections with pathogens and PD. Despite of the fact that the confirmation of the original hypothesis was not completed, it received a lot of opinions and acceptance from some researchers and rejection by others (2).

Several studies indicate of a relationship between PD and some infectious diseases. For example, there is a relationship between the presence of *Helicobacter pylori* in the stomach and Parkinson's disease, although the exact mechanism is not known with accuracy, the cases of stomach ulcers have increased in

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patients with Parkinson's. It was thought it could be one of the symptom affecting the digestive system of patients with Parkinson's disease, until the researchers diagnosed a contagious helical bacteria, which is believed to have a relationship with the disease (3-6). However, one of the proposed mechanisms is that bacteria show high toxicity, which affects the nervous system by increasing glycosides and cholesterol levels as well as by the degradation of dopamine neurons in the brain. In addition, it is believed that bacteria release chemicals increase activation of specific parts of the brain that lead to brain damage (3). Another supposed mechanism clarifies that the immune system cannot eliminate bacteria and this lead to the development of Parkinson's disease because of destroying dopamine cells in the brain (7). Some researchers attributed the relationship between these bacteria and Parkinson's to the ability of bacteria to trigger programmed cell death when it crosses the blood-brain barrier after swallowed it orally or inhaled it by the nose (8). In addition to bacteria, viruses may contribute to the mechanism of this disease, it was found that hepatitis C virus may invade the central nervous system after the liver infection. Both HCV and Parkinson's disease cause similar damage that affects nerves, and secrete similar inflammatory vital signs, HCV causes dopaminergic nerve cell death by 60% in the glial neuronal implant system in mice. Further evidence supports this finding by discovering that HCV infection releases inflammatory cytokines, which may play a role in the pathogenesis of Parkinsonism (9). Parasitic infections play a major role in neurological diseases, *Toxoplasma gondii* is a protozoon parasite widespread in the world with an estimated global infection percentage of 20-90%, most cases without symptoms, but it may cause serious symptoms in immunocompromised individuals and infections acquired by the fetus from the infected mother, as well as causing problems for pregnancy (10-12). Two Previous studies recorded the association between Parkinson's disease and infection with *Toxoplasma gondii* (13; 14). Park (15) recorded symptoms of PD in a patient with *Plasmodium vivax* in South Korea.

MATERIALS AND METHODS

Samples

Eighty samples were collected, including 35 samples for individuals with Parkinson's (19 males and 16 females) and 45 samples for healthy volunteers (33 males and 12 females). IgG antibodies were detected against toxoplasma parasite, which indicate chronic or latent parasite infection. ELISA test was used to examine the samples, which were collected during the period from November 2017 to March 2018. The collected samples for the control group included donors from Najaf governorate, while samples for patients with Parkinson's were collected from various governorates (Najaf, Babylon and Baghdad). The ages of the people ranged between 22-86 years and at average of 53.63 years old, where the ages of patients with Parkinson's disease ranged from 22 to 86 years and average of 55.53 years old. The healthy control group, ages ranged between 28-85 years and at average of 52.28 years old. Questionnaire was designed to collect information about all participants under the study. The Questionnaire includes several questions about: name, gender, age, marital status, illness (other diseases if any), pregnancies (for females), family history for Parkinson's disease, occupation, the stage of the disease, taking treatment for the diseases (Carbidopa-Levodopa) or no, and smoking status.

Collection of samples

Blood samples were collected using disposable syringes. 4-5 ml of venous blood was drawn and collected in plane tubes. The sample left in the lab for 15 minutes to allow it to coagulate at room temperature. The samples were centrifuged at a rotational speed 3000 rpm for 15 minutes to separate the serum. Then the sera were transferred to Eppendorf tubes, and stored in deep Freezer -80 ° C until use.

Diagnosis of Toxoplasma IgG antibody

In order to accomplish this test, Quantification of IgG antibodies was performed on *Toxoplasma gondii* infection using Toxoplasma IgG ELISA kit (Calbiotech Inc.). The test and interpretation of results were done based on the manufacturer's information in the guide.

Statistical analysis:

Chi-square distribution and 0.05 percent approval were used for significant dependence.

RESULTS

The current study included 80 samples, of which 35(19 males and 16 females) were patients with Parkinson's disease and 45 (33 males and 12 females) were not infected as control group. The range of age for all participants in all groups was 22-86 years old.

