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ANTI-TOXOPLASMA GONDII ANTIBODIES IN EGYPTIAN PATIENTS WITH SCHIZOPHRENIA

[*1,2]Sherif Mohsen Elsherbini

[1]Biology department, Faculty of Science, Al-Baha University

[2]Molecular Biology department, Genetic Engineering and Biotechnology Research Institute, Sadat City University, Egypt, 32897

Corresponding Author:
firstsherif_2000@yahoo.com

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ABSTRACT

For nearly 100 years, infectious microbes dominated discourse on the causes of schizophrenia, Toxoplasma gondii is an obligate intracellular parasite and is found in 2 forms in humans. Toxoplasma gondii has been associated with several congenital CNS anomalies and more subtle delayed neurologic sequelae, The evidence of infection as a cause of schizophrenia was supported by the brain histopathological changes found in patients with schizophrenia, the risk of schizophrenia increased among individuals who were exposed in utero to elevated maternal T. gondii immunoglobin G (IgG) antibody, based on assay of archived maternal sera, was more than twice that of comparison subject, The main aim of this study was to compare the prevalence of T. gondii infection between individuals with schizophrenia and healthy controls in Egyptian choret samples.

100 patients with schizophrenia, and 100 healthy donors where screened for Toxoplasma gondii IgG and IgM antibodies in serum by ELISA.

A significant increase in the incidence of Toxoplasma gondii IgG positive antibody in patient group compared to control group (P= 0.004)

INTRODUCTION

For nearly 100 years, infectious microbes dominated discourse on the causes of schizophrenia. Fueled by the biomedical revolution and consequent advances in several other disciplines of medical research, however, interest in microbial pathogens beyond their classical role in infectious diseases began gradually to wane. Rather, medical research on diseases other than those considered to be infectious in nature continued to favor genetic and non-microbial etiologies of human illness [1]. The evidence of infection as a cause of schizophrenia was supported by the brain histopathological changes found in patients with schizophrenia [2, 3]

Dopamine's role in schizophrenia is well documented. The tyrosine hydroxylase converted L-Dopa to dopamine. An excess of dopamine as a pathological basis for schizophrenia was substantiated by the fact that antipsychotic drugs decreased the brain dopamine thus reducing the symptoms of schizophrenia [4, 5]. In addition, antipsychotics inhibited the replication of Tg [6, 7]. Tg infection of the brain increased levels of dopamine [8, 9] and caused psychotic symptoms resembling schizophrenia [10, 11]. Artemether, an antiparasitic agent, significantly reduced negative symptoms of schizophrenia compared to controls[12]. Schizophrenia disorder is characterized by delusions, hallucinations, disturbances in thinking and communication, and withdrawal from social activity, and affects approximately 1% of the adult population in the USA and Europe. [13]

Toxoplasma gondii, worldwide in distribution, is closely related to other coccidia. This organism 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 [14]. T. gondii can form dormant microscopic cysts in the brain, which cannot be detected with MRI or routine CSF analysis. T. gondii, in its dormant, tissue cyst form, is generally not associated with symptoms [15].
T. