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ORIGINAL ARTICLE

The Association between Toxoplasmosis and Some Psychiatric Disorders: A Case Control Study

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ABSTRACT

Background: Psychiatric disorders negatively affect individuals' quality of life. It is believed that latent toxoplasmosis is associated with mental illnesses and personality changes due to its neurotropic nature. Experimental evidence in rodent modelsand controlled behavioral studies in people that show elevated seropositivity of anti-*Toxoplasma* antibodies in individuals with mental problems all strongly support this theory. In this study, we tried to shed light on the role of toxoplasmosis as a risk factor for some psychiatric disorders, aiming to treat those patients and improve their life performance.

Methods: A case control study was performed in the psychiatry outpatient clinic, Zagazig University Hospital and Medical Parasitology Department, Faculty of Medicine, Sharkia Governorate, Egypt. This study included 152 subjects (76 patients with major psychiatric disorders and 76 healthy control subjects). The diagnosis of psychiatric disorders was according to the DSM-5 criteria for major psychiatric disorders. ELISA was used to test patients for anti-*T. gondii* IgG seropositivity.

Results: According to our findings, psychiatric patients had a greater seroprevalence of *Toxoplasma* IgG (64.5%; 49/76) than the control group (13.2%; 10/76) ($p<0.001$). Also, patients with major depressive disorders (MDD) had the highest prevalence of latent *T. gondii* infection, followed by patients suffering from schizophrenia and bipolar.

Conclusions: Patients with some psychiatric disorders showed higher seropositivity of anti-*Toxoplasma* IgG compared with the control group. This was evident in those with MDD. Understanding the risk factors for *Toxoplasma* infection may be the first step in developing future preventative measures for patients with mental illness.

Keywords: *Toxoplasma gondii*; Major Depressive disorders; Schizophrenia; Bipolar.

INTRODUCTION

Toxoplasma gondii (*T. gondii*) is the most common obligatory intracellular parasite that causes a disease called toxoplasmosis. Depending on environmental variables, cultural traditions, and age, toxoplasmosis prevalence varies from 20 to 80% in the human population **[1]**. According to **[2]**, in the general population of Egypt, the seroprevalence of *Toxoplasma* IgG varied between 3% and 42.5%. Although it exists in wealthy countries as well, it is more prevalent in poor nations **[3]**.

T. gondii's primary and only definitive host is cats. The parasite releases its oocysts found in cats' small intestine into the environment with their feces; yet any animal with warm blood, including humans, can serve as the parasite's intermediate host **[1]**.

Human infections with *T. gondii* are primarily brought on by eating meat containing parasite cysts that is either uncooked or undercooked, drinking contaminated water or food with oocysts from cat feces, or receiving the infection by vertical transmission from mother to child **[3]**.

There are two clinically different stages of toxoplasmosis in humans. The rapid development of tachyzoites in different host body cells is the hallmark of the acute phase. This phase's

symptoms are similar to those of a bacterial or viral illness. This phase changes into a latent stage in immunocompetent humans spontaneously, whereby bradyzoites slowly grow in tissue cysts. Heart, liver, the central nervous system, skeletal muscles, kidneys, lungs, and reproductive systems are among the body parts that may develop tissue cysts. The infection lasts the rest of an infected person's life, and when immune function is compromised, tissue cysts may be triggered **[1]**.

The prevalent form of toxoplasmosis is latent toxoplasmosis, which is an infection without symptoms. It has been connected to mental health issues **[4]**.This could be because the parasite directly affects the structure and function of neurons or due to the host immunological reaction**[5]**. On the other hand, the theory of parasite manipulation suggests that *T. gondii* infects brain cells and uses host behavior manipulation to increase the rate of transmission **[6]**.

Recent research has revealed a correlation between alterations in behavior, neurochemistry, and neuronal architecture with chronic *T. gondii* infection in the brain **[7]**.

There is a close relationship between neuroinflammation and neuropsychiatric illnesses, including schizophrenia and mood disorders. There's growing evidence that depression and inflammation are mutually reinforcing **[8]**. Toxoplasmosis has been linked to neurotic illnesses like depression, schizophrenia, and Alzheimer's illness since the CNS is one of the anatomic organs where *Toxoplasma* localizes. There is strong evidence to recommend that the pathophysiology of mental illnesses may be influenced by toxoplasmosis.**[9]**.

Persistent toxoplasmosis in humans is linked to abnormal host behavior **[10]** and affects the course of mental illnesses **[11]** like bipolar disorder, schizophrenia, and obsessive-compulsive disorder **[12]**, according to a growing research corpus.