Table (1) shows that the percentage of chronic infection with *T. gondii* (Positive IgG anti-toxoplasma antibodies) was significantly higher (P <0.05) in individuals with Parkinson's (65.71%) than in healthy volunteers (37.77%) by using Chi-square (X^2) statistical analysis.

TABLE 1: Percentage of IgG antibodies of *Toxoplasma gondii* in healthy volunteers and Parkinson's patients.

Groups	Total numbers	Seropositive	Seronegative	P value
Non-infected with Parkinson	45	17 (37.77%)	28(62.22%)	P= 0.01317 p<0.05
Infected with Parkinson	35	23(65.71%)	12(34.28%)	significant value
Total summation	80	40(50.0%)	40(50.0%)	

The study also included an investigation of the effect of gender on the occurrence of chronic toxoplasmosis. Although the table (2) indicates that the percentage of infection in females are higher than that of males, the statistical analysis proved there is no significant differences among all study groups.

TABLE 2: The relationship of the sex factor to the incidence of toxoplasmosis in the study groups.

Groups	Gender	Total numbers	Seropositive	Seronegative	P value
Infected with Parkinson	Male	19	11(57.89%)	8(42.1%)	P= 0.288 p>0.05
	Female	16	12(75.0%)	4(25.0%)	non-significant value
Non-infected with Parkinson	Male	33	12(36.36%)	21(63.63%)	P= 0.7455 p>0.05
	Female	12	5(41.66%)	7(58.33%)	non-significant value
total	Male	52	23(44.23%)	29(55.76%)	P= 0.1596 p>0.05
	Female	28	17(60.71%)	11(39.28%)	non-significant value

DISCUSSION

The current study recorded a significant relationship between the incidence of Parkinson's and chronic infection with *T. gondii* (P <0.05), where the serum prevalence of IgG in patients with Parkinson's was

65.71% comparing with the control group, which was 37.77%. This study is the first study to investigate the possible relationship between chronic infection with toxoplasmosis and Parkinson's disease in Iraq. Several studies were conducted around the world about this kind of relationship. In Iran, the study of Oskouei *et al.* (13) showed that there was no significant relationship between the incidence of Parkinson's disease and chronic toxoplasmosis, but the same study recorded a significant correlation between Parkinson's infection rate and the consumption of not fully cooked eggs and possession or raising of cat. These two factors are considered a dangerous source of infection with *Toxoplasma*.

The results of the study of Alvarado-Esquivel *et al.* (16) in Mexico didn't support the relationship between *T. gondii* infection and Parkinson's disease, however the infection affected some symptoms of the disease in patients with Parkinson's disease. On the other hand, the result of the current study is consistent with the study of Ramezani *et al.* (14) in Iran, as it found a significant relationship between toxoplasmosis and Parkinson's disease where, IgG antibody levels were high in individuals with Parkinson's disease (82.5%), comparing with 65% in healthy group. In addition, the same study was recorded the serum prevalence of IgG for people with other neurological diseases such as dementia, epilepsy, headache and stroke, which was 65.2%.

Fallahi *et al.* (17) in a study was conducted in Iran on the relationship of PD and toxoplasmosis showed that there were no significant differences between the disease and seropositive IgG and IgM antibodies of the parasite. While they recorded a significant difference in parasite infection rates between the groups of healthy people and Parkinson's patients when the molecular diagnosis of *Toxoplasma* parasite was used where, the infection rate was 10.4% and 19.3%, respectively. The positive relationship between chronic toxoplasmosis and PD could be attributed to the reason that the parasite infection includes the region of the basal ganglia in the brain, which is the same region that is important anatomical site in the mechanism of development of Parkinson's disease (18). In addition, the infection with *T. gondii* causes inflammation of the nerve cells in the brain, which is also an important factor in the development of Parkinson's disease (19).

AL-Hadad *et al.* (20) found that chronic infection with the *Toxoplasma* parasite leads to changes in serological concentrations of some neurotransmitters released into the blood, including dopamine, and these substances interfere with the mechanism of injury in PD. Also Parkinson's disease effects on serological concentrations of the same neurotransmitters that were estimated in the previous study (21). Arbune *et al.* (22) attributed the relationship between Toxoplasmic Encephalitis and Parkinson's in people with AIDS to several reasons, some of them related to viruses, which are the loss of basal ganglia as a result of HIV virus replication or due to the potential neurotoxicity of antiretroviral drugs. Some others related to the parasite which are the destruction of the substantia nigra region in the brain by abscesses generated by the *Toxoplasm* parasite, or the interference of the parasite with dopamine metabolism, because it has the gene encoding the enzyme specific to dopamine. The parasite caused a lack of supply of cerebral vasculature and rare immune states that lead to brain damage.

