

Toxoplasma gondii as an Underrated Cause of Schizophrenia

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Abstract

Introduction: Schizophrenia is a neuropsychiatric disease of uncertain cause. It was assumed that schizophrenia is genetically determined. *Toxoplasma gondii*, a coccidian protozoon of the apicomplexa family, chronic infection with *Toxoplasma gondii* is more frequent in individuals with schizophrenia than in psychiatrically healthy controls.

Aim of work: In the present study, the relationship between elevated Toxoplasma antibody and risk of adult schizophrenia was examined and comparing this with other identified schizophrenia risk factors.

Materials and methods: 100 patients with schizophrenia, 50 with depressive disorder, and 50 healthy volunteers were investigated to detect the seropositivity rate of anti-Toxoplasma antibodies by ELISA and comparing this with other risk factors.

Results: Highest percent of Toxoplasma IgG positive cases was in schizophrenia group and it was double the depressive group and more than triple the control group. In depressive group female gender was high risk, and age group ≤ 40 twice more susceptible for development of depressive disorders.

In schizophrenia age group ≤ 40 was twice more susceptible for development of schizophrenia and male sex was a risk factor.

Conclusion: Toxoplasma have a role in development of schizophrenia especially in patients less than 40 years, this may help to reach a new approach in schizophrenia treatment.

Keywords: Depressive disorders • Seropositivity • Patients

Introduction

Schizophrenia is a pervasive, neuropsychiatric disease of uncertain cause that affects approximately 1% of the adult population in the United States and Europe, in Egypt the prevalence of schizophrenia reached 1% an increased occurrence of schizophrenia in family members of affected individuals suggests that genetic factors may play a role in its etiology [1]. For many years, it was assumed that schizophrenia is genetically determined and translating the human genome would lead to an understanding of schizophrenia's etiology [2].

In 1896, an article named "Is Insanity Due to a Microbe?" was published thereby opened the door for the possibility of infectious etiology of schizophrenia. Awareness in the theory was widespread in the early years of the 20th century, and then faded [3]. The infectious etiology of psychiatric disorders remained unexplored till recently, most of the studies tried to link toxoplasmosis with schizophrenia through serological studies but other factors remain unclear as the role of cytokines, effect of maternal toxoplasmosis on children, and neurotransmitter changes (Chaudhury and Ramana).

Genome wide association studies (GWAS) of the disease have revealed a few weak-effect associations, which account for only a small part of the genetic risk [4]. The failure of the genetic studies led to a renewed interest in non genetic risk factors and how these might affect predisposing genes [5].

Epidemiological studies had established that winter spring birth, urban birth, and perinatal and postnatal infections are all risk factors for the disease developing in later life. These environmental studies have reawakened

interest in the possible role of infectious agents in schizophrenia [1].

Recent studies have linked schizophrenia with perinatal exposure to viruses such as influenza a virus, rubella virus, herpes simplex virus type, varicella-zoster virus and polioviruses and with postnatal exposure to viral and bacterial agents causing meningitis and encephalitis [6]. The largest number of studies linking an infectious agent to schizophrenia had involved *Toxoplasma gondii* [3].

Toxoplasma gondii, a coccidian protozoon of the apicomplexa family, was first described in 1908. It is an obligate intracellular parasite and is found in 2 forms in humans. The actively proliferating trophozoites or tachyzoites are usually seen in the early, more acute phases of the infection in immune competent individuals. The resting bradyzoites or tissue cysts are primarily found in muscle and brain, probably as a result of the host immune response. About 20% of the US population is seropositive for IgG antibodies for *T. gondii*, making this one of the most prevalent protozoan infections and probably the only chronic parasitic infection lasting a human lifetime without any known consequences [7].

In 1939, *T. gondii* was linked to a congenital syndrome that includes deafness, retinal damage, seizures, mental retardation, and intracranial calcifications [8]. In immune compromised individuals, it may produce severe Central Nervous System (CNS) symptoms [3].

Postnatal transmission may produce lymphadenopathy and nonspecific symptoms of infection, but most cases are asymptomatic. The definitive hosts of this organism are cats and other felines. Transmission of *T. gondii* to humans may come about through ingestion or inhalation of oocysts shed by infected cats into litter boxes, gardens, sandboxes, or other children's

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Received date: 04 August, 2021; Accepted date: 18 August, 2021; Published date: 25 August, 2021

play areas. The organism may also be transmitted through the ingestion of tissue cysts by the eating of undercooked meat containing tissue cysts from sheep, goats, or other animals that have been infected from cats. When *Toxoplasma gondii* infection occurs during pregnancy, the offspring have a markedly increased risk of CNS congenital abnormalities, including microcephaly, hydrocephalus, mental retardation, convulsions, cerebral calcifications, and chorioretinitis [9].