METHODS

A case control study was performed on patients at Zagazig University Hospital's Psychiatry outpatient clinic and healthy controls from 15 September 2023 to 15 March 2024. The sample size was 152 subjects (76 patients with major psychiatric disorders and 76 healthy controls). The sample was selected by a simple random technique. All study participants provided written informed permission, and the research ethics committee (Institutional Review Board, Faculty of medicine, Zagazig University) licensed the study. (IRB number 10614/ 29-3-2023). Patients' selection for participation was based on inclusion and exclusion criteria. The inclusion criteria of patients include patients with psychiatric disorders e.g., schizophrenia, depression, etc., patients' age between 18 and 50 years, patients of both genders and every social class were included. The exclusion criteria of patients include patients' age below 18 or above 50 and patients taking antiparasitic treatment. The control group was healthy volunteers free from any apparent physical or neuropsychiatric morbidity and had no family history of any psychiatric disorders. They were recruited from workers and employees working in Zagazig University hospitals to participate in the study. They were matched for gender, age and demographic variables as far as possible with patients' groups.

Clinical assessment was done by socio-demographic Questionnaire (Table 1), psychiatric semi-structured interview and diagnosis according to the DSM-5 criteria for major psychiatric disorders. Laboratory procedures: Participants (cases and controls) had venous blood samples (5 ml) drawn using sterile disposable syringes according to aseptic procedures. After being mixed and placed in potassium-EDTA sample tubes, the blood samples were let to stand for two to five minutes, and immediately transferred to the Parasitology Department's laboratory, Faculty of Medicine, Zagazig university and were centrifuged at 3000 rpm for 5 min. Plasma was separated and every sample was examined for anti-*T. gondii* IgG presence using ELISA kit, Enzyme immunoassay test kit for *Toxoplasma* IgG, no. 10234 by PerkinElmer Health Sciences, Inc., Hayward CA, USA. The test was conducted in compliance with the guidelines provided by the manufacturer. The optical density (OD) values at 450 nm were read using an automated microplate reader. In order to distinguish between positive and negative sera, the cut-off value was 1.0.

Statistical analysis:

Software version 25 of the SPSS (Statistical Package for Social Science) application was used to computerize and statistically analyze the gathered data. Qualitative data were shown as numerical values, relative percentages, and Pearson's chi square ($\chi 2$) test which was utilized to determine the distinctions between qualitative variables. The mean, range, and standard deviation (SD) were used to express the quantitative data. The difference between quantitative variables in two groups of normally distributed data was calculated using the independent T test. The level of statistical significance (S) was established at 5% ($P<0.05$),

the p-value ≥ 0.05 was defined as statistically insignificant (NS), and a highly significant difference existed if p ≤ 0.001 (HS). The correlations between two variables were predicted using bivariate logistic regression analysis.

RESULTS

Analysis of the sociodemographic data of patients with major psychiatric disorders and controls revealed that patients' and controls' mean ages were 31.89 ± 8.55 years range (19-49 years) and 32.5 ± 8.3 years range (20-48 years), respectively (Table 1). Working and education status were significantly different between psychiatric patients and healthy controls (P<0.001). Some psychographic data showed statistically significant variations between the groups under study as sources of drinking water and dealing with cats or animals (P = 0.038 and P = 0.017, respectively) (Table 2). There were no statistically significant differences between the studied groups in medical status except for neurological examination (rigidity and instability) p = 0.029 (Table 3).

Our findings revealed significantly increased levels of serum IgG antibodies to *T. gondii* in patients with psychiatric disorders 49/76 (64.5%) when compared to controls 10/76 (13.2%), P<0.001. The OR for this association was 11.978 with a 95% CI= 5.314 to 27.041 (Table 4).

Regarding the frequency of psychiatric disorders, we found that, out of the 76 patients included in our study, the most prevalent detected psychiatric disorder was schizophrenia (32 patients), followed by MDD (25 patients), then bipolar disease (19 patients). Out of schizophrenic patients, 14 patients (43.75%) were presented with acute symptoms, and 18 patients (56.25%) presented with chronic symptoms. While in patients diagnosed with MDD, 14 patients (56%) presented with acute symptoms and 11 patients (44%) presented with chronic symptoms. Regarding bipolar disease, 7 patients (36.8%) were presented with acute symptoms, while 12 patients (63.2%) were presented with chronic symptoms (Table 5). Among the bipolar patients included in our study, 11 patients (57.9%) were IgG positive, 21 patients out of the 32 schizophrenia patients (65.6%) were IgG positive, and 17 patients out of the 25 MDD patients (68%) were IgG positive (Figure 1).

