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The impact of chronic toxoplasma gondii infection on serum dopamine and adrenaline levels in patients with neuropsychiatric disorders compared to healthy individuals

Sherine Elsharkawy
Lecturer of Physiology, Physiology Department, Faculty of Medicine, Banha University, Egypt
Corresponding author email: sherinesharkawy1981@gmail.com
ORCID: 0009-0003-8197-2134

Reda Mohamed Abdrabbou Fayyad
Lecturer of Pharmacology Faculty of Medicine, Al-Azhar University, Cairo, Egypt
Email: drredafayyadccmorc@gmail.com

Faten Abouelmagd
Lecturer of Medical Parasitology, Department of Medical Parasitology, Faculty of Medicine, Sohag University, Egypt
Email: faten.rashad@gmail.com, faten_hassan@med.Sohag.edu.eg

***Abstract*---**Background: Toxoplasma gondii is an intracellular parasite whose life cycle is completed in felids especially cats, the definitive host. Humans and many other animals can also be infected and serve as intermediate hosts. This study aimed to assess the role of chronic toxoplasmosis in changes of neurotransmitters levels in human serum. Methods: This case control study was conducted on 41 patients by examining the serofrequency of T. gondii among IgG and IgM antibodies patients with neuropsychiatric disorders and cross-matched 41 healthy individuals without any known neuropsychiatric disorders were included as a control group. All patients were subjected to full history taking, general examination, laboratory investigation, renal function test analysis, Psychiatric diagnosis and measurement of serum concentrations of three neurotransmitters (dopamine, adrenaline, and noradrenaline). Results: T. gondii IgG was significantly higher in group A compared to group B (58.5% vs. 31.7%, P=0.026). The mean dopamine level was significantly higher in group A compared to group B (92.7 ± 17.94 pg/ml vs. 45.4 ± 22.48 pg/ml, P<0.001). The mean adrenaline level was significantly higher in group A compared to group B (272.5 ± 135.04 pg/ml vs. 147.4 ± 71.44

pg/ml, P<0.001). The mean dopamine level was significantly higher in Ig G positive patients compared to Ig G negative patients (87.4 ± 20.54 pg/ml vs. 49.4 ± 24.61 pg/ml, P< 0.001). The mean adrenaline level was significantly higher in Ig G positive patients compared to Ig G negative patients (271.6 ± 111.39 pg/ml vs. 171.0 ± 48.38 pg/ml, P= 0.001). Conclusions: Chronic infection by T. gondii causes a change in some neurotransmitters (dopamine and adrenaline) and may be explained by the occurrence of certain neurological diseases in the incidence of latent toxoplasmosis.

***Keywords*---**Neurotransmitters, dopamine, adrenaline, T. gondii, Toxoplasmosis.

Introduction

Toxoplasma gondii is an intracellular parasite whose life cycle is completed in felids especially cats, the definitive host. Humans and many other animals can also be infected and serve as intermediate hosts (Tomasina and Francia, 2020). T. gondii infection (toxoplasmosis) is widespread among the tissues of animals and birds, and infection in humans occurs through eating tissue cysts in undercooked meat or from oocysts released in infected cat faeces (Kochanowsky and Koshy, 2018).

Cats pass the oocysts in their faeces and contaminate the environment, so that humans may be infected. Irrespective of the mode of infection, T. gondii initially multiplies in almost every tissue of the body in the fast-dividing tachyzoite stage, before transforming into the slowly dividing bradyzoite stage in which long-lived cysts are formed in skeletal muscle and the central nervous system (CNS) (Attias et al., 2020).

T. gondii infection causes various neurological disease in host and alters neurological signalling pathways. Toxoplasma gondii has a neurotropic nature, this nature and other features may help in pathogenic mechanisms implicating in mental and behavioural disorders (Samojłowicz et al., 2019). T. gondii uses a complex mechanism to gain access to the brain with preferred sites at cerebral hemispheres, basal ganglia, cerebellum, and brain stem (Zaki et al., 2016). Once enters CNS, it invades various brain cells, including astrocytes and neurons, where it forms cysts containing bradyzoites. Then, it can establish a continuous infection within the CNS, influencing host behaviour, and can cause neurological and psychiatric symptoms in some infected individuals (Del Grande et al., 2017).

