

## Original papers

# Seroprevalence of *Toxoplasma gondii* among patients with schizophrenia and bipolar disorder in Upper Egypt: a comparative study with a control group

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**ABSTRACT.** Schizophrenia and bipolar disorder are serious neuropsychiatric disorders. Studies have found a high seroprevalence of *Toxoplasma gondii* in psychiatric patients. This study aimed to estimate the seroprevalence of *T. gondii* infection among schizophrenia and bipolar disorder patients. A case-control study was conducted in Assiut University Hospitals on 53 patients with schizophrenia, 57 patients with bipolar disorder, and 50 healthy volunteers. The psychiatric patients were recruited from the psychiatry department and the controls from their relatives. Both groups were subjected to socio-demographic assessment. Neither of them was immunodeficient nor with any other psychiatric disorders. Anti-*Toxoplasma* IgG antibodies were detected by indirect-ELISA to find the relationship between *T. gondii* infection and psychiatric disorders. Data were analysed using Chi-square test. The seropositivity rate, among patients with schizophrenia (50.9%) and patients with bipolar disorders (52.6%), was significantly higher than control group (30%) ( $P = 0.031$  and  $0.018$  respectively). We found no statistically significant difference among all groups regarding environmental risk factors associated with *T. gondii* infection, except cat contact which was higher in schizophrenia and bipolar disorder patients ( $P = 0.011$  and  $0.007$  respectively). The results of our study confirm that *T. gondii* infection is significantly correlated with schizophrenia and bipolar disorder and significantly associated with cat contact rather than beef consumption.

**Keywords:** schizophrenia, *Toxoplasma*, bipolar disorder, seroprevalence, Egypt, ELISA

## Introduction

Schizophrenia and bipolar disorder are major, chronic, and often debilitating neuropsychiatric disorders with a significant negative impact on the social environment and the quality of patients' life and their families [1,2]. Schizophrenia is characterized by relapsing episodes of psychosis with effects on thought, perception, emotion, and behaviour [3]. It is challenging and currently affects over 21 million people worldwide; it has been estimated that approximately seven individuals per 1000 will develop schizophrenia disorder during

their lifetime [4]. Bipolar disorder is a primary mood disorder, in which episodes of hypomania, mania, or mixed episodes occur. Several studies have estimated its lifetime prevalence to range from 3–8% [5-7].

In Egypt, mental disorders represent a huge challenge to health workers. The most recent study was conducted in 2009 and aimed to determine the prevalence of different mental disorders in Egypt. This study concluded that 17% of Egyptians suffered from some kind of mental illness [8].

As a common intracellular organism, *Toxoplasma gondii* has a variable prevalence world widely.

The prevalence of infection with *T. gondii* is 30–60% of the population in both developed and developing countries [9]. *T. gondii* tissue cysts found in undercooked meat and oocytes containing sporozoites found in water, soil, and children sandboxes, are common routes for human infection. On the other hand, congenital toxoplasmosis may occur through the trans-placental transmission of trophozoites from the mother to the foetus during pregnancy [10].

It usually causes asymptomatic latent infections, except during pregnancy or in immunocompromised patients [11]. The parasite has a complex life cycle, whereby it needs to end up in the intestines of cats (felines) to be able to sexually reproduce [12]. In other hosts than cats (intermediate hosts, all warm-blooded animals), it invades the body after ingestion, whereby it quickly duplicates until the immune system of the host subdues the parasite [13]. The parasite then forms intracellular cysts in muscles, liver, and neuronal cells to reside in a latent stage potentially for the rest of the host's life [14].

Many researches have shown that behavioural changes in mice and humans can be the result of latent toxoplasmosis [15,16]. Moreover, there is substantial evidence suggesting increased prevalence of *T. gondii* infection in schizophrenia. Multiple studies showed that patients with schizophrenia have 2.7 odds ratio (OR) of being seropositive to *T. gondii* in comparison to healthy controls [3,17].

