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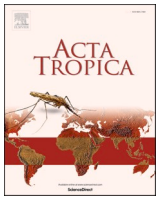

Seroprevalence and sociodemographic characteristics of *Toxoplasma gondii* infection in patients with psychiatric disorders in Malaysia

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ABSTRACT

Toxoplasma gondii is a neurotropic protozoan parasite that affects neuronal processing in the brain. This study aimed to investigate the prevalence of *T. gondii* infection in psychiatric disorder patients. We also investigated the potential association between sociodemographic, clinical manifestation, and behavior of *Toxoplasma*-seropositive patients with psychiatric disorders. Commercial ELISAs (IgG, IgM, and IgG avidity) using serum and PCR using buffy coat were performed on samples from 54 individuals in each of the following groups: patients diagnosed with depressive disorder, bipolar disorder, and schizophrenia, as well as psychiatrically healthy subjects (control group). They were recruited from the Hospital Universiti Sains Malaysia in Kelantan, Malaysia. Of 54 patients with depressive disorder, 24/54 (44.4 %) were seropositive for IgG, and four (16.7 %) were IgG+/IgM+. Among the latter, a high avidity index indicating a past infection was observed in half of the samples (50.0 %), and the other half (50.0 %) showed a low avidity index, indicating a possible recent infection. Meanwhile, 30/54 (55.6 %) patients with bipolar disorder were seropositive for IgG+, five (16.7 %) were IgG+/IgM+, and four of them had a high avidity index, and one had a low avidity index. Patients with schizophrenia showed 29/54 (53.7 %) seropositive for IgG, two of them (6.9 %) were IgG+/IgM+; one of latter had a high avidity index, and one had a low avidity index. Of 54 people in the control group, 37.0 % (20/54) were seropositive for *T. gondii* IgG antibodies. However, no significant difference was observed in seroprevalence between the control group and each patient group. No PCR-positive results were documented. A Chi-Square and multiple logistic regression showed that age ($p = 0.031$), close contact with cats/pets ($p = 0.033$) and contact with soil ($p = 0.012$) were significantly associated with *Toxoplasma* seropositivity in patients with psychiatric disorders. Additional research is needed to elucidate the causal relationships and underlying mechanisms.

1. Introduction

One-third of the world's population is infected with *Toxoplasma gondii*, with marked geographical variations that make it one of the most common zoonotic diseases (Montoya and Liesenfeld, 2004). *T. gondii* is a facultatively heteroxenic and polyxenic protozoon that can infect all warm-blooded animals, including humans (Parlog et al., 2015; Bay-Richter et al., 2019). Human *Toxoplasma* infection occurs via ingestion of tissue cysts in contaminated undercooked meat and sporulated oocysts from feces of infected felines that contaminate food or water.

The prevalence of *T. gondii* infection in humans varies widely across the world depending on the regional environment, sociodemographic, and risk factors (Cong et al., 2015; Muflikhah et al., 2018; Achaw et al., 2019; Hokelek, 2020). Previous studies reported that the seroprevalence rates were 13.3–85.3 % in Asia, 40–76 % in Europe, 21.74–74.8 % in Africa, and 7.3–26.5 % in North America (Minbaeva et al., 2013; Wilking et al., 2016).

The prevalence of psychiatric disorders is a significant concern, affecting around 450 million people globally. In Malaysia, a quarter of families have at least one member with a psychiatric disorder at any

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time (Malaysia Mental Health Association MMHA, 2023). Specifically, psychiatric diseases affect 12 % of Malaysians aged between 18 and 60 years old, as reported by the National Health and Morbidity Survey (NHMS) in 2011. According to the NHMS 2015, psychiatric disorders among adolescents (15–24 years) increased from 10.7 % in 1996 to 29.2 % in 2025. The highest prevalence of mental disorders was observed in the rural areas of East Malaysia (43 %), followed by Kuala Lumpur (40 %) (Noor Ani et al., 2015). These findings highlight the importance of addressing and understanding the prevalence and risk factors of psychiatric disorders to develop effective approaches for mental health support and intervention in Malaysia.

