Research Article

The relationship between Toxoplasma gondii Infection and Schizophrenia

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Abstract
Background: Toxoplasma gondii is a ubiquitous protozoan parasite that chronically infects approximately 25% of the world's human population. A growing evidence links T. gondii to several mental disorders. Decades of serological investigations have corroborated a relationship between T. gondii and schizophrenia. **Objectives & Aim of the study:** To estimate the presence of Toxoplasma infection among patients with schizophrenia. To investigate effect of Toxoplasma infection on the course and outcome of schizophrenia. **Subjects and methods:** A cross sectional study was done on 200 subjects were selected from persons attended psychiatric clinic of Minia Psychiatric Hospital and inpatient department, who were equally divided to four groups as the following: group A (50 patients with psychotic disorders), group B (50 patients with mood disorders), group C (50 patients with anxiety disorders) and group D (50 subjects without current or past history of psychiatric illness). **Results:** Toxoplasma infection in patients with Schizophrenia, schizotypal and delusional disorders more than control. Frequency of admission has relative factor with Toxoplasma infection. **Conclusions:** A High strong statistical significance can be found when we compare between frequency of admission in psychiatric hospitals and Toxoplasma infection. Correlation was positive between toxoplasmosis severity and psychotic group in age grouping and number of abortion variables.
Key words: Toxoplasma gondii, Infection and Schizophrenia

Introduction
The world is suffering from an increasing burden of mental disorders and a widening treatment gap: about 450 million people suffer from a mental or behavioral disorder, yet only a small minority receives even the most basic treatment (WHO, 2000).

Epidemiological studies of the prevalence of mental disorders in Egypt are few. Providing accurate data about the prevalence of mental disorders in the community would help to justify the allocation of scarce resources and planning of health services (Hamdi et al., 2007 and Ghanem et al., 2009).

Schizophrenia is the most common chronic psychosis in Egypt and accounts for the majority of in-patients in our mental hospitals. Persecutory delusions with ideas of reference are the rule. Religious delusions are frequent, owing to the highly religious nature of Egyptian society. Political delusions are positively correlated with the level of political sanctions and pressure. Many patients present with an undifferentiated type of schizophrenia, exhibiting a wide variety of symptoms such as confused thinking and a turmoil of emotion manifested by perplexity, ideas of reference, fear, dream states and dissociative phenomena (Okasha, 1993).

In humans, T. gondii is one of the most common parasites in developed countries (Centers of Diseases control and prevention, 2013). Serological studies estimate that 30–50% of the global population has been exposed to and may be chronically infected with T. gondii, although infection rates differ significantly from country to country (Flegr et al., 2014).

Psychiatric patients have increased rates of toxoplasmic antibodies, the differences between cases and controls being greatest in individuals who are assayed near the time of the onset of their symptoms. The increase of dopamine in the brain of infected subjects can represent the missing link between toxoplasmosis and schizophrenia (Fond et al., 2013).

Subjects and Methods
Subjects of the study:
The subjects of the present study were selected from persons attended psychiatric clinic of Minia Psychiatric Hospital and inpatient department. They were 200 subjects of both sexes who were equally divided to four groups as the following: group A (50 patients with psychotic disorders), group B (50 patients with mood disorders), group C (50 patients with anxiety disorders) and group D (50 subjects without current or past history of psychiatric illness). They will be diagnosed according to the International Statistical Classification of Diseases and Related Health Problems; diagnostic criteria for research (ICD-10).

Inclusion criteria
1- Age was between 18 and 60 years.
2- Both males and females were included.
3- Patients presenting with psychotic disorders (including schizophrenia and other psychotic disorders), mood disorders (including bipolar affective and depressive disorders) and anxiety disorders according to the ICD-10.
4- Controls must not have had a current or past history of any a psychiatric illness.

5- Patients consent to participate in the study after full explanation of its procedures.

Exclusion criteria
1. Patients under 18 years and above 60 years.
2. Current or past diagnosis of autistic disorder or another pervasive developmental disorder.
3. Patients with History of substance abuse.
4. Patients who refuse to engage in the study.
The total number of subjects included in the research was 200 of those 93 were males and 107 were females

Study tools
A. Sheet: A well-prepared sheet had been used for the evaluation of subjects of the study. This sheet included several parts; each part was directed to a certain area that could serve in the study.
B: Serological test (for detection of anti-Toxoplasma gondii antibodies in serum):
1. Collection of blood samples.
2. Indirect Haemagglutination test.