To explain causality, many theories have been postulated to clarify this association. First, Prandovszky et al. [18] showed that *T. gondii* may increase dopamine production *in vitro*. Second, *T. gondii* infection induced-immune response in patients with schizophrenia has been suggested to lead to dangerous effects [19,20]. An extensive literature demonstrating immunological abnormalities in psychoses is available, including changed serum levels of cytokines in schizophrenia patients [21], changes in the immune-modulatory kynurenine pathway enzymes [22,23], *in vivo* glial cells activation and injury [24], the antipsychotics immunosuppressive and/or anti-infectious effects [25], and activation of human endogenous retrovirus [26].

*T. gondii* infection causes alteration of the structure and function of corticolimbic circuits, which are involved in the modulation of impulsivity and aggression, this might be another explanation for behavioural changes observed in infected

animals and humans [27,28].

Dopamine and immunological disturbances are not unique to schizophrenia. Both have been reported in other psychiatric disorders [29–33]. Therefore, *T. gondii* could be involved in other psychiatric disorders besides schizophrenia. Associations of *T. gondii* infection with other psychiatric disorders, such as bipolar disorder [34] and obsessive-compulsive disorder (OCD) [35], have been reported. The correlation between the presence of *T. gondii* IgG antibodies and schizophrenia varies between different studies. Whether the *T. gondii* infection happens before the mental illness and whether the seriousness of the disease is an important factor, are still topics for discussion and debate [36].

We think that this study was the first to be conducted in Upper Egypt to explore further the association between *Toxoplasma* infection and psychiatric disorders especially, schizophrenia and bipolar disorders. It compared the amount of anti-*Toxoplasma* IgG antibodies among patients with schizophrenia, bipolar disorders and non-schizophrenia control group by ELISA.

## Materials and Methods

**Study design and subjects.** The study was conducted at Assiut University Hospitals, Egypt. The present study was conducted over 6 months from Feb to July 2016. This case-control study was conducted on a total of one hundred-ten patient divided into (53) patients with schizophrenia and (57) patients with bipolar disorder. The other group of population is the control group which consisted of (50) healthy volunteers. The psychiatric patients were recruited from the psychiatry department and the controls from the relatives of the patients and other medical departments. Both groups were matched in terms of age, gender, race and socioeconomic status. The inclusion criteria included patients aged 18 to 60 years. The subjects of two groups were not immune-deficient and did not have any other major psychiatric disorder or neurological disease other than bipolar disorder or schizophrenia. All subjects signed informed consent before participation in the study. The patients' diagnosis was made by a psychiatrist through structured clinical interview for Diagnostic and Statistical Manual of mental disorders, 4th edition (DSM-IV-TR) [37]. The mean age for patients' group was ( $34.65 \pm 12.93$ ) and for the control was ( $33.66 \pm 12.89$ ). The objectives and procedures of

Table 1. Sociodemographic characteristics of schizophrenia patients, bipolar disorder patients and control groups

	Schizophrenia (n=53)		Mood disorder (n=57)		Control (n=50)		P-value
	No.	%	No.	%	No.	%	
Age:							
< 30 years	26	26	49.1	31	54.4	22	0.733
30 - < 40 years	14	14	26.4	19	33.3	17	
40 - < 50 years	7	7	13.2	4	7.0	6	
> 50 years	6	6	11.3	3	5.3	5	
mean $\pm$ SD	34.65 $\pm$ 12.93		35.42 $\pm$ 11.32		33.66 $\pm$ 12.89		0.6457
Sex:							
male	42	79.2	44	77.2	37	74.0	0.817
female	11	20.8	13	22.8	13	26.0	
Educational level:							
illiterate	12	22.6	20	35.1	15	30.0	0.685
read & write	6	11.3	6	10.5	9	18.0	
basic education	12	22.6	7	12.3	10	20.0	
secondary	18	34.0	19	33.3	12	24.0	
high education	5	9.4	5	8.8	4	8.0	
Occupation:							
farmer	7	13.2	12	21.1	5	10.0	0.002*
employer	11	20.8	5	8.8	12	24.0	
skilled worker	10	18.9	24	42.1	12	24.0	
no work	19	35.8	4	7.0	13	26.0	
housewife	6	11.3	12	21.1	8	16.0	
Residence:							
rural	37	69.8	39	68.4	35	70.0	0.981
urban	16	30.2	18	31.6	15	30.0	
Marital status:							
single	32	60.4	34	59.6	30	60.0	0.998
married	16	30.2	19	33.3	15	30.0	
divorced	4	7.5	3	5.3	4	8.0	
widow	1	1.9	1	1.8	1	2.0	
Social class:							
low	6	11.3	2	3.5	5	10.0	0.612
middle	41	77.4	49	86.0	40	80.0	
high	6	11.3	6	10.5	5	10.0	

\*: significant at  $P < 0.05$

the research were explained to the subjects. Since this study involves invasive procedures, a written consent form was filled up by respondents before the blood samples were collected. Approval was granted by the ethical committee of Faculty of Medicine, Assiut University, with an ethical approval number; R15.

**Socioeconomic assessment scale for family.** We gathered information about socio-demographic information using this scale, which prepared by Professor Abdel Tawab Abdullah, Faculty of Education, Assiut University, in 1998 and modified

in 2010. It includes four main variables: 1) the educational level of the father and mother; 2) the occupation; 3) total family income; 4) life style of the family [38]. Putative risk factors comprised cat contacts, meat consumption (red meat, chicken, and fish), and wash hands before eating, wash hands after toilet, working in gardens [39].

**Serological assays.** To examine the relationship between the presence of immunoglobulin G (IgG) antibodies against *T. gondii* and schizophrenia or mood disorders, 5 ml blood from all studied individuals were collected by venipuncture under

Table 2. Distribution of anti-*Toxoplasma* antibodies by ELISA in schizophrenic and control individuals

	No.	Gender		Age (year) (M±SD)	ELISA positive		P-Value
		Male	Female		No.	%	
schizophrenia	53	44	13	34.65 ± 12.93	27	50.9	0.031*
control	50	37	13	33.66 ± 12.89	15	30	

\*: significant at P<0.05

sterile conditions and sent to the Parasitology Laboratory of Assiut University, Faculty of Medicine. Serum samples were obtained by the centrifugation (at 3000 rpm for 10 min) of collected blood and kept at -20°C pending ELISA tests [40]. Sera were analysed by qualitative and quantitative methods for *T. gondii* IgG antibodies with the commercially available enzyme immunoassay kit „*Toxoplasma* IgG” (Prechek Bio, Inc., CA 92801, USA) and final results were recorded by ELISA reader (optical absorbance, OD=450).

**Statistical analysis.** SPSS software ver. 20 was used for analysis. Age among the groups was compared by the student's t-test. Chi-square analysis was performed to compare the seroprevalence of anti-*Toxoplasma* IgG antibodies among schizophrenia, mood disorder patients and controls. Adjusted Odds Ratio (OR) and 95% confidence interval (CI) were calculated by multivariate analysis using conditional logistic regression, thus determining the level of risk involved in the study putative environmental risk factors and the subsequent association with *T. gondii* seropositivity. A value of P<0.05 was considered statistically significant.

## Results

### Socio-demographic characteristics

Table 1 shows the sociodemographic characteristics of the study and the control groups. The overall number of the individuals in the study

group was 110 patients, 53 with schizophrenia and 57 with bipolar disorder. The mean age was 34.65 ± 12.93 and 35.42 ± 11.32 for schizophrenia and bipolar patients respectively. About 80% of them are males and 20% are females. Nearly 30% of them live in urban areas and 70% live in rural areas. Their occupations varied between farmers 17.3%, employers 14.5%, skilled workers 30.9%, housewives 16.4% and not working 20.9%. 7.3% of the study group belonged to the high socioeconomic status group, 81.8% belonged to the moderate socioeconomic status group and 10.9% belonged to the low socioeconomic status group. Comparison between sociodemographic data of control and study group shows no statistically significant difference between the study and control groups in terms of age, gender, residence, educational level, and socioeconomic status. There are only significant differences between the study and control groups in terms of occupation (P = 0.002).