Recent research has shed light on the potential link between *T. gondii* infection and psychiatric disorders. Epidemiological studies have highlighted that the pathogenesis of psychiatric disorders, such as mental retardation, schizophrenia and bipolar disorder, may be linked to *T. gondii* infection (Del Grande et al., 2017; Muflikhah et al., 2018). There is also an increasing interest in understanding the parasite's biology, its interactions with the brain and the immune system, and its association with psychiatric disorders (Tyebji et al., 2019).

In Malaysia, the probable associations and risk factors of *T. gondii* infection are poorly studied in psychiatric patients. Most studies focused on the association between *T. gondii* infection and schizophrenia (Emelia et al., 2012; Omar et al., 2015; Sutterland et al., 2019). Thus, the present study aimed to investigate and compare the prevalence of *T. gondii* infection among patients with schizophrenia, bipolar disorders, and depressive disorders at a major hospital in the Malaysian peninsular's east coast. Additionally, our study aimed to elucidate any association between *Toxoplasma*-seropositive patients with their sociodemographics, clinical manifestations, and behavioral factors.

2. Materials and methods

2.1. Study design and study population

A cross-sectional study was conducted from February 2020 to July 2022 at the Hospital Universiti Sains Malaysia (Hospital USM), Kelantan, Malaysia. A total of 216 subjects were recruited using convenience sampling: patients with schizophrenia ($n = 54$), bipolar disorders ($n = 54$), depressive disorders ($n = 54$), and 54 psychiatrically healthy individuals (control group). Cases were randomly selected upon admission to the psychiatry ward or when they came for follow-up at the psychiatry clinic. An experienced psychiatrist made the clinical diagnosis according to the "Diagnostic and Statistical Manual of Mental Disorders" criteria, fifth edition (DSM-V). The psychiatrist reassessed selected cases using the "Mini International Neuropsychiatric Interview (MINI)", version 6.0.0 DSM (Sheehan et al., 1998) to confirm the diagnosis. These patients were also screened for any immunocompromising and immunologic disorders. The severity of psychiatric symptoms was further evaluated using the "Brief Psychiatric Rating Scale (BPRS)" for schizophrenia, the "Young Mania Rating Scale (YMRS)" for bipolar disorders, and the "Hamilton Rating Scale for Depression (HAM-D)" for depression. The inclusion criteria were as follows: patients aged more than 18 years old, diagnosed with schizophrenic or bipolar disorders or depression (mild, moderate, or severe) for more than six months to ensure the stability of diagnosis, and agreed to participate (consented by the patient or relative). The exclusion criteria were patients who were immunocompromised or with immunological disorders, including patients on chemotherapy, immunosuppressive drugs after organ transplantation, patients on glucocorticoids, with leukemia, lymphoma, multiple myeloma, and acquired immunodeficiency syndrome (AIDS). We also excluded pregnant women since it has been reported that physical, social, and emotional changes in pregnancy may lead to mental health issues such as anxiety and depression (Chauhan and Potdar, 2022). The control group consisted of 54 psychiatrically healthy volunteers recruited through advertisements at Hospital USM. The inclusion criteria for the control group were older than 18 years old and free from psychiatric illness based on the MINI screening.

2.2. Sociodemographic, clinical manifestations, and behavioral data

All participants provided sociodemographic data (age, gender, ethnicity) and family history of mental disorders. However, we did not match the sociodemographic data of the psychiatrically healthy volunteers with that of the patients. The behavioral data collected were on animal contact, cleaning of cat feces, consumption of raw or undercooked meat, unpasteurised milk or milk products, unwashed raw vegetables, or fruits, and contact with soil via gardening or agriculture. Clinical data (severity of symptoms, duration of illness) were also collected from their hospital records.