Regression bivariate analysis revealed an association between some characteristics in psychiatric patients, including contact with cats or other pets, and the source of drinking water (P = 0.040 and 0.044) (Figure 2).

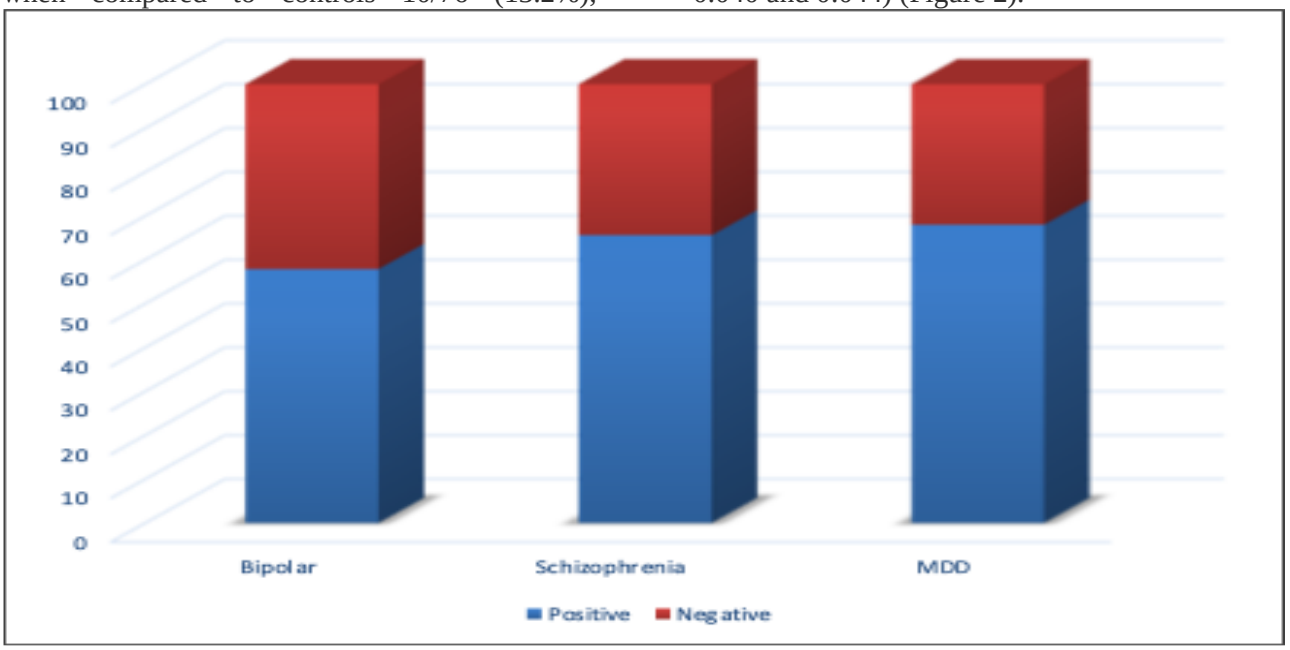

Figure (1): Seropositivity of anti-*T. gondii* IgG among our psychiatric patients.