### Anti-*Toxoplasma* antibody seroprevalence

Total, 53 cases with schizophrenia and 50 control individuals were compared for the anti-*Toxoplasma* antibody by ELISA. The difference of anti-*T. gondii* antibodies between schizophrenia patients (50.9%, 27 out of 53 patients) and control group (30%, 15 out of 50 patients) was statistically significant (P = 0.031) (Table 2). 57 cases with bipolar disorder and 50 control individuals were compared for anti-*Toxoplasma* antibody by ELISA. The difference of the anti-*T. gondii* antibodies between bipolar patients (52.6%, 30 out of 57 patients) and control

Table 3. Distribution of anti-*Toxoplasma* antibodies by ELISA in bipolar patients and control individuals

	No.	Gender		Age (year) (M±SD)	ELISA positive		P-Value
		Male	Female		No.	%	
bipolar disorder	57	42	11	35.42 ± 11.32	30	52.6	0.018*
control	50	37	13	33.66 ± 12.89	15	30	

\*: significant at P<0.05

Table 4. Results of *Toxoplasma* test according to the type of schizophrenia in the studied patients

Type of schizophrenia	<i>Toxoplasma</i> test				P-value
	Positive (n=27)		Negative (n=23)		
	No.	%	No.	%	
paranoid	20	58.8	14	41.2	0.440
disorganized	4	44.4	5	55.6	
undifferentiated	2	33.3	4	66.7	
catatonic	1	100	0	0.0	

group (30%, 15 out of 50 patients) was statistically significant (P = 0.018) (Table 3). The seropositivity rate for anti-*T. gondii* IgG antibodies in patients compared with the control group showed a possible relationship between *Toxoplasma* infection on one hand and schizophrenia, bipolar disorder on the other hand.

As regards to the seropositivity prevalence for anti-*T. gondii* IgG antibodies among different types of schizophrenia, we found no statistically significant difference between these types ( $\chi^2(1) = 0.597, P = 440$ ) (Table 4).

**Effect of environmental and sociodemographic variables**

The comparison between schizophrenia, bipolar disorder and control groups regarding putative

environmental risk factors associated with *T. gondii* infection such as cat contacts, meat consumption (red meat, chicken, fish), wash hands before eating, wash hands after toilet and working in gardens, showed no statistically significant difference between the three groups except in cat contact which was higher in schizophrenia and bipolar disorder patients (P = 0.011 and 0.007 respectively) (Table 5). There is also no statistically significant difference between those with positive ELISA results and those with negative ELISA results regarding the studied sociodemographic characters: age, sex, educational level, occupation, residence and social class (Table 6).

**Discussion**

The present study was conducted to evaluate the

Table 5. Comparison between schizophrenia, bipolar disorder and control groups regarding putative environmental risk factors associated with *T. gondii* infection

	Schizophrenia (n=53)		Mood disorder (n=57)		Control (n=50)		P1	P2	P3
	No.	%	No.	%	No.	%			
smoking	36	67.9	40	70.2	34	68.0	0.799	0.933	0.808
WHBF	34	64.2	45	78.9	33	66.0	0.085	0.844	0.133
WHAT	35	66.0	45	78.9	34	68.0	0.129	0.832	0.199
WIG	18	34.0	29	50.9	17	34.0	0.073	0.997	0.079
cat contact	25	47.17	27	47.3	11	22.0	0.488	0.011*	0.007*
other M:									
chicken	19	35.8	21	36.8	19	38.0	0.570	0.977	0.592
fish	12	22.6	8	14.0	10	20.0			
red meat	5	9.4	9	15.8	4	8.0			
all	17	32.1	19	33.3	17	34.0			

1: Comparison between schizophrenia and mood disorder; 2: Comparison between schizophrenia and control; 3: Comparison between mood disorder and control; \*: significant at P<0.05

Table 6. Results of *Toxoplasma* test according to sociodemographic characteristics in the studied patients