2.3. Blood collection

The study's rationale was explained verbally to the participants and written informed consent from all the participants, or their legal guardians was obtained before sample collection. Three millilitres of EDTA-blood samples were collected from all subjects, centrifuged at 1000 x *g* for 15 min to obtain plasma, and then stored at −20 °C.

2.4. Serological assay

The commercial *Toxoplasma* enzyme-linked immunosorbent assay (ELISA) kits from BioRad (USA), i.e., Platelia™ TOXO IgG (cat. no. 72,840), Platelia™ TOXO IgM (cat. no. 72,841), and Platelia™ TOXO IgG avidity (cat. no. 72,842), were used for testing. All plasma samples were tested in duplicates, following the protocols described by the manufacturer. The optical density (OD) results were read at 420 nm with 650 nm as the reference wavelength, using a Varioskan Flash Plate Reader (Thermo Fisher Scientific, USA). For IgG ELISA, ⟨ 6 IU/mL was read as a negative result, 6 to 9 IU/mL as equivocal, while ⟩ 9 IU/mL was interpreted as a positive result. Furthermore, IgG-positive sera were classified into two serointensity groups, i.e., low IgG antibody titer (9–60 IU/mL) and high IgG antibody titer (> 60 IU/mL). For IgM ELISA, an OD ratio <0.80 was considered a negative result, a ratio between 0.80 and 1.00 was considered equivocal, while a ratio ≥ 1.00 was interpreted as positive. An IgG avidity assay was performed on samples positive for both IgG and IgM. An avidity index (AI) < 0.40 denotes low avidity IgG (antigen-antibody binding is readily dissociated) which indicates probable recent infection of fewer than 20 weeks. AI higher or equal to 0.50 shows high IgG avidity (antigen-antibody binding is not readily dissociated), which indicated a previous infection of more than 20 weeks. The avidity intermediate zone is shown by 0.40 ≤ AI < 0.50; in this study, intermediate AI was considered as high AI.

2.5. Polymerase chain reaction (PCR)

T. gondii is an intracellular organism; thus, tachyzoites do not freely circulate in the blood. The buffy coat, which contains approximately ten times more white blood cells than whole blood, was utilized for DNA extraction (Mychaleckyj et al., 2011; Zhou et al., 2016; Arefkhah et al., 2019). Briefly, the buffy coat was isolated from the blood sample after centrifuging at 1000 x g for 15 min. DNA was extracted from the buffy coat using the QIAmp DNA Blood Minikit (Qiagen, Germany) following the manufacturer's instructions. The extracted DNA's concentration and purity (A260/A280 ratio) were measured using a spectrophotometer (Eppendorf, USA).

A triplex polymerase chain reaction (PCR) was used to amplify the *T. gondii* B1 gene by using BF1R1 primer and the ITS region by using ITSFR primer, as described by Rahumatullah et al. (2012). The *Vibrio cholerae* HemM gene recombinant plasmid (0.5 μL) was used as an internal control for success of the amplication. The PCR products were visualized on a 1.8 % agarose gel stained with FloroSafe DNA stain (Axon Scientific Sdn Bhd., Malaysia), and the images were captured

under ultraviolet light using the Gel Doc image analyzer (Bio-Rad, USA).

2.6. Data analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) software version 25. A chi-square test, at a 5 % significance level ($p < 0.05$), was used to compare IgG antibody seroprevalence and serointensity rates between psychiatric patients and control group. For each specific psychiatric disorder and the control group, logistic regression was used to analyze the association between sociodemographic variables, clinical manifestations, and behavioural factors with low and high IgG antibody titers.