Many toxoplasmic immunological reactions and reactivation mechanisms led to behavioural disorders in human. Many health disorders and diseases were correlated with toxoplasmosis including Alzheimer's, schizophrenia, Parkinson, depression and epilepsy (Bayani et al., 2019). They reported higher incidence of chronic toxoplasmosis in patients suffered from various psychiatric disorders (Hinze-Selch, 2015). Behavioural disorders due to psychoactive substances are also reported in toxoplasmosis patients. It induces behavioural changes in human and rodents, also a significant association between T. gondii infection and suicide

attempts was reported. T. gondii infection proved to have a role in traffic accidents, work accidents, and mental illnesses (Milne et al., 2020).

Many studies correlated these symptoms with alterations in hormones concentrations in host, that include sex hormones and neurotransmitters hormones (Zouei et al., 2018). One factor that pay to the vague changes and neurological disorder in human and animal is modulate of neurotransmitters levels during chronic toxoplasmosis such as dopamine (Milne et al., 2020). We established this study to assess the role of chronic toxoplasmosis in changes of neurotransmitters levels in human serum.

Patients and Methods

This case control study was conducted on patients with study examining the serofrequency of *T. gondii* among IgG and IgM antibodies patients with neuropsychiatric disorders**,** aged >18 years old, both sexes admitted to Benha University Hospitals and cross-matched 41 healthy individuals without any known neuropsychiatric disorders were included as a control group. An informed written consent was obtained from the patients. The study was performed after approval of the institutional ethical committee of Benha University Hospitals, in the period from March 2020 to August 2020. Patients' refusal, patients with congenital anomalies, mental retardation were excluded.

The patients were divided into two equal groups, group A (case group) (n=41) included patients with neuropsychiatric disorders and group B (control group) (n=41) included healthy individuals matched in age and sex. All patients were subjected to full history taking (the socio-demographic data included age, gender, residence, urban or rural habitation, marital status, educational level, occupation, and socioeconomic status.

Regarding the clinical features, we investigated (health status, history of lymphadenopathy, blood transfusions, transplantation and surgeries, presence of frequent headache, dizziness, and impairments in vision, hearing, memory and reflexes. In female patients, obstetric history was also obtained. In addition, history of aggressiveness, suicidal ideation and suicide attempt were also collected from each study subject. Physical examination were done on all the patients.

General examination (heart rate, blood pressure, temperature), Laboratory Investigation (CBC (Hb, WBCs, platelets), renal function test analysis (serum creatinine, urea, BUN). Information on potential risk factors such as direct contact with cats or dogs or litter's box, contact with other animals, eating behavior like consumption of raw or undercooked meat and its frequency, consumption of unwashed raw vegetables and fruits, contact with soil, and type of flooring at home.

Five mL of venous blood was collected aseptically from 42 neuropsychiatric patients (subjects) and 42 subjects without neuropsychiatric manifestations (controls) from Benha University Hospitals, in the period from March 2020 to August 2020. The serum was separated from the whole blood by centrifugation at

3000 rpm for ten minutes at room temperature. The separated serum was labelled and kept at -20 C until tested for anti-T. gondii IgG and IgM antibodies using ELISA test kit (Human Gesllschaft for biochemical and diagnostic, Max Plank, Germany) following the manufacturer's instruction. Samples absorbance were read using microtiter plate reader at absorbance of 450/620 nm. The sera of both patients and controls were obtained from blood at the time of interviews. Each sample was tested in duplicate to ensure reliability. All experiments were done in strict sterile conditions. Serum concentrations of three neurotransmitters (Dopamine, Adrenaline, and Noradrenaline) were measured using Elisa method (Elabscience biotechnology Co., Ltd)

Sample size calculation

The sample size calculation was performed using G. power 3.1.9.2 (Universität Kiel, Germany). The sample size was calculated according to the mean difference of adrenaline between case group (IgG +ve) and (IgG-ve) was according to a previous study (AL-Hadad et al., 2019). Based on the following considerations: 0.05 α error and 80% power of the study, allocation ration 1:1. 6 cases were added to overcome dropout (3 cases in each group). Therefore, 82 patients were be allocated.