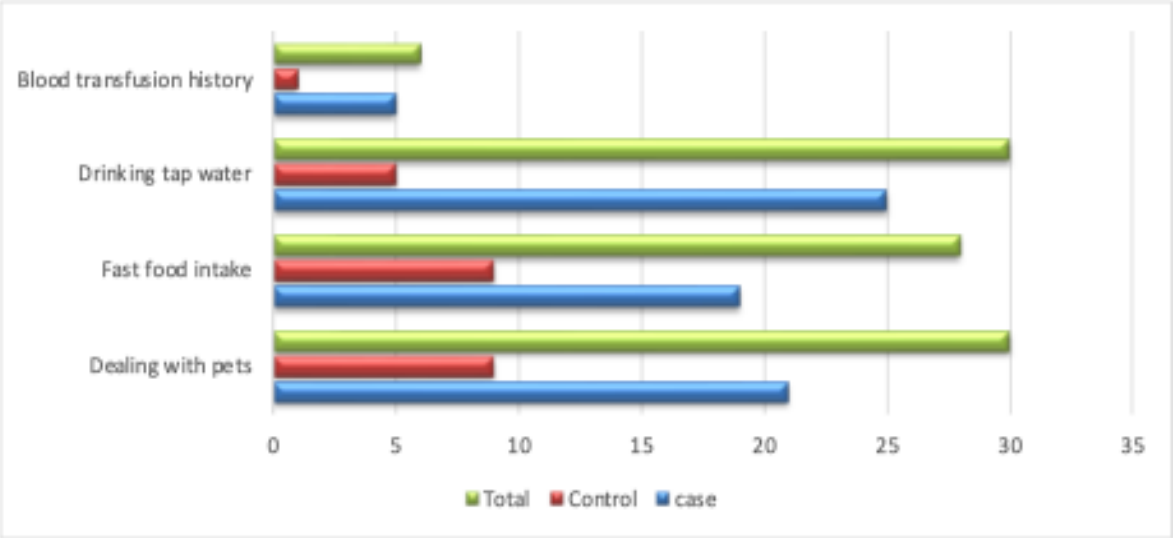

Figure (2): Positive anti- *T. gondii* IgG among the studied groups according to risk factors of infection.

DISCUSSION

Toxoplasma gondii, a protozoan, offers a compelling illustration of manipulation that modifies host behavior specifically to improve transmission. However, the exact process causing these changes is still unknown**[13]**.

In addition to helping clarify the pathophysiology of significant psychiatric disorders from the standpoints of pathogen infection and immunity, research on chronic toxoplasmosis and host psychiatric behavioral disorders can also aid in the identification of novel therapeutic targets and the investigation of the molecular mechanism underlying the behavioral changes in hosts brought on by *T. gondii*. Additionally, it aids in the development of fresh approaches to effectively prevent and control the combined problems of the two diseases **[14]**.

The current study included 152 individuals divided into 76 patients with psychiatric disorders (schizophrenia, depression and bipolar) and 76 healthy controls matched with each other in sociodemographic data and BMI (except for occupation status and education level). Working and education level showed significant differences between the two studied groups ($p<0.001$).

The majority of neuropsychiatric illnesses typically coexist with low levels of education and unemployment. This is primarily related to patient infection exposure because these individuals may reside in an unsanitary and unfavorable environment that might act as infection triggers **[15]**.

We compared the seropositivity of anti-*T.gondii* IgG between healthy controls and psychiatric patients. We also studied the relation between psychiatric patients' characteristics and*T. gondii*infection.

We found that about (64.5%) of psychiatric patients were seropositive for anti-*T. gondii* IgG antibodies. On the other hand, the chronic *Toxoplasma* infection in the control group was (13.2%) having a difference that is statistically significant ($p < 0.001$).

The disparity in sanitary conditions between the control and psychiatric subjects may account for at least some of the prevalence difference between the two groups. In fact, the majority of psychiatric patients lived in substandard housing and belonged to lower socioeconomic groups than the control groups.

Our findings were in line with numerous studies that documented high toxoplasmosis prevalence rates in people with psychiatric illnesses.**[3]** discovered that there were statistically significant differences between the two groups, with the anti-*Toxoplasma* IgG positive rate in psychiatric patients being (3.03%) and in the general population being (1.05%). Also, **[16]** revealed that psychiatric individuals had a considerably higher seroprevalence of *Toxoplasma* IgG antibodies (67.86%).Moreover, in a study conducted by **[17]** in a northern Mexican city, out of 180 controls, 16 (8.9%) and 25 (18.2%) of 137 psychiatric inpatients tested positive for anti-*T. gondii* IgG antibodies, suggesting latent toxoplasmosis.

On the other hand, **Chen *et al.*[18]** contained two groups: 681 healthy controls and 798 psychiatric patients. It was discovered that there were no statistically significant differences in the seropositivity rates of anti-*Toxoplasma* IgG between the two groups ($P = 0.145$).

This disparity can be caused by variations in study sample sizes, community habits, or our approach to population study selection. Other factors, including variations in control group selection, genetic vulnerability, and the use of antipsychotic medications, may possibly be responsible for the variation in outcomes among these studies.

Analyzing the results of toxoplasmosis prevalence among various psychiatric disorders showed that patients with major depressive disorders (MDD) had the highest prevalence of latent toxoplasmosis (68%), followed by patients with schizophrenia and bipolar (65.6% and 57.9% respectively).