Serological methods for detection of *Toxoplasma* include direct detection of the parasite, immunoassays for serum immunoglobulin (Ig) M antibody, and elevation of maternal IgG antibody to *Toxoplasma*. Elevation of *Toxoplasma* IgG may reflect primary active or reactivated infection; however, unlike IgM antibody, which is a specific indicator of recent infection, increased IgG may persist for years in subjects with dormant infection [6].

The availability of serological assays has allowed for the testing of exposure to *T. gondii* in large numbers of individuals. Studies using these assays have indicated that *Toxoplasma* infection is worldwide and varies in geographic regions and among individuals with different demographic characteristics. There has been interest in investigating a possible association between exposure to this organism and the development of severe psychiatric disorders [3].

A positive antibody titer is thought to reflect the persistence of parasites in the CNS or other body sites. Tissue cysts containing bradyzoites may spontaneously rupture, thus releasing parasites that cause antibody titers to remain elevated [10].

Increased IgG titers to *Toxoplasma* have been associated with both severe and subtle neuropsychiatric abnormalities [11].

Chronic infection with *Toxoplasma gondii* is more frequent in individuals with schizophrenia than in psychiatrically healthy controls. Furthermore, first-episode patients might differ from patients with recurrent or chronic course by having more frequent *T. gondii* infection and/or a more intense immune response. However, to date, the results are not equivocal, with subjects generally characterized as (psychiatric patients) are shown to be more frequently affected than healthy controls or non-psychiatric patients [12].

In a recent study it was found that *Toxoplasma* is 3 folds more prevalent in schizophrenic patients, this was explained by the role of *Toxoplasma* infection in increasing dopamine release from dopaminergic neurons, NMDA receptors activation and neural disruption. In addition, chronic inflammation in toxoplasmosis had been related to cognitive impairment.

In the present study, the relationship between elevated *Toxoplasma* antibody and risk of adult schizophrenia was examined. We investigated the seropositivity rate for anti-*Toxoplasma* IgG and IgM antibodies by Enzyme Linked Immunosorbent Assay (ELISA) in patients with schizophrenia to ascertain a possible relationship between *Toxoplasma gondii* and schizophrenia and comparing this with other identified schizophrenia risk factors. Such as having family history, residence (urban or rural), cannabis use, having physical anomalies, history of traumatic brain injury, sex abuse in childhood or prenatal stress. We selected 100 patients with schizophrenia, 50 with depressive disorder, and 50 healthy volunteers to investigate the seropositivity rate of anti-*Toxoplasma* antibodies by ELISA. We assumed that a positive antibody titer (IgG) reflects chronic infection and the presence of tissue cysts within the CNS or other body tissues.

Materials and Methods

Descriptive study was conducted from 12 April to 20 July 2020 to assessment side effects of antipsychotics medication among patients with schizophrenia at Al-Dewaniyah teaching hospital. The instrument of the study consists of demographic characteristics of sample and clinical symptoms of side effects by using (Simpson-Angus Scale [3]. Non-probability (purposive) sample of 50 schizophrenic patients who has

a medical diagnosis with schizophrenia and treated with antipsychotic medication was selected from Al-Dewaniyah Teaching Hospital psychiatric department. Data were collected by using unstructured interviews were constructed with chronic schizophrenia patients and their family who were attended Al-Dewaniyah teaching Hospital psychiatric department to take their medications. After permission was arranged from Al-Dewaniyah Teaching Hospital psychiatric department as well as the oral permission was taken from all of the participants and their family. Criteria of inclusion: Patients who have schizophrenia. The patients who were over 18 years old. Who has side effects of antipsychotic medication? Face validity of the questionnaire was determined throughout the panel of experts within psychiatric specialists. They were evaluating it and give some adjustments that made in form of questionnaire. The reliability was determined through the implicated the test and retested technique on five patients with schizophrenia after two weeks of the first interview, the result of reliability test was $r=0.87$ this result refer to this questionnaire is highly reliable because the study instrument is based on scale that was used. Statistical analysis was used in result of study is divided into descriptive statistic and inferential statistic according to (Spss version 22).

Materials and Methods

In this study, 100 patients with schizophrenia only were selected from patients attending outpatient clinic, Psychiatry department, Faculty of medicine, Cairo University.

Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Diagnosis was confirmed according to DSM IV-TR

50 patients with depressive disorder and 50 healthy volunteers as control group were examined. The healthy volunteer group was chosen from among health care workers and from among the relatives/ visitors of the patients. They were screened to rule out physical and other psychiatric diseases.