Statistical analysis

Statistical analysis was done by SPSS v26 (IBM Inc., Armonk, NY, USA). Quantitative variables were presented as mean and standard deviation (SD) and compared between the two groups utilizing unpaired Student's t- test. Qualitative variables were presented as frequency and percentage (%) and were analyzed utilizing the Chi-square test or Fisher's exact test when appropriate. A two tailed P value < 0.05 was considered statistically significant.

Results

Demographic data (age, sex, BMI, residence, marital status, education level, socioeconomic status and working status) were insignificantly different between the studied groups. Table 1

Table 1: Demographic data between the studied groups

		Group A (n = 41)	Group B (n = 41)	P value
Age (years)		37.7 ± 8.95	36.6 ± 9.58	0.585
Sex	Male	38 (92.68%)	36 (87.8%)	0.712
	Female	3 (7.32%)	5 (12.2%)	
BMI (Kg/m^2)		26.90 ± 2.05	26.95 ± 2.05	0.914
Residence	Urban	23 (56.1%)	19 (46.34%)	0.507
	Rural	18 (43.9%)	22 (53.66%)	
Marital status	Single	26 (63.41%)	22 (53.66%)	0.501
	Married	15 (36.59%)	19 (46.34%)	
Education level	High	21 (51.22%)	18 (43.9%)	0.658
	Low	20 (48.78%)	23 (56.1%)	

		Group A (n = 41)	Group B (n = 41)	P value
Socioeconomic status	High	7 (17.07%)	10 (24.39%)	0.596
	Medium	19 (46.34%)	15 (36.59%)	
	Low	15 (36.59%)	16 (39.02%)	
Working status	Working	22 (53.66%)	26 (63.41%)	0.501
	Not	19 (46.34%)	15 (36.59%)	

Data are presented as mean ± SD or frequency (%), BMI: body mass index.

There were 16 (39.02%) patients in group A and 12 (29.27%) patients in group B had a past history of surgery. Cat exposure was found in 7 (17.07%) patients in group A and 5 (12.2%) patients in group B. Consumption of raw meat was presented in 21 (51.22%) patients in group A and 10 (24.39%) patients in group B. Past history of surgery and cat exposure were insignificantly different between the studied groups whereas consumption of raw meat was significantly higher in group A (case group) compared to group B (control group) (P=0.023). Table 2

Table 2: Clinical history between the studied groups

	Group A (n = 41)	Group B (n = 41)	P value
Past history of surgery	16 (39.02%)	12 (29.27%)	0.485
Contact with cats	7 (17.07%)	5 (12.2%)	0.754
Consumption of raw meat	21 (51.22%)	10 (24.39%)	**0.023***

Data are presented as mean ± SD or frequency (%), *: statistically significant as P value <0.05.

T. gondii IgG was significantly higher in group A compared to group B (58.5% vs. 31.7%, P=0.026) whereas T. gondii IgM was insignificantly different between both groups (14.6% vs. 9.8%). Table 3

Table 3: T. gondii between the studied groups

		Group A (n = 41)	Group B (n = 41)	P value
IgM	Positive	6 (14.6%)	4 (9.8%)	0.737
	Negative	35 (85.4%)	37 (90.2%)	
IgG	Positive	24 (58.5%)	13 (31.7%)	**0.026***
	Negative	17 (41.5%)	28 (68.3%)	

Data are presented as mean ± SD or frequency (%), IgM: immunoglobulin M, IgG: immunoglobulin G, *: statistically significant as P value <0.05.

