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Seroprevalence of anti-*Toxoplasma gondii* IgG antibody in patients with schizophrenia

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Abstract. Schizophrenia is a pervasive neuropsychiatric disease of unknown cause. Previous studies have reported that toxoplasmosis may be a possible cause of schizophrenia. To ascertain possible relationship between *Toxoplasma gondii* and schizophrenia, a cross sectional study, employing an enzyme-linked immunosorbent assay (ELISA) was performed to study the seroprevalence of anti-*T. gondii* IgG antibody in schizophrenic patients. Furthermore, demographic data analysis from schizophrenic patients were analysed to associate toxoplasmosis with schizophrenia. A total of 288 serum samples from schizophrenic patients (n=144) and psychiatrically healthy volunteers (n=144) were recruited in this study. Interestingly, a significant result in the serointensity rate of anti-*T. gondii* IgG antibody (> 60IU/mL) in schizophrenic patients (61.1%) was demonstrated as compared to psychiatrically healthy volunteers (40.8%) ($X^2 = 4.236$, $p < 0.050$). However, there was no significant difference between the seropositivity rate of anti-*T. gondii* IgG antibody between the two groups. Analysis from demographic data revealed that the seropositivity rate of anti-*T. gondii* IgG antibody in schizophrenic patients was significantly associated with age group of more than 40 years old (p=0.007) and between ethnic (p=0.046). Nevertheless, no significant association between seropositivity rate of anti-*T. gondii* IgG antibody with gender (p=0.897), duration of illness (p=0.344) and family history of schizophrenia (p=0.282) in these patients. Thus, this finding is essential as a preliminary data in Malaysia to establish the association between *T. gondii* and schizophrenia.

INTRODUCTION

Toxoplasma gondii is a protozoan parasite found worldwide. Toxoplasmosis is a common infection and has a high prevalence rate among Malaysian population (Nissapatorn & Khairul, 2004). It is an obligate intracellular parasite in humans, and occurs in two forms. The actively proliferating trophozoites or tachyzoites are usually seen in the acute stage of the infection. The resting bradyzoites or tissue cysts are primarily found in muscle and brain, probably as a result of the host immune response (Garcia & Bruckner, 1997). These organisms persist intracellularly, including in neuron and glia (Halonen *et al.*, 1996; Fischer *et al.*, 1997; Luder *et al.*, 1999). Its definitive hosts are cats and other Felidae. Human infections with *T. gondii* occur mainly by ingesting food or water contaminated with oocyst or eating undercooked or raw meat containing tissue

cyst (Dubey, 2004; Montoya & Liesenfield, 2004; Dawson, 2005). Human also might be infected by *T. gondii via* blood transfusion, organ transplantation or transplacental transmission.

There are several studies that reported acute or chronic *T. gondii* infections of the central nervous system are related to neurological and psychiatric abnormalities including psychosis (Minto & Roberts, 1959; Kocher *et al*., 1969; Delgado, 1979; Quiying *et al*., 1999) and behavior change (Flegr *et al*., 1996). In humans, chronic infection with *T. gondii* can produce psychotic symptoms similar to those displayed by persons with schizophrenia. Recent study on humans suggests that latent infection with *T. gondii* may also alter the host's behavior, psychomotor skills, or personality (Havlicek *et al*., 2001; Flegr *et al*., 2003). Schizophrenia is a pervasive neuropsychiatric disorder of uncertain etiology. The research done by Robert & Christopher (2007) suggests the following hypothetical sequence of events: *T. gondii* infection, by activating astrocytes, increase kynurenic acid (KYNA) formation in the brain. This effect is augmented in persons with elevated brain tryptophan dioxygenase (TDO) activity, i.e., individuals with a genetic predisposition for schizophrenia. Increased brain KYNA levels, in turn, cause or contribute to the excessive inhibition of glutamatergic and nicotinergic neurotransmitter, which is believed to play an important role in the cognitive impairments seen in schizophrenia.

Toxoplasma gondii has been identified as a candidate infectious agent related to schizophrenia (Torrey & Yolken, 2003). A study by Mortensen *et al.* (2007) revealed that newborns who have antibodies to *T. gondii* have an increased risk of later being diagnosed with schizophrenia. Apart from that, environmental factors such as infections with *T. gondii* is found to be more frequent in individuals with schizophrenia than in psychiatrically healthy controls, as indicated in several studies from different countries (Torrey & Yolken, 2001, 2003). To investigate possible associations between *T. gondii* infection and schizophrenia, we examined the seroposivity and serointensity rate of anti-*T. gondii* IgG antibody in individuals with schizophrenia and psychiatrically healthy volunteers.