Results
Firstly, presenting distribution of diagnoses and main symptoms

(Table 1): Distributions of sub-categories diagnoses:

Diagnosis		Sub-diagnosis	Frequency	Percent
Group I	**F20**	Schizophrenia	21	42
	F21	Schizotypal disorder	3	6
	F22	Persistent delusional disorders	6	12
	F23	Acute and transient psychotic disorders	2	4
	F24	Induced delusional disorder	2	4
	F25	Schizoaffective disorders	14	28
	F28	Other nonorganic psychotic disorders	1	2
	F29	Unspecified nonorganic psychosis	1	2

Although there are more than 20 sub-categories diagnoses in our study, there are only 5 diagnoses consider to be 40.5 % of the whole sample (200 subjects), as when we make analysis, we found that 42% of patients in group I were diagnosed to had schizophrenia, 28% had schizoaffective and 12% had persistent delusion.

(Table 2): percentage of main symptoms:

Diagnosis	predominant symptoms	Frequency	Percent
Group I	Auditory hallucination	8	16
	Visual hallucination	3	6
	Delusion of persecution	15	30
	Delusion of reference	9	18
	Delusion of grandiosity	4	8
	Delusion of infidelity	4	8
	Negative symptoms	6	12
	Thoughts of death or any suicidal behavior	1	2

the most predominant symptoms in **group I** was delusion of persecution with a percentage of 30%. Secondly, presenting course of psychiatric illness:

(Table 3): Duration of illness in:

	Diagnosis			Total = 150
	Group I N=50	Group II N=50	Group III N=50	
<1	2	7	9	18
	4.0%	14.0%	18.0%	12.0%
1-5	8	9	11	28
	16.0%	18.0%	22.0%	18.7%
5-10	14	15	20	49
	28.0%	30.0%	40.0%	32.7%
10-20	14	13	10	37
	28.0%	26.0%	20.0%	24.7%
>20	12	6	0	18
	24.0%	12.0%	0.0%	12.0%

Because of the duration of illness history is important, we express this duration through the **(Table 3),** and this table represents the different percentages for each group.

(Table 4): Distribution of age at onset groups in our sample:

	Diagnosis			Total = 150
	Group I N= 50	Group II N= 50	Group III N= 50	
12-20	20	17	4	41
	40.0%	34.0%	8.0%	27.3%
21-30	21	23	19	63
	42.0%	46.0%	38.0%	42.0%
31-40	9	9	17	35
	18.0%	18.0%	34.0%	23.3%
41-55	0	1	10	11
	0.0%	2.0%	20.0%	7.3%
Mean ± SD	23.7±6.4	24.7±7	32.7±8.8	20.2±13.8

In **(Table 4)** discussing a different issue in the Socio-demographic characteristics, as when we analyze the age groups related to the onset of disease, we find that the mean age at onset of disorders in patients is 20.2±13.8.

(Table 5): frequency of admits:

	Diagnosis			Total = 150
	Group I N=50	Group II N=50	Group III N=50	
No	19	26	41	86
	38.0%	52.0%	82.0%	57.3%
1-5	23	16	8	47
	46.0%	32.0%	16.0%	31.3%
>5	8	8	1	17
	16.0%	16.0%	2.0%	11.3%

As to continue explaining the illness history, **(Table 5)** made to express the times of admits for the patients whom had a long duration of illness history.

Therefore, we can find that a No. of 86 patients (57.3%) had never admitted in hospital before, compare to 17 patients (11.3%) were admitted more than 5 times in hospitals.

Thirdly, correlation between Toxoplasma infection and schizophrenia:

(Table 6): Distribution of positive and negative Toxoplasma infection in psychiatric illness:

	Diagnosis			Total = 150
	Group I N=50	Group II N=50	Group III N=50	
Yes	38	23	17	78
	76.0%	46.0%	34.0%	52%
No	12	27	33	72
	24.0%	54.0%	66.0%	48%

We find that (76.0%) of psychotic patients, (46.0%) of mood patients and (34.0%) of neurotic patients have Toxoplasma infection as shown in **(Table 6).**

(Table 7): comparison between the duration of illness in our sample:

	Duration of illness in years						p-value
	Control	<1yr	1-5 yr	5-10 yr	10-20 yr	>20 yr	<0.001***
Positive = 84	6 (7.1%)	9 (10.7%)	13 (15.5%)	24 (28.6%)	20 (23.8%)	12 (14.3%)	
Negative =116	44 (37.9%)	9 (7.8%)	15 (12.9%)	25 (21.6%)	17 (14.7%)	6 (5.2%)	

In a comparison between duration of illness and Toxoplasma infection in **(Table 7)** there is a high strong statistical significance can be found (p less than 0.001) compared with the control group.