The mean dopamine level was significantly higher in group A compared to group B (92.7 ± 17.94 pg/ml vs. 45.4 ± 22.48 pg/ml, P<0.001). The mean adrenaline level was significantly higher in group A compared to group B (272.5 ± 135.04 pg/ml vs. 147.4 ± 71.44 pg/ml, P<0.001). The mean noradrenaline level was insignificantly different between both groups. Table 4

Table 4: Level of neurotransmitters between the studied groups

	Group A (n = 41)	Group B (n = 41)	P value
Dopamine (pg/ml	92.7 ± 17.94	45.4 ± 22.48	**<0.001***
Adrenaline (pg/ml)	272.5 ± 135.04	147.4 ± 71.44	**<0.001***
Noradrenaline (ng/ml)	4.5 ± 2.27	3.8 ± 1.78	0.108

Data are presented as mean ± SD or frequency (%), *: statistically significant as P value <0.05.

The mean dopamine level was significantly higher in Ig G positive patients compared to Ig G negative patients (87.4 ± 20.54 pg/ml vs. 49.4 ± 24.61 pg/ml, P< 0.001). The mean adrenaline level was significantly higher in Ig G positive patients compared to Ig G negative patients (271.6 ± 111.39 pg/ml vs. 171.0 ± 48.38 pg/ml, P= 0.001). The mean noradrenaline level was insignificantly different between both Ig G positive and Ig G negative patients. Table 5

Table 5: Relation of T. gondii IgG positivity and serum neurotransmitters level

	Ig G positive (n = 24)	Ig G negative (n = 17)	P value
Dopamine (pg/ml	87.4 ± 20.54	49.4 ± 24.61	**<0.001***
Adrenaline (pg/ml)	271.6 ± 111.39	171.0 ± 48.38	**0.001***
Noradrenaline (ng/ml)	3.13 ± 1.48	3.06± 0.8	0.869

Data are presented as mean ± SD or frequency (%), IgG: immunoglobulin G, *: statistically significant as P value <0.05.

Discussion

Mental and behavioural disorders represent a major public health problem. It affects about 10-16% of the population in any given year (Rehm and Shield, 2019). These disorders contribute by twelve percent to the global disease burden. The treatment is mostly symptomatic because the etiology is still obscure (Banaschewski et al., 2017). Although it is hypothesized to be multifactorial and related to genetic and environmental mediation, there is a great assumption for the role of microbial agents in the causation of psychiatric disorders. The infectious agents receiving attention of being accused include Toxoplasma gondii, herpes simplex virus, cytomegalovirus and influenza virus (Severance and Yolken, 2020, Ouabbou et al., 2020).

Many may be unaware of the dangers of toxoplasmosis, and many consider it a secondary and transient disease, but recent studies have indicated that most psychiatric and neurological diseases affecting people are caused by this parasitic infection (Desmettre, 2020, Flegr and Horáček, 2019).

The toxoplasma parasite is one of the most important parasites that manipulate its host, which contributes to the successful completion of its life cycle (Zhu et al., 2019). Studies have shown that mice infected with toxoplasmosis become not afraid of predators, cats, but rather become attracted to it (Boillat et al., 2020, Flegr, 2017). Toxoplasma parasites manipulate more than thousand genes in a body of infected host, ones have genes that encode the enzymes involved in the synthesis of neurotransmitters An important gene encodes the tyrosine

hydroxylase enzyme which is involved in the synthesis of dopamine (Leroux et al., 2018).

Subjects with various neuropsychiatric disturbances, as personality disorders, obsessive compulsive disorder, bipolar disorder, unipolar depression, drug abuse disorder, suicides, homicides, generalized anxiety, panic disorders and mood disturbances, have been reported to be more often infected with Toxoplasma than normal controls (Flegr, 2015).

One of the reported explanations for the psychobehavioral changes in toxoplasmosis-infected humans was the study of Prandovszky et al. (Prandovszky et al., 2011) which proved direct correlation between the number of infected dopaminergic cells in brain with T. gondii and the amount of dopamine released.