MATERIALS AND METHODS

Study population

In this study, 144 schizophrenia patients were selected randomly when they were admitted to the psychiatry ward or came for follow up at the psychiatry clinic between February 2011 and April 2011 at Universiti Kebangsaan Malaysia Medical Centre (UKMMC), Kuala Lumpur. They were already diagnosed clinically with schizophrenia by experienced psychiatrists. The diagnosis was assigned according to DSM-IV. The Mini International Neuropsychiatric Interview (MINI) version 6.0.0 DSM (October 1,2009) (Sheehan *et al.*, 2009) was used for screening patients for schizophrenia during data collection. These patients were also screened for any immunocompromised and immunologic disorder. In this study, we excluded all the patients who were immunocompromised including patients on chemotherapy, immunosuppressive drugs after organ transplantation, glucocorticoids, leukemia, lymphoma, multiple myeloma and acquired immunodeficiency syndrome (AIDS). The patients' demographic data such as age, gender, ethnic, duration of disease, family history of schizophrenia and number of hospitalization due to schizophrenia were taken. Informed consent was taken from patients prior to the blood taking. The control group consisted of 144 psychiatrically healthy volunteers from inpatient in medical wards. They were free of psychiatric illnesses after screening using MINI test.

Ethical aspects

This study was approved by the research Ethical Committee of UKMMC. The study purpose was explained to all patients and healthy volunteers before written informed consents were provided.

Collection and analysis of blood samples
Three mls of blood was taken from each schizophrenia patient and psychiatrically healthy volunteer by venipuncture under sterile conditions. Collected blood samples were centrifuged at 3.000 g for 15 minutes to obtain serum samples and stored at -20ºC until use. The level of specific IgG antibodies of *T. gondii* in the serum samples were measured using enzyme linked immunosorbent assay (ELISA), a commercial kit (Platelia Toxo IgG ELISA BioRad, USA). The IgG antibody titers were read at optical density (OD) of 420 nm and 650 nm using automatic ELISA reader (SKANIT Software 2.5.1). Based on the kit interpretation, sera IgG titer < 6 IU/mL was considered negative for anti-*T. gondii* IgG antibodies; between 6 IU/mL and 9 IU/mL was considered equivocal and ≥9 IU/mL was considered positive. In addition, sera that were positive with IgG were further divided into two groups: i), low positive sera (IgG titer between 9-60 IU/mL) and ii), high positive sera (IgG titer of >60 IU/mL).

Statistical analysis
SPSS software version 19 was used for statistical analysis. The relative proportions were calculated with confidence interval of 90%. Any possible associations were identified using Chi-Square statistical tests at a significant level of 5%.

RESULTS

As shown in Table 1, 37.5% (54/144) schizophrenia cases and 34% (49/144) psychiatrically healthy volunteers were positive for anti-*T. gondii* IgG antibody. Although the percentage of anti-*T. gondii* IgG antibody of schizophrenia cases was higher than the psychiatrically healthy volunteers, there was no statistical difference between both groups ($X^2 = 0.378$, $p = 0.539$). Interestingly, Table 2 showed that 61.1% (33/144) of schizophrenia cases and 40.8% (20/144) psychiatrically healthy volunteers had high positive anti-*T. gondii* IgG antibody titers (>60 IU/mL). This result indicated that the serointensity rate of anti-*T. gondii* IgG antibody (>60IU/mL) in schizophrenia patients (61.1%) was higher than psychiatrically healthy volunteers (40.8%) ($X^2 = 4.236$, $p < 0.05$).

Socio-demographic variables in schizophrenia patients are shown in Table 3 and Table 4 . As demonstrated in Table 3, the seropositivity rate of anti-*T. gondii* IgG antibody in schizophrenia patients was not significantly associated with gender ($p = 0.897$), duration of illness ($p = 0.344$) and family history of schizophrenia ($p = 0.282$). However, comparison among age group with seropositivity rate of anti-*T. gondii* IgG antibody in schizophrenia patients showed a significant difference ($p < 0.05$) in age group of more than 40 years old ($p = 0.007$). Comparison between ethnicity also showed a significant difference ($p = 0.046$). Meanwhile, in Table 4, the serointensity rate of positive anti- *T. gondii* IgG antibody serum

Table 1. Seropositivity of anti-*T. gondii* IgG antibody in schizophrenia patients and healthy volunteers

	Schizophrenia patients (n=144) (%)	Healthy volunteers (n=144) (%)
IgG (+)	54 (37.5)	49 (34.0)
IgG (-)	90 (62.5)	95 (66.0)

$X^2 = 0.378$, $p = 0.539$, Chi-Square Test

Table 2. Serointensity of anti-*T. gondii* IgG antibody in schizophrenia patients and healthy volunteers

	Schizophrenia patients (n=54) (%)	Healthy volunteers (n=49) (%)
Low positive antibody titer (9-60 IU/mL)	21 (38.9)	29 (59.2)
High positive antibody titer (>60 IU/mL)	33 (61.1)	20 (40.8)

$X^2 = 4.236$, $p = 0.040$, Chi-Square Test
Cut off: a result equal or greater than 9 IU/mL was considered positive.