3. Results

3.1. Seroprevalence and serointensity rates of anti-T. gondii antibody in patients with schizophrenia, bipolar disorder, depressive disorder, and psychiatrically healthy subjects

We determined the anti-*Toxoplasma* IgG level and IgM antibodies from each group. Typically, IgM antibodies indicate recent or acute infection, while IgG antibodies imply past exposure or chronic infection (Hamidinejat et al., 2010). We further divided the IgG-positive sera into two serointensity groups, i.e., low, and high antibody titers. High IgG levels indicate an active or recent infection, previous exposure to an antigen, or ongoing immune response. Conversely, low IgG levels may indicate immunodeficiency or inadequate immune response. We also performed IgG avidity test as the results would indicate chronic or possible recent infection (Holec-Gąsior and Sołowińska, 2022). Thus, *T. gondii* IgM and IgG avidity tests in combination may help in detection of a recent infection (Ikuta et al., 2023). Data from patients in each group of psychiatric disorders are shown in Table 1S (Supplementary material). Among 54 patients with depressive disorder, 44.4 % (24/54) were seropositive for *T. gondii* IgG antibodies, and 4/24 (16.7 %) were IgG+, IgM+. Two of these patients exhibited a high IgG avidity index (AI), while the other two displayed a low AI. In patients with bipolar disorder, 55.6 % (30/54) were seropositive for *T. gondii* IgG antibodies, with 16.7 % (5/30) were IgG+, IgM+. Among these, four patients had a high AI, while one had a low AI. For patients diagnosed with schizophrenia, 53.7 % (29/54) tested positive for *T. gondii* IgG antibodies, and 6.9 % (2/29) were IgG+, IgM+. One patient in this subgroup had a high AI, while the other had a low AI. In the control group, 37.0 % (20/54) were seropositive for *T. gondii* IgG antibodies, with none tested positive for IgM. Statistical analysis revealed no significant difference in seropositivity rates between depressive disorder and the control group ($p = 0.068$), bipolar disorder and the control group ($p = 0.068$), or schizophrenia and the control group ($p = 0.082$) (Table 2S).

Regarding serointensity rates, no significant difference in high IgG antibody titer was observed between the depressive disorder and control groups ($p = 0.535$), the bipolar disorder and control groups ($p = 0.440$), or the schizophrenia and control groups ($p = 0.100$) (Table 2S).

3.2. Association between sociodemographic data, clinical manifestation, behavioural risk factors and toxoplasma seropositivity rate

The sociodemographic, clinical manifestation, behavioural risk factors and *Toxoplasma* seropositivity data from each group of patients with psychiatric disorders and the control group are shown in Tables 3S, 4S, 5S and 6S (in Supplementary materials). The information can be summarized as follows: The majority of the seropositive patients with depressive disorder were females (62.5 %), aged between 36 and 60 years (66.7 %), and of Malay ethnicity (100 %). Most were ill for less than ten years (75.0 %), and most had no family history of depressive disorders (91.7 %). For patients with bipolar disorder, there is also a greater representation of seropositive females (66.7 %), aged between 36 and 60 years old (60.0 %), and of Malay ethnicity (90.0 %). The duration of illness was more than ten years (56.7 %), and there was no family history of bipolar disorder (83.3 %). For patients with schizophrenia, majority of the seropositive patients were females (51.7 %), aged between 18 and 35 years old (51.7 %), of Malay ethnicity (100 %), the duration of illness was more than ten years (72.4 %), and no family history of schizophrenia (65.5 %). In the control group, majority of the seropositive patients were females (55.0 %), aged between 36 and 60 years old (75.0 %), and of Malay ethnicity (95.0 %).

In terms of their behavioral characteristics, the majority of the seropositive patients with depressive disorder did not have close contact with cats (79.2 %) or soil (79.2 %), did not clean up cat feces/litter (83.3 %), did not consume undercooked meat (91.7 %) or unpasteurized milk/milk products (100 %). For patients with bipolar disorder, majority of them did not have close contact with cats (70.0 %) and soil (76.7 %), did not clean up cat feces/litter (83.3 %), did not consume undercooked meat (96.7 %) and unpasteurized milk/milk products (100 %). In patients with schizophrenia, most did not have close contact with cats (65.5 %) or soil (82.8 %), did not clean up cat feces/litter (72.4 %), or consume undercooked meat (96.6 %) and unpasteurized milk/milk products (100.0 %). As for the control group, most had close contact with cats (60.0 %) and soil (75.0 %), but they did not consume undercooked meat (80.0 %) and unpasteurized milk/milk products (100.0 %). All participants practiced good hygiene. Comparison of number of individuals with *Toxoplama* seronegative and seropositive results showed that age (OR=3.455; 95 % CI=1.119–10.669; $p = 0.031$), close contact with cats/pets (OR=3.378; 95 % CI=1.103–10.347; $p = 0.033$), and soil (OR=0.21; 95 % CI=0.03–0.70; $p = 0.012$) were significantly associated with *Toxoplasma* seropositivity among patients with psychiatric disorders.