Patients were asked to complete a short questionnaire on risky eating habits (consuming raw or undercooked meat at least several times) and close and risky cat contacts (cat ownership, cat in the same household, playing closely with cats, cleaning cat litters) to ensure that the patients didn't acquire *Toxoplasma* after appearance of schizophrenia.

Serological technique

A Blood samples 5 milliliters was taken from both patients and control group then centrifuged at 1000 r.p.m., and the sera were stored at -20°C until the analysis. The micro-ELISA technique for *T. gondii*. (commercial ELISA kit (BIO-RAD, France) was used for detection of anti-*T. gondii* IgG and IgM antibodies). This technique was performed according to the manufacturer's instructions.

Statistical methods

Data was coded and impact using the statistical package SPSS version 21. Data was summarized using number and percent for qualitative data; comparisons between groups were done using Qui-square test or Fisher's exact test for qualitative variables. Multinomial logistic regression analysis was done to test for significant predictors of depressive disorders and schizophrenia. P-value less than or equal 0.05 was considered statistically significant.

Results

Study was done on 3 distinctive groups: schizophrenia group, depressive disorders group and healthy control group.

Analysis of results showed that age, residence, family history, physical disability, cannabis use, head trauma and childhood sexual abuse showed no statistical significance, while sex showed statistically significant difference (P-value<0.001) (Table 1).

Table 1. Base line characteristics of the studied groups.

		Groups						P-value
		Schizophrenia		Depressive disorders		Control		
		No.	%	No.	%	No.	%	
Age	≤ 40	44	44.00%	27	54.00%	15	30.00%	0.051
	>40	56	56.00%	23	46.00%	35	70.00%	
Sex	F	22	22.00%	30	60.00%	17	34.00%	<0.001
	M	78	78.00%	20	40.00%	33	66.00%	
Residence	Rural	58	58.00%	36	72.00%	36	72.00%	0.116
	Urban	42	42.00%	14	28.00%	14	28.00%	
Family history	P	86	86.00%	46	92.00%	46	92.00%	0.399
	N	14	14.00%	4	8.00%	4	8.00%	
Physical disability	P	98	98.00%	47	94.00%	48	96.00%	0.462
	N	2	2.00%	3	6.00%	2	4.00%	
Cannabis use	P	92	92.00%	47	94.00%	47	94.00%	0.878
	N	8	8.00%	3	6.00%	3	6.00%	
Head trauma	P	96	96.00%	48	96.00%	48	96.00%	1
	N	4	4.00%	2	4.00%	2	4.00%	
Childhood sexual abuse	P	95	95.00%	47	94.00%	46	92.00%	0.925
	N	5	5.00%	3	6.00%	4	8.00%	

Highest percent of Toxoplasma IgG positive cases was in schizophrenia group and it was double the depressive group and more than triple the control group with statistically significant difference (P-value<0.001).

Regarding IgM only 3 positive IgM cases were detected (1 in the depressive group and 2 in the schizophrenia group and no cases in the control group) with no statistical significance (Table 2).

Table 2. Toxoplasma IgG among studied groups.

		Groups						P-value
		Schizophrenia		Depressive disorders		Control		
		No.	%	No.	%	No.	%	
IgG	P	51	51.0%	13	26.0%	8	16.0%	<0.001
	N	49	49.0%	37	74.0%	42	84.0%	

Note. *P-value<0.5 is considered statistically significant

Nominal regression was done for age, sex, and IgG as a predictor for development of schizophrenia or depressive disorder with control group as a reference category.

In depressive group age and sex were statistically significant predictors (P-value 0.042 and 0.037) with male gender being protected, and age group ≤ 40 twice more susceptible for development of depressive disorders, while IgG level was not statistically significant.

In schizophrenia group age, sex, and IgG level were statistically significant predictors with P-value of 0.031, 0.032 and <0.001 respectively. With age group ≤ 40 being twice more susceptible for development of schizophrenia and female sex being protected, also patients with elevated IgG level are 6 times susceptible for schizophrenia than other groups (Table 3).

Table 3. Predictors for depressive disorders and Schizophrenia among study groups.

Diagnosis	Variable	P-value	Odd's Ratio (OR)	95% Confidence interval for OR	
				Lower bound	Upper bound
Depressive disorder	Age (≤40 vs. >40)	0.037	2.468	1.056	5.768
	Sex (M vs. F)	0.042	0.418	0.18	0.967
	IgG (P vs. N)	0.234	1.852	0.671	5.115
Schizophrenia	Age (≤40 vs. >40)	0.031	2.364	1.083	5.161
	Sex (M vs. F)	0.032	2.459	1.078	5.609
	IgG (P vs. N)	<0.001	6.367	2.638	15.366

Note. *P-value<0.5 is considered statistically significant

Discussion

Scientists failed to find a genetic background for development of schizophrenia which directed the attention towards the non genetic background including infectious factors [5].