Numerous studies have documented the relationship of chronic toxoplasmosis to various neurological diseases such as Alzheimer's, schizophrenia, epilepsy, etc. Schizophrenia is associated with a defect in the dopamine-generating region (23; 24) which is a characteristic of Parkinson's disease, Prandovszky *et al*. (25) found that the amount of dopamine produced in the brain is closely related to the number of dopaminergic cells that are infected with *T. gondii*.

Our current study show that the percentage of chronic infection with *Toxoplasma* between males and females are not significantly different, although there is a noticeable increase in the rates of infection in females. The prevalent principle is that females are more resistant to microbial pathogens than males, but there are some exceptions. Escobedo *et al*. (26) attributed the difference in response to parasites between male and female hosts to immune factors instead of being linked to gender. The diversity of immune response against parasites is based on the species of parasite, its number and strategies during different times of infection and the parasite's location in the host. Some research has indicated that mice infected with the parasite *T. gondii* produce more quantities of certain cytokines (IFN-γ and TNF-α) in males than in females (27; 28). This interpretation supports the current findings that is unimportant increasing in the percentage of infection in males compared to females.

In conclusion, our study found a close relationship between Parkinson's diseases and chronic toxoplasmosis.

REFERENCES

1. R. Balestrino and A.H.V. Schapira, Parkinson disease (Review Article). 2020; 27(1):27-42.
2. Y. Chao; S. C. Wong and E. K. Tan, Evidence of Inflammatory System Involvement in Parkinson's Disease. Bio Med Research International.(2014) Volume Article ID 308654, 9 pages.10.1155/2014/308654
3. Y. Tsuboi and T. Yamada, Prevalence of Helicobacter pylori infection among patients with Parkinson's disease impact on clinical manifestations, Movement Disorders.2008; 23(1).
4. R. J. Dobbs, Helicobacter hypothesis for idiopathic Parkinsonism: before and beyond, Helicobacter. 2008; 13(5): 309-322.
5. W. Y. Lee, *Helicobacter pylori* infection and motor fluctuations in patients with Parkinson's disease, Movement Disorders.2008; 23(12): 1696-1700.
6. D. Włodarek; W. Pakszys and J. Bujko, *Helicobacter pylori* infection and its influence on Parkinson disease. Polski Merkuriusz Lekarski.2003; 15(89): 428–431.
7. M. Lyte, Microbial endocrinology as a basis for improved L-DOPA bioavailability in Parkinson's patients treated for Helicobacter pylori, Med Hypotheses. 2010; 74(5): 895-7.
8. T. H. Saey, Mouse study finds stomach ulcer-causing microbes may also affect brain, Science Daily. 2011; 179(13).
9. W.Y.Y. Wu ; K. H. Kang ; S. L. S. Chen ; S. Y.-H. Chiu ; A. M.-F. Yen ; J. C.-Y. Fann ; C.-W. Su ; H.-C. Liu ; C.-Z. Lee ; W.-M. Fu ; H.-H. Chen and H.-H. Liou, Hepatitis C virus infection: a risk factor for Parkinson's disease. Journal of viral hepatitis.2015; 22(10): 784-791.
10. S. Singh, Prevalence of torch infections in Indian pregnant women. Indian J Med Microbiol. 2002; 20:57-8.
11. S.K. Halonen and L. M. Weiss, Toxoplasmosis. Handb. Clin. Neurol. 2013; 114:125-45.
12. H. S. Hadi; R. A. Kadhim and R. T. O. AL-Mammori, Seroepidemiological aspects for *Toxoplasma gondii* infection in women of Qadisiyah province, Iraq. International journal of Pharm Tech research. 2016; 9(11):252-259.
13. M. M. Oskouei; F. Hamidi; M. Talebi; M. Farhoudi; A. A. Taheraghdam; T. Kazemi; H. Sadeghi-Bazargani and E. Fallah, The correlation between *Toxoplasma gondii* infection and Parkinson's disease: a case-control study. J. Parasit. Dis.2016; 40(3):872–876.
14. M. Ramezani ; M. Shojaii ; M. Asadollahi ; E. Karimialavijeh and K. Gharagozli, Seroprevalence of *Toxoplasma gondii* in Iranian patients with idiopathic Parkinson's disease. Clinical and Experimental Neuroimmunology.2016; 361–365.
15. J. E. Park, Pakinsonism and tremor in a patient with *Plasmodium vivax* malaria. Tremor and other hyperkinetic movements.2017; 7.doi: 10.7916/D8P55V23.
16. C. Alvarado-Esquivel; E.M. Méndez-Hernández; J. M. Salas-Pacheco and et al, *Toxoplasma gondii* exposure and Parkinson's disease: a case–control study. BMJ Open.2017; 7:e013019. Doi: 10.1136/bmjopen-2016-013019.
17. S. Fallahi ; A. Rostami ; E. Fallahi ; F. Kheirandish and A. Fallahi, Parkinson's disease and *Toxoplasma gondii* infection: seromolecular assessing the possible link among patients. The congress of 27th ECCMID, Vienna, Austria 22-25 April, 2017.
18. Y.C. Ho; H. Y. Sun; M. Y. Chen; S. M. Hsieh; W. H. Sheng and S. C. Chang, Clinical presentation and outcome of toxoplasmic encephalitis in patients with human immunodeficiency virus type 1 infection. J Microbiol Immunol infect. 2008; 41: 386–92.
19. O. Miman; O. Y. Kusbeci; O. C. Aktepe and Z. Cetinkaya, The probable relation between Toxoplasma gondii and Parkinson's disease. Neurosci Lett.2010; 475: 129–31.
20. M.T.S. AL-Hadad; R. A. Kadhim and A. F. Al-Rubaye , Effect of chronic toxoplasmosis on levels of some neurotransmitters (Dopamine, Adrenaline, and Noradrenaline) in human serum. Journal of Pharmaceutical Sciences and Research.2019; 11(2):402-405.
21. M.T.S. AL-Hadad ; R. A. Kadhim and A. F. Al-Rubaye , Effect of Parkinson's disease on the serological levels of some neurotransmitirs and interleukin-5. Biochem. Cell. Arch. 2019; 19(2): 4471-4476.
22. A-A. Arbune; M. Arbune and V. Stefanescu, Parkinsonian Syndrome and Toxoplasmic Encephalitis. The Journal of Critical Care Medicine.2016; 2(2):89-92.