Table 3. Socio-demographic data of positive and negative anti-*T. gondii* IgG antibody in schizophrenia patients

	IgG positive n (%)	IgG negative n (%)	X^2	*P*
Gender				
Male	27 (18.8)	44 (30.6)	0.017	0.897
Female	27 (18.8)	46 (31.9)		
Age (years)				
21-40	17 (11.8)	48 (33.3)	7.172	0.007
>40	37 (25.7)	40 (27.8)		
Ethnic				
Malay	29 (20.1)	33 (22.9)	3.996	0.046
Non-Malay	25 (17.4)	57 (39.6)		
Duration of illness (years)				
0-10	25 (17.4)	49 (34.0)	0.897	0.344
>10	29 (20.1)	41 (28.5)		
Family history of schizophrenia				
Present	15 (10.4)	18 (12.5)	1.156	0.282
Absent	39 (27.1)	72 (50.0)		

Table 4. Socio-demographic data of low positive and high positive anti-*T. gondii* IgG antibody titer in schizophrenia patients

	Low Positive Antibody Titer (9-60 IU/mL) n (%)	High Positive Antibody Titer (>60 IU/mL) n (%)	X^2	*P*
Gender				
Male	12 (22.2)	15 (27.8)	0.701	0.402
Female	9 (16.7)	18 (33.3)		
Age (years)				
21-40	5 (9.3)	12 (22.2)	0.938	0.333
>40	16 (29.6)	21 (38.9)		
Ethnic				
Malay	11 (20.4)	18 (33.3)	0.024	0.876
Non-Malay	10 (18.5)	15 (27.8)		
Duration of illness (years)				
0-10	8 (14.8)	17 (31.5)	0.930	0.335
>10	13 (24.1)	16 (29.6)		
Family history of schizophrenia				
Present	5 (9.3)	10 (18.5)	0.270	0.604
Absent	16 (29.6)	23 (42.6)		

revealed no significant difference between gender (p=0.402), age (p=0.333), ethnicity (p=0.876), duration of illness (p=0.335) and family history of schizophrenia (p=0.604).

DISCUSSION

This is the first preliminary study in Malaysia that looked at the association between *T. gondii* and schizophrenia. An interesting finding was demonstrated, in which patients with schizophrenia had a high and significant anti-*Toxoplasma* IgG antibody (61.1%) with serointensity rate of >60 IU/mL than psychiatrically healthy volunteers (40.8%) ($X^2 = 4.236$, $P < 0.05$). This was supported by other studies from Turkey which found higher levels of antibody titers in schizophrenic patients than in the control group (Yolken *et al.*, 2001; Leweke *et al.*, 2004; Dogruman-al *et al.*, 2009). High antibody titer was associated with higher inflammatory responses (Hinze-Selch *et al.*, 2007), whereby interferon-gamma (IFN-y) and indoleamine 2,3-deoxygenase (IDO) enzyme play a role (Daubener & Hadding, 1997; Daubener *et al.*, 2001; Fujigaki *et al.*, 2002, 2003; Oberdorfer *et al.*, 2003). When *T. gondii* causes an infection, activated T-helper cells secrete IFN-y, which induces IDO. This enzyme degrades the tryptophan that is needed for the tachyzoite phase of *T. gondii*. Consequently, activated parasites die by tryptophan depletion (Daubener & Hadding, 1997). The high tryptophan degradation products that accumulate via the kynurenine pathway (Miller *et al.*, 2004) may result in excess dopaminergic activity. Thus, the host defence system might produce less serotonin and an accumulation of dopaminergic activity as seen in schizophrenia. Higher antibody titer is associated with an increase risk of an individual to develop psychotic symptoms.