3.3. Association between sociodemographic data, clinical manifestations, behavioural risk factors, and low and high anti-T. gondii IgG antibody titers

Most patients with depressive disorder who had high anti-*T. gondii* IgG antibody titers were males (66.7 %), aged between 36 and 60 years old (62.5 %), had a duration of illness of more than ten years (83.3 %), and a family history of depressive disorder (100 %). Additionally, most patients had close contact with cats and soil (60.0 %). Among patients with bipolar disorder, the majority with high anti-*T. gondii* IgG antibody titers were females (55.0 %), aged between 18 and 35 (66.7 %), had a duration of illness of more than ten years (47.1 %), did not have a family history of bipolar disorder (52.0 %), and had close contact with cats (55.6 %). For patients with schizophrenia, the majority with high anti-*T. gondii* IgG antibody titers were males (57.1 %), aged between 18 and 35 (66.7 %), had a duration of illness of more than ten years (42.9 %), and had a family history of schizophrenia (60.0 %). Most of these patients did not have close contact with cats or soil. In the control group, high anti-*T. gondii* IgG antibody titers were observed in males (88.9 %), aged between 36 and 60 years old (66.7 %), and had close contact with cats (66.7 %) and soil (73.3 %). However, no significant difference was observed among high and low IgG titers between patients in each group of psychiatric disorders and the control group.

3.4. PCR detection of T. gondii infection in patients with schizophrenia, bipolar disorders, depressive disorder, and the control group

As shown in Figure 1S (Supplementary material), triplex PCR did not amplify the B1 gene and ITS-1 region in all samples.

4. Discussion

We performed a cross-sectional study to investigate the prevalence of T. gondii infection among psychiatric patients at a major public hospital in Malaysia and the associations of sociodemographic factors, clinical manifestations, and behavioral factors among *Toxoplasma*-seropositive

patients with psychiatric disorders. There were 216 participants, with equal representation ($n = 54$) from groups with depressive disorder, bipolar disorder, schizophrenia and a control group.

Individuals with *Toxoplasma* IgG+/IgM- results, indicating past exposure to the parasite, were observed in 44.4 % of patients with depressive disorder, 55.6 % with bipolar disorder, 53.7 % with schizophrenia, and 37.0 % controls. Although the prevalence of *T. gondii* infection among the three patient groups seemed to be higher than the control group, the difference was insignificant ($p = 0.068$). It indicates common and 'equal' exposure of individuals to *T. gondii* infection in the population. Other studies also reported no significant difference between the control group and each of the psychiatric disorders, i.e., depressive disorder (Gale et al., 2016; Abd El-Aal et al., 2016; Suvisaari et al., 2017), bipolar disorder (Alvarado-Esquivel et al., 2019), and schizophrenia (Emelia *et al.*, 2012; Anis et al., 2021). On the other hand, some studies reported significant differences between the control group and each of the psychiatric disorders, i.e., depressive disorder (Liu et al., 2022), bipolar disorder (Hussein et al., 2020; Liu et al., 2022), and schizophrenia (Fuglewicz et al., 2017; Ademe et al., 2022; Juanah *et al.*, 2013; Grada et al., 2022; Gutiérrez-Fernández et al., 2015; Hussein et al., 2020; Latif, 2022; Omar et al., 2015).