Few data exist concerning the clinical correlates of *T. gondii* infection in persons with schizophrenia, Studies done on healthy adults having elevated level of serum antibodies to *T. gondii* conveyed alterations in behavior and psychomotor skills [7]. Many studies showed psychiatric changes in Toxoplasma positive patients even if clinically unapparent [13].

In this study analysis of results showed that residence, family history, physical disability, cannabis use, head trauma and childhood sexual abuse showed no statistical significance.

while age and sex showed statistically significant difference with higher risk for depressive disorders in females less than 40 years and higher risk of schizophrenia in males less than 40 years.

Similar to our study reported that childhood sexual and head trauma showed little significance in development of schizophrenia [14,15].

On the contrary of our study stated that female gender is more susceptible for schizophrenia showed that urban residence increases the risk of schizophrenia by more than 2 times, which may be attributed to cultural differences [16-18].

Also, Mortensen reported that family history is a risk factor for development of schizophrenia with increased risk by 9 times in case of mother affection, 7 times in father affection and 6 times in case of affection of one of the siblings [19]. Same was reported with Pederson. It should be taken into consideration that patients and their relatives in our culture usually deny presence of family history for fear of stigma [18].

Regarding cannabis use, Semple, Henquet and Moore stated that cannabis use increases the risk of schizophrenia by 3 times, 2 times and 2.5 times respectively. To be taken into consideration that patients may deny cannabis use for legal reasons [20-22].

The mechanism by which *T. gondii* causes psychosis is not known, but it is assumed that the presence of cysts in the brain may affect the concentrations of dopamine, nitric oxide or form antibodies against globulins [23].

In our study, the seropositivity rate for anti-Toxoplasma IgG antibodies in schizophrenia patients (51%) was twice that of depressive disorders (26%) and more than triple that of control group (16%). patients with elevated IgG level are 6 times susceptible for schizophrenia than other groups.

This is in accordance with Yolken, Leweke, Torrey, Cetinkaya, Niebuhr, Tamer, Hamidinejat, Alipour, and Emelia how showed that anti- *T. gondii* antibodies were higher in schizophrenia patients than in all the selected control groups. Also, Pedersen cited that high levels of *T. gondii*-specific IgG antibodies participates significantly in elevated risk of developing schizophrenia [1,7,18,23-28].

A recent study explained the relation between toxoplasmosis and schizophrenia by the presence of genes encoding for tyrosine hydroxylase enzyme in Toxoplasma genome in the which eventually raises the concentration of dopamine in the Toxoplasma tissue cyst, in addition causes down regulation of Dopamine receptors and monoamine oxidase the dopamine metabolizing enzyme, besides chronic infection results in increased extracellular glutamate and neurotoxicity (Chaudhury and Ramana)

On the contrary Daryani reported that there was no significant association between *T. gondii* antibodies and schizophrenia. He attributed this result to that more than 90% of the patients in his study received anti-schizophrenia treatment [29-32].

In the current study the level of IgM antibodies were not significantly

different between groups. This may be due to decreased level of IgM after the acute phase of the disease subsides while IgG level remains high [23].

Conclusion

In the current study we found that *T. gondii* antibodies were significantly higher in schizophrenia when compared with depressive disorders and healthy control, this finding may help to find a new approach in treatment of schizophrenia.

The actual relation between Toxoplasma infection and development of schizophrenia needs further studies utilizing a larger sample size to clarify the possible association between *T. gondii* and the symptoms and clinical course of schizophrenia.

Another important point is that routine diagnosis of schizophrenia based only on clinical and psychiatric assessments is not sufficient, and serological detection of Toxoplasma should be done routinely in psychotic patients.

Acknowledgement

Authors acknowledge the research committee, Faculty of Medicine, Cairo University for funding this research.

Funding

Work was funded by the Faculty of Medicine, Cairo University, Egypt.

Conflict of Interest

The authors declare that they have no competing interests.

Availability of Data and Material

All data and specimens used are available.

Author Contribution

All manuscript authors contributed to every activity of it; idea of paper, study design, collection of materials, methodology, writing the paper and revising it.

Ethical Approval

The research was approved from the Scientific Research Ethical Committee, Faculty of Medicine Cairo University.

Consent to Participate

All procedures were explained to patients and informed consents were obtained.

Submission Declaration

The work has not been published previously and it is not under consideration for publication elsewhere, the publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright holder.

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How to cite this article: Al-Antably, Abeer Said Abd El-Ghany and Maged Al-Adrousy Gomaa. "Toxoplasma gondii as an Underrated Cause of Schizophrenia" *Clin Schizophr Relat Psychoses* 15S (2021). Doi:10.3371/CSRP.AAGM.091721.