Toxoplasma gondii has been linked to the development of depression by inducing the production of proinflammatory cytokines (TNF and IL-6) by the host immune system. The indoleamine-pyrrole 2,3-dioxygenase (IDO) enzyme is activated as a result of the activated cells' production of IFN-γ. The enzyme depletes tryptophan and prevents *T. gondii* from growing. Depression results from a decrease in serotonin synthesis in the brain**[19]**.

Schizophrenia patients are more susceptible to pica and coprophagia, and they often lack basic hygiene and self-care abilities**[21]**. This might be the reason for the link between schizophrenia and toxoplasmosis.

Despite extensive research, the connection between *T. gondii* infection and the development of bipolar disorder (BD) remains poorly understood and documented **[20]**.

These findings appear to be in accordance with the **[17]** study, which found high positive rates of anti-*Toxoplasma gondii* IgG in patients with psychiatric disorders (MDD, schizophrenia then bipolar) (33.3%, 26.3% and 16.7%, respectively). Also,**[3]** reported the same order with different rates (3.57%, 3.22% and 2.41%, respectively).

Sugden*et al.*[9] reported the relation between toxoplasmosis infection and psychiatric disorders MDD (14.8%) and schizophrenia (3.4%). However, **[21]** found high positive rates of anti-*Toxoplasma* IgG in patients with psychiatric disorders (MDD, bipolar and schizophrenia), which were (51.4%, 47.1% and 40.1%) respectively. Similar findings were reported by **[22]** with different positive rates of anti-*T. gondii* IgG (33.3%, 25% and 16.6%) respectively.

Grada*et al.* [23]in astudy on the prevalence of *T. gondii* IgG antibodies in psychiatric disorders, revealed that patients with schizophrenia and major depressive disorder had greater seroprevalences of *Toxoplasma* IgG antibodies than those with bipolar disorder, with rates of 70.7%, 70.4%, and 62.9%, respectively.

Genotypes of *T. gondii* may be the cause of the disparate results found in research on the parasite and mental illnesses. The virulence, reproduction, and unique neuropathogenic potentials of this protozoan vary among its genotypes **[24]**. Also, it may be attributed to the nature of the study, selection of cases and difference in sample size between different studies.

According to reports, the seroprevalence values of *Toxoplasma gondii* infection changed depending on culture, hygiene, socioeconomic status, interaction with felines, environmental condition, populations sampled and types of laboratory techniques that are used **[25]**. Moreover, the prevalence of *T. gondii* infection could vary, even within a country **[26]**.

A number of risk factors have been identified, including close contact with cats or pets, cleaning up cat litter or feces, eating undercooked meat, coming into direct contact with soil, consuming unpasteurized milk or milk products, eating unwashed fruits or vegetables, having an inadequate water supply, and not practicing good hygiene **[25]**.

In the current study, our linear regression bivariate analysis of some variables in cases and controls and their association with *T. gondii* seropositivity revealed that contact with cats and/or animals, drinking tap (contaminated) water, and fast-food intake were associated with a high seroprevalence rate of anti-*Toxoplasma* IgG (49.2%, 69.8%, and 49.1%, respectively).

These findings agreed with **[27]** bivariate analysis, which reported several sociodemographic and behavioral characteristics concerned with an increased sero-frequency rate of *Toxoplasma* IgG. These include cats/dogs at home and exposure to soil. Also,**Zaki*et al.*[15]** linear regression bivariate analysis revealed nearly similar findings (P <0.0001); however, they added that a positive history of blood transfusion and eating raw or undercooked meat were also associated with a higher sero-frequency rate of *Toxoplasma* IgG.

Nevertheless, **Lopes*et al.*[28]** stated that consuming processed foods made from smoked or cured pork, eating unwashed fresh vegetables or fruit, and handling soil without gloves were the risk factors for acquiring *T. gondii* infection (listed in increasing order of their OR).

Additional behavioral traits include cleaning up cat waste, traveling, eating meat from goats, chickens, turkeys, or pigeons, eating pork,

beef, lamb, or other animals, eating meat frequently, eating dried or processed meat, drinking unpasteurized milk or untreated water, and eating raw fruits that haven't been cleaned **[29]**.

CONCLUSIONS

Finally, we concluded that toxoplasmosis may be a risk factor for some major psychiatric disorders, such as MDD and schizophrenia. Additional research would improve the understanding of the underlying factors of mental illnesses and improve treatment and prevention strategies.

Declarations:

Authors' contribution

All authors have participated in the concept and design, analysis and interpretation of data, drafting and revising of the manuscript and all authors have approved the manuscript as submitted.

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