23. L. Y. Juanah ; J. Jalaludin ; M. Osman and Z. J. Osman, Seroprevalence of *Toxoplasma gondii* Among Schizophrenics at Hospital Kajang. American Journal of Infectious Diseases.2013; 9 (1): 11-16.
24. T. Çelik; S. Kartalci; Ö. Aytaş; G. A. Akarsu; H. Gözükara and S. Ünal, Association between latent toxoplasmosis and clinical course of schizophrenia – continuous course of the disease is characteristic for *Toxoplasma gondii*-infected patients. Folia Parasitologica. 2015; 62: 015:1-6.
25. E. Prandovszky ; E. Gaskell ; H. Martin ; J. P. Dubey ; J. P. Webster, et al. The Neurotropic Parasite *Toxoplasma gondii* Increases Dopamine Metabolism. PLoS ONE. 2011; 6(9): e23866. doi:10.1371/journal.pone.0023866.
26. G. Escobedo; M. A. De Leo´n-Nava and J. Morales-Montor, "Sex Differences in Parasitic Infections: Beyond the Dogma of Female-Biased Resistance" in *Sex Hormones and Immunity to Infection* edited by S.L. Klein and C.W. Roberts (Springer-Verlag Berlin Heidelberg, 2010), pp.187-204.
27. C.W. Roberts; S. M. Cruickshank and J. Alexander, Sex-determined resistance to *Toxoplasma gondii* is associated with temporal differences in cytokine production. Infect Immun.1995; 63:2549– 2555.
28. W. Walker; C.W. Roberts; D.J. Ferguson; H. Jebbari and J. Alexander, Innate immunity to *Toxoplasma gondii* is influenced by gender and is associated with differences in interleukin12 and gamma interferon production. Infect Immun. 1997; 65(3):1119–21.