	<i>Toxoplasma</i> test				P-value
	Positive(n=57)		Negative (n=53)		
	No.	%	No.	%	
<b>Age:</b>					
< 30 years	29	50.9	28	49.1	0.803
30 - < 40 years	17	51.5	16	48.5	
40 - < 50 years	5	45.5	6	54.5	
> 50 years	6	66.7	3	33.3	
<b>Sex:</b>					
male	46	53.5	40	46.5	0.507
female	11	45.8	13	54.2	
<b>Educational level:</b>					
illiterate	17	53.1	15	46.9	0.378
read & write	5	41.7	7	58.3	
basic education	10	52.6	9	47.4	
secondary	17	45.9	20	54.1	
high education	8	80.0	2	20.0	
<b>Occupation:</b>					
farmer	8	42.1	11	57.9	0.582
employer	9	56.3	7	43.8	
skilled worker	21	61.8	13	38.2	
no work	10	43.5	13	56.5	
housewife	9	50.0	9	50.0	
<b>Residence:</b>					
rural	34	44.7	42	55.3	0.056
urban	23	67.6	11	32.4	
<b>Social class:</b>					
low	5	62.5	3	37.5	0.709
middle	45	50.0	45	50.0	
high	7	58.3	5	41.7	

association between *Toxoplasma* infection and schizophrenia and bipolar disorder. Our results showed a higher seroprevalence of anti-*T. gondii* IgG antibodies in schizophrenia and bipolar disorder patients than in controls matched by age, gender and race, thus confirming results of many recent studies e.g. [41–44]. On the other hand, few studies did not find the contamination with *Toxoplasma gondii* as a risk factor for bipolar disorder [7]. Torrey et al. [17] was the first study to investigate the possible role of *T. gondii* antibodies in 1953. They found that nearly half of the psychiatric patients enrolled in their study had *T. gondii* antibodies in comparison to only 25% of the control group. Moreover, they found significantly higher levels of IgG antibodies in psychiatric patients in comparison to controls. These results are following serological studies on patients with schizophrenia which showing that anti-*T. gondii* antibodies were higher in patients

than control groups [39,45,46].

This study showed an association between *T. gondii* exposure and the risk of BD and schizophrenia which agrees with several literatures conducted in the recent years [33,46–50]

The relationship between *T. gondii* antibodies and mood disorders was investigated in a big cross-sectional study conducted on a population-based sample in the United States. The study reported that *T. gondii* seroprevalence is higher in patients with a history of bipolar disorder type 1, but is not elevated in unipolar mood disorders patients [46].

There are some possible explanations for our results. Some studies reported that in patients with encephalitis due to *T. gondii* infection, trophozoites were abundantly present in the glial cells of those patients [10,51]. Other studies that investigated toxoplasmic encephalitis, found *T. gondii* bradyzoites in the cerebellar Purkinje cells [10,52].

Additionally, other studies detected *T. gondii* cysts in astrocytes in humans [10,53]. Another possible explanation is that neurotransmitters, such as dopamine and norepinephrine, might be affected by toxoplasmosis which affects schizophrenic people as well [54,55].

We found also, a positive association between cat contact and *T. gondii* infection in both schizophrenia and bipolar patients ( $P = 0.011$  and  $0.007$  respectively). This suggests that infection might be acquired by cleaning cat excrement containing the parasites. Association between *T. gondii* seropositivity and cat contact was also found in studies done by Alvarado Esquivel et al. [43] in which cleaning cat excrement was significantly associated with *T. gondii* infection ( $P = 0.001$ ).

We did not find an association between *T. gondii* infection and other studied behavioural characteristics including meat consumption (beef meat, chicken or fish). This can be explained by the fact that Egyptian people, especially middle and low social class, mostly prefer to consume different types of meat in a very well-cooked manner. This agrees with the fact that, in humans, *T. gondii* is commonly acquired by the oral ingestion of tissue cysts containing bradyzoites, through the consumption of undercooked meat infected with *T. gondii* [56,57].

The results of our study confirm recent findings that *T. gondii* infection is significantly associated with schizophrenia and bipolar disorder. Toxoplasmosis might be a very serious but ignored public health problem. This study throws light on the assumption that *T. gondii* is a risk factor for schizophrenia. The results also show that *T. gondii* is not significantly associated with beef consumption. We think that the Egyptian way of eating the meat well-cooked is a protective factor. Our limitations included a relatively lower sample size. Nonetheless, these findings are essential in establishing an association between *T. gondii* and psychiatric disorders in Egypt. We recommend larger studies to confirm a significant association and to establish a clearer relationship between *T. gondii* infection and psychiatric patients in Egypt.

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