In some studies, a dynamic interplay was suggested between the time of *T. gondii* infection (recent or chronic) and the onset or exacerbation of psychiatric symptoms (Holec-Gąsior and Sołowińska, 2022; Achaw et al., 2019). The AI varied within groups in the present study, with about half of the IgG+, IgM+ samples showing a high AI. However, little can be inferred from the IgG avidity results due to the low numbers of samples (IgG+, IgM+) tested for AI. Some researchers recommend testing IgG avidity for IgG-positive samples, regardless of IgM results (Teimouri *et al.*, 2020), since IgM may be "transient or diminished" (Fricker-Hidalgo *et al.*, 2013).

In terms of serointensity rates, high IgG titers were observed in 25.9 % of individuals with depressive disorder, 25.9 % with bipolar disorder, and 27.8 % with schizophrenia, and 25.9 % controls. High *T. gondii* IgG levels may indicate a past or previous exposure to the parasite (chronic infection). Our study did not find any significant difference in the serointensity rates between patients and the control group. However, Emelia *et al.* (2012) reported a significant serointensity rate of anti-*T. gondii* IgG antibody in schizophrenic patients as compared to psychiatrically healthy volunteers.

The discrepancies among results of different studies could be due to differences in factors such as the severity of psychiatric disorders, control group selection, genetic susceptibility, type of antipsychotic drugs, type of serological assays, manner of result interpretation, and *T. gondii* genotypes in the population which vary in pathogenicity and replication rates (Emelia et al., 2012; Karabulut et al., 2015).

Our study showed that age, close contact with cats/pets and soil were significantly associated with *Toxoplasma* seropositivity among patients with psychiatric disorders. Other studies also reported that age and close contact with cats/pets were significantly associated with the transmission of *Toxoplasma* to the psychiatric patients (Achaw et al., 2019; Aref et al., 2022). Most of the abnormalities in people with neurological and behavioural disorders associated with chronic *Toxoplasma* infection may be caused by an increase in dopamine and changes in the levels of GABA, serotonin, glutamate, nitric oxide, noradrenaline, and kynurenic acid in the brain (Virus et al., 2021).

All patients and control groups in our study were PCR-negative. The precise kinetics of parasitemia in the body are unknown. The negative PCR findings could be due to the very short duration of parasitemia in the human's peripheral blood or the very small amount of circulating tachyzoites, which are undetectable by the conventional PCR used in our study.

A limitation of our study is that during participant recruitment, the sociodemographic data of the psychiatrically healthy volunteers was not matched with that of the patients. The confounding variables could vary across different groups of participants, so we may have yet to fully capture the complex interaction of factors influencing the study outcomes. Future research should address the confounding variables to enhance the reliability of the findings.

5. Conclusion

The present study found no significant difference in *T. gondii* prevalence rates among patients with depressive disorder, bipar disorder, and schizophrenia compared to the control group. However, sociodemographic factors (age) and behavioral risk factors (close contact with cats and soil) showed significant correlations with *Toxoplasma* seropositivity. This study provides some insights into the *T. gondii* infection in patients with psychiatric disorders in Malaysia. Further studies with larger sample sizes and the inclusion of other psychiatric disorders are necessary to thoroughly assess the risk factors and outcomes of *T. gondii* infection in this population. Investigating metabolic changes associated with *Toxoplasma* infection and psychiatric disorders may also provide new insights into their pathogenesis and help develop strategies to enhance mental health outcomes for those affected.

Ethics statement

This study was approved by the Research Ethics Committee (Human) of Universiti Sains Malaysia (1001/PPSG/8,012,313).

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CRediT authorship contribution statement

Alia Maisarah: Writing – original draft, Validation, Methodology, Investigation. **Suharni Mohamad:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization. **Maruzairi Husain:** Writing – review & editing, Supervision, Data curation. **Sarimah Abdullah:** Writing – review & editing, Supervision, Formal analysis. **Rahmah Noordin:** Writing – review & editing, Validation, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.actatropica.2024.107241.

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