In the present study, the mean dopamine and adrenaline levels were significantly higher in group A compared to group B ($P<0.001$) whereas no significant difference was found in the mean noradrenaline level between both groups. These results were different from that reported by AL-Hadad et al. (AL-Hadad et al., 2019) which showed no significant difference in the concentrations of dopamine and noradrenaline between the group of chronic toxoplasma parasites and the control group, although there was a slight increase in concentration in the infected group from control group. The level of serum adrenaline in latent T. gondii infected human in these trials was significantly higher than the control human. The changes recorded during this study in some neurotransmitters may result in? from neurons infection or as a result of an immune response to the infection.

Melzer et al. (Melzer et al., 2010) identified the presence of toxoplasma cysts in neurons solely and astrocytes cells are free from infection in brain of mice during chronic infection by using FITC-Dolichos biflorans dye with a confocal fluorescence microscope. Carbel et al. (Cabral et al., 2016) pointed out that neurons are the main target cell of chronic T. gondii CNS infection and that the presence of bradyzoite stage limited in neurons during brain infection. There are several studies have shown that an increase in the concentration of dopamine in the brain of rodents, such as mice, also other studies have linked the increase in the concentration of brain dopamine with some neurological diseases such as schizophrenia in human (Skallová et al., 2006, Prandovszky et al., 2011).

Both study of Juanah et al. (Juanah et al., 2013) and Çelik et al. (Celik et al., 2015) were showed that there was a relationship between chronic infection with Toxoplasma and schizophrenia, this relationship was interpreted at the time by increasing the concentration of dopamine. However, AL-Hadad et al. (AL-Hadad et al., 2019) found no significant difference between both case and control group as regard dopamine.

Also, previous research showed that the schizophrenic patients with toxoplasmosis showed different serum dopamine levels (Flegr et al., 2003). Also, the increased dopamine levels in the seropositive schizophrenic cases compared to seronegative schizophrenic cases was accountable for the behavioural changes (Mahmoudvand et al., 2015). Ali et al. (Ibrahim Ali et al., 2020) reported that the

behavioural changes in the T. gondii seropositive patients were related to increase in the serum dopamine level. This neurotransmitter played the noteworthy role in schizophrenia (Hodkova et al., 2007). Prandovszky et al. (Prandovszky et al., 2011) found that serum dopamine increase levels to risk deterioration of schizophrenia.

Alsaady et al. (Alsaady et al., 2019) found suppressing of the noradrenergic system with decreasing of norepinephrine (NE) levels in vitro in neural cells of infected animals as rat and in infected human brain (Johnson and Koshy, 2020), as well, increased of neuroactive metabolites levels which may disturb glutamatergic and dopaminergic and stimulates tryptophan degradation due to cytokine-mediated activation of indoleamine-2,3-dioxygenase (IDO) and reduce the amount of serotonin (Alsaady et al., 2019). As well as a very active of genes expression Drd1 and Drd2 to dopamine receptor in mice with high cyst burden (Lindová et al., 2012).

In Toxoplasma infected mice Ihara et al. (Ihara et al., 2016) results demonstrated decrease in levels of norepinephrine in the cortex and amygdala. Zhou et al. (Zhou et al., 2018) shown difference metabolites connected to changes in metabolism of some lipids and amino acid (phenylalanine, tyrosine, alanine, tryptophan, aspartate, and glutamate) during acute and chronic stage of T. gondii infection in mice.

One of the functions of adrenalin is to help induce the release of the prolactin hormone. Dzitko et al. (Dzitko et al., 2008) explained that women who have a high concentration of prolactin have greater resistance to infection by Toxoplasma gondii. The adrenalin hormone is mainly extracted from the adrenal gland in the human body (80%) and the rest is produced within brain cells (20%) (Hartmann et al., 2019). Our study had some limitation, it is single centre study was relatively small sample size.

Conclusions

Chronic infection by T. gondii causes a change in some neurotransmitters (dopamine and adrenaline) and may be explained by the occurrence of certain neurological diseases in the incidence of latent toxoplasmosis. Nevertheless, efforts must be directed to toxoplasmosis prevention by the health education and arising awareness of its risk factors as to the stray and/or pet cats, eating habits especially of raw vegetables and fruits, hand-washing and hygienic behaviour.

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Running title: Toxoplasma in neuropsychiatric disorders

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