Although many previous studies showed that the seropositivity for anti-*T. gondii* IgG antibodies in schizophrenia patients was higher than in the control group (Centikaya *et al.*, 2007, Dogruman-al *et al.*, 2009), the present study shows that there is no statistical difference between seroprevalence rate of anti-*T. gondii* IgG antibody in schizophrenia patients (37.5%) and psychiatrically healthy volunteers (34%) ($X^2 = 0.378$, $p > 0.05$). Our result however is in concordance with a study by Ahmad Daryani *et al.* (2010) in a survey in Iran which showed 35% of schizophrenia patients and 25.3% of the control group were seropositive for anti-*T. gondii* IgG antibody and the difference was not statistically significant. Other studies also demonstrated that there was no significant difference in seropositivity rate between schizophrenia and control groups (Hinze Selch *et al.*, 2007; Saraei-Sahnesaraei *et al.*, 2009). These findings could be due to many reasons such as the difference in selection of control group, difference in genetic susceptibility and consumption of antipsychotic drugs. A study by Leweke *et al.* (2004) demonstrated that schizophrenic patients treated with anti-psychotic drugs may affect anti-*T. gondii* IgG levels. The reasons for the effect of treatment on antibody levels is not known with certainty, but may be related to an increased period of time from exposure to the infectious agent or to the effect of the medication on microbial replication or the immune response to infection. It is noted that in terms of the possible effect of medications some of the therapeutic agents commonly employed for the treatment of schizophrenia and bipolar disorder have the ability to inhibit the replication of *T. gondii* tachyzoites in cell culture (Jones-Brando *et al.*, 2003). The fact that more than 95% of subjects in this study received anti-psychotic drugs could be one of the possible reasons for the non significant finding. For the selection of the control group, the socio-demograhic data of the psychiatrically healthy volunteers were not matched with the socio-demographic data of the schizophrenia patients. Thus, this may also contribute to this finding. Another possibility is that toxoplasmosis is an opportunistic infection. Although the disease causes severe infection in immuno-compromised individuals, the infection is also common in healthy individuals. The interaction of the lifelong persisting parasite with the human immune response will

produce IgG antibody which persists for life. Therefore, it is normal for an individual to acquire infection (positive for anti-*T. gondii* antibody). For immunocompetent individuals, they are usually asymptomatic. However, in immunocompromised individuals, they presented with clinical features of severe toxoplasmosis such as chorioretinits, encephalitis and brain abscess.

The seropositivity and serointensity of anti- *T. gondii* IgG antibody in schizophrenia patients were not significantly associated with gender, duration of illness and family history of schizophrenia. Although some studies showed that there were an increase risk of schizophrenia with family history, however numerous studies have failed to identify single genes which carry a high risk for acquiring schizophrenia (Burmeister *et al.*, 2008). This findings were consistent with the hypothesis that genetic factors are necessary for causing schizophrenia, but they are not sufficient and environmental factors, possibly including an infectious agent, are also major determinants for the disease (Mortensen *et al.*, 1999). In the present study we observed that the highest positivity rate for anti-*T. gondii* IgG antibody was seen in those age >40 years old. This finding could be explained by the fact that between the two age groups in this study, the age group (>40 years old) consisted the highest number of subjects. Comparison between ethnic groups, Malay and non-Malay showed a significant difference. This may be due to differences in the social background and eating habits among Malay and non-Malay population in Malaysia. The fact that Malay have a habit of keeping cats in their house possibly leads to close contact where they will be more likely to be exposed to contamination of cat faeces (Tan & Zaman, 1978; Thomas *et al.*, 1980). Furthermore, culturally Malay usually use hand to eat, hence tranmission of toxoplasmosis is greater if proper hygiene is not practised.

There was some controversy concerning the question of whether schizophrenia patients acquired *Toxoplasma* infection after onset of schizophrenia. However, a study by Leweke *et al.* (2004) documented that individuals with first episode of schizophrenia who had not received prior anti-psychotic treatment at the time of presentation had increased level of serum and cerebrospinal fluid (CSF) IgG antibodies to the potentially neurotropic infectious agent such as *T. gondii*. One study showed that mothers having antibodies to *T. gondii* late in pregnancy, even though the infection was not necessarily recent, had an increased risk of giving birth to offsprings who later were diagnosed with a schizophrenia spectrum disorder (Mortensen *et al.*, 2007). There was a study which demonstrated that the behavioural changes associated with *T. gondii* can be effectively reduced by anti-psychotic drug especially the second-generation agents (olanzapine, clozapine, quetiapine, ziprasidone, risperidone and aripiprazole) which inhibit parasite replication *in vitro*. This may provide further evidence for the potential role of *T. gondii* in the aetiology of schizophrenia, and the actions of anti-psychotics may work in part *via* parasite inhibition (Webster *et al.*, 2006).

Multiple studies have reported that *T. gondii* is a possible cause of schizophrenia. However, there were few studies on the possible association between individuals who had high level of anti-*T. gondii* IgG titers with increased risk for development of schizophrenia. Further studies are needed on the possible association between *T. gondii* infection and the symptoms or clinical course of schizophrenia. Our study has revealed high titer of anti-*T. gondii* IgG antibody in schizophrenia patients as compared to healthy individuals. Thus, this finding is essential as a preliminary data in Malaysia to establish the association between toxoplasmosis and schizophrenia. Further study needs to be done to ascertain the role of *T. gondii* as a possible aetiological agent that contributes to schizophrenia. Moreover, this study may open the door to new methods for diagnosis, treatment, as well as for prevention of schizophrenia.

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