- Note that No. of 6 subjects from the normal control sample (7.1%) also were infected with Toxoplasma.

(Table 8): comparison between the times of admission in patients with control group:

	Times of admission			
	controls	No admission	1-5 times	> 5 times	p- value
Positive = 84	6 (7.1%)	37 (44%)	30 (35.7%)	11 (13.1%)	**<0.001***
Negative = 116	44 (37.9%)	49 (42.2%)	17 (14.7%)	6 (5.2%)	

✽ **p-value among cases only = 0.705**

A High strong statistical significance can be found when we compare between frequency of admission in psychiatric hospitals and Toxoplasma infection (p value less than 0.001) compared with control group, referred to **(Table 8)**, We can easily find the distribution.

- Note that No. of 6 subjects from the normal control sample (7.1%) also were infected with Toxoplasma, and they never admitted in a psychiatric hospital.

(Table 9): Relation between presence of Toxoplasma infection and medical variables:

All patient s (n=200)	Toxoplasma test		P value
	-Ve (n=116)	+Ve (n=84)	
Age at onset Range Mean ± SD	(12-50) 28±8.7	(12-52) 26.2±8.3	0.194
Age at onset 12-20 21-30 31-40 41-55	20(27.8%) 26(36.1%) 19(26.4%) 7(9.7%)	21(26.9%) 37(47.4%) 16(20.5%) 4(5.1%)	0.426
Duration of illness < 5 y 1-5 y 5-10 y 10-20 y > 20 y	9(12.5%) 15(20.8%) 25(34.7%) 17(23.6%) 6(8.3%)	9(11.5%) 13(16.7%) 24(30.8%) 20(25.6%) 12(15.4%)	0.705
Frequency of admission No 1-5 >5	49(68.1%) 17(23.6%) 6(8.3%)	37(47.4%) 30(38.5%) 11(14.1%)	**0.039***
Types of treatment Mono-therapy Double therapy Triple therapy	44(61.1%) 7(9.7%) 21(29.2%)	36(46.8%) 12(15.6%) 29(37.7%)	0.199
Compliance on treatment Yes No	48(66.7%) 24(33.3%)	41(52.6%) 37(47.4%)	0.079
Presence of rodents or cats Yes No	80(69%) 36(31%)	57(67.9%) 27(32.1%)	0.868
Eating of uncooked food Yes No	56(48.3%) 60(51.7%)	48(57.1%) 36(42.9%)	0.215
Pre. Treatment of Toxoplasma Yes No	1(0.9%) 115(99.1%)	1(1.2%) 83(98.8%)	0.818

We found strong statically relation between frequency of admission and presence of Toxoplasma infection among the patients.
And there was no relation with age at onset, duration of illness, types of treatment, compliance on treatment, presences of rodents and cats, eating of uncooked food and previous treatment of Toxoplasma infection as shown in **(Table 9).**

(Table 10): Correlation between presence of Toxoplasma infection and Schizophrenia, schizotypal and delusional disorders group:

Group I (n=50)	Toxoplasma test		P value
	-Ve (n=12)	+Ve (n=38)	
Age at onset			
Range	(15-34)	(12-37)	0.514
Mean ± SD	22.7±6.3	24.1±6.5	
Age at onset			
12-20	6(50%)	14(36.8%)	
21-30	4(33.3%)	17(44.7%)	0.707
31-40	2(16.7%)	7(18.4%)	
41-55	0(0%)	0(0%)	
Duration of illness			
< 5 y	0(0%)	2(5.3%)	
1-5 y	2(16.7%)	6(15.8%)	
5-10 y	2(16.7%)	12(31.6%)	0.483
10-20 y	3(25%)	11(28.9%)	
> 20 y	5(41.7%)	7(18.4%)	
Frequency of admission			
No	3(25%)	16(42.1%)	
1-5	6(50%)	17(44.7%)	0.459
>5	3(25%)	5(13.2%)	
Types of treatment			
Mono-therapy	2(16.7%)	12(32.4%)	
Double therapy	2(16.7%)	8(21.6%)	0.436
Triple therapy	8(66.7%)	17(45.9%)	
Compliance on treatment			
Yes	3(25%)	14(36.8%)	0.450
No	9(75%)	24(63.2%)	
Presence of rodents or cats			
Yes	11(91.7%)	22(57.9%)	0.031*
No	1(8.3%)	16(42.1%)	
Eating of uncooked food			
Yes	9(75%)	24(63.2%)	0.450
No	3(25%)	14(36.8%)	
Pre. Treatment of Toxoplasma			
Yes	0(0%)	0(0%)	-----
No	12(100%)	38(100%)	

We found no significant relation in age at onset, duration of illness, frequency of admission, types of treatment, compliance on treatment, presences of rodents and cats, eating of uncooked food and previous treatment of Toxoplasma infection variables with presence of Toxoplasma infection among psychotic group of our entire sample as shown in **(Table 10).**

(Table 11): Correlation between Toxoplasmosis severity and Schizophrenia, schizotypal and delusional disorders group:

Group I	Toxoplasmosis severity	
	R	p value
Age at onset	0.042	0.773
Duration of illness	-0.270	0.058
Frequency of admission	-0.221	0.123
Types of treatment	-0.239	0.098
Presence of rodents or cats	0.234	0.102
Eating of uncooked food	-0.021	0.887
Compliance on treatment	-0.103	0.476
Age grouping	**-0.302**	**0.033***
Marital status	-0.230	0.108
Educational level	-0.116	0.423
Social level	-0.004-	0.976
No. of children	-0.205-	0.153
No. of abortion	**-0.293-**	**0.039***

• **Spearman's rho correlation**

This table shows that the correlation was positive between toxoplasmosis severity and psychotic group in age grouping and number of abortion variables. However, the correlation was not statistically significant in age at onset, duration of illness, frequency of admission, types of treatment, presence of rodents or cats, eating of uncooked food, compliance on treatment, marital status, social level and number of children variables.

Discussion

Based on ICD-10, we diagnosed our patients into 3 groups (psychotic, Mood and neurotic disorders).

The main relation that we found in our study is the relation between the diagnosis of patients and Toxoplasma Gondii infection, as we found 48.7% had psychotic disorders, 29.5% had mood disorders, and 21.8% had neurotic disorders with positive Toxoplasma infection compare to the total number of patients and we found that there was a strong relation between Toxoplasma infection and schizophrenia disorders although there is no association between Toxoplasma infection and both recurrent depressive disorders and obsessive compulsive disorders.

A study found the positivity rate of anti-T. gondii IgG antibodies among individuals with schizophrenia (57.1%) was significantly higher than in healthy controls (29.2%) (Hamidinejat et al., 2010) similar to our results, although Patients with schizophrenia had a significantly

higher mean of serum IgG antibodies to T. gondii compared to controls that proved that the rate of IgG antibody in the schizophrenia patients was 74.8% compared 53.8% in controls (Esshili et al., 2016).

Also there is a study made in turkey, found that 66 of the 100(66%) cases with schizophrenia, 12 of the 50(24%) cases with depressive disorder, and 11 of the 50(22%) healthy volunteers were positive for IgG titers and found that statistically significant between the schizophrenia group and the control groups (P < .01) (Cetinkaya et al., 2007).

Course and outcome of psychiatric illness
Age at onset:
In our study, we found that there is no relationship between the age at onset of disorders grouping and the severity of Toxo-plasma infection (p=0.724), although a different study in Prague by Holub et al., (2013) found a significant relation between the age at onset of schizophrenia and Toxoplasma infection in their study (p = 0.006).

Times of admits:
Regarding patients' times of admits, there was a high significant relation can be found between frequency of admission in psychiatric hospitals and Toxoplasma infection as the (p = 0.038), and this is different to another study found insignificant relation between the times of admits of schizophrenia patients and Toxoplasma infection (p = 0.158) (Holub et al., 2013).

Duration of illness:
We found in our study that a no significant relation between the duration of illness and Toxoplasma Gondii infection (p = 0.704) as to be a same results compare to another study that investigated the relationship between duration of illness and Toxoplasma gondii antibody seropositivity and observed that the seropositivity rate did not differ significantly with length of illness (Cetinkaya et al., 2007).

Summary
 A. Comparison between the group with positive& negative group of Toxoplasma infection
There was strong statistical significance between psychiatric illness, gender and frequency of admission and Toxoplasma infection. The most important thing we can see in the comparisons between the diagnosis of patients and Toxoplasma infection, and 48.7% had psychotic disorders especially schizophrenia, 29.5% had mood disorders and 21.8% had neurotic disorders and this differences are high statically significant.
 B. Correlation between severity of Toxoplasma and the independent variables:
There is a very highly significant correlation between severity of Toxoplasma infection and diagnosis of patients, the subcategories diagnoses and the predominant symptoms in the patients also found a strong association between Toxoplasma infection and the symptoms of visual hallucinations, disorganized speech, inflated self- esteem, decrease need for sleep, depressed mood, pre occupation of serious illness, sleep disturbance.

Conclusion
 (1) Presence of Toxoplasma infection among the psychiatric patients.

 (2) Toxoplasma infection in patients with Schizophrenia, schizotypal and delusional disorders more than patients with Mood [affective] disorders more than patients with Neurotic, stress-related and somatoform disorders.
 (3) Frequency of admission has relative factor with Toxoplasma infection.

References
 1. Centers of Diseases Control and Prevention (2013) "Toxoplasmosis – Microscopy Findings".
 2. Cetinkaya, Z., Yazar, S., Gecici, O. and Namli, MN. (2007) Anti-Toxoplasma gondii antibodies in patients with schizophrenia—preliminary findings in a Turkish sample. Schizophrenia Bulletin, 33:789–91.
 3. Esshili, A., Thabet, S., Jemli, A., Trifa, F., Mechri, A., Zaafrane, F., Gaha, L., Juckel, G., Babba, H. and Bel Hadj Jrad, B. (2016). Toxoplasma gondii infection in schizophrenia and associated clinical features. Psychiatry Research,245:327-332.
 4. Flegr, J., Klapilová, K. and Kaňková, S. (2014). "Toxoplasmosis can be a sexually transmitted infection with serious clinical consequences. Not all routes of infection are created equal". Medical Hypotheses, 83 (3): 286–289.
 5. Fond, G.1, Capdevielle, D., Macgregor, A., Attal, J., Larue, A., Brittner, M., Ducasse, D. and Boulenger, J.P. (2014). Comparative analysis of anti-toxoplasmic activity of antipsychotic drugs and valproate. European Archives of Psychiatry and Clinical The Journal of Neuroscience, 264: 179–183.
 6. Ghanem, M., Gadallah, M., Meky, FA., Mourad, S. and El-Kholy G. (2009). National Survey of Prevalence of Mental Disorders in Egypt: preliminary survey. Eastern Mediterr Health Journal,15(1):65-75.
 7. Hamdi, E., Ramy, H., Sabry, N., Rakhawy, Mo., Rakhawy, Mu. and Loza, N. (2007). Psychiatric Morbidity in Upper Egypt: One Year Prevalence., Cairo.
 8. Hamidinejat, H., Ghorbanpoor, M., Hosseini, H., Alavi, S.M., Nabavi, L., Jalali, M.H., Borojeni, M.P., Jafari, H. and Mohammadaligol, S. (2010). Toxoplasma

gondii infection in first-episode and inpatient individuals with schizophrenia. International Journal of Infectious Diseases, 14(11):978-981.

9. Holub, D., Flegr, J., Dragomirecká, E., Rodriguez, M., Preiss, M., Novák, T., Čermák, J., Horáček, J., Kodym, P., Libiger, J., Höschl, C. and Motlová, L.B. (2013). Differences in onset of disease and severity of psychopathology between toxo-plasmosis-related and toxoplasmosis-

unrelated schizophrenia. Acta psychiatrica Scandinavica. 127:227–238.

10. Okasha, A. (1993). Psychiatry in Egypt. Psychiatric Bulletin, 17: 548 -551.

11. WHO International Consortium in Psy-chiatric Epidemiology (2000). Cross-national comparisons of the prevalences and correlates of mental disorders. WHO International Consortium in Psychiatric Epidemiology. Bulletin of the World Health Organization,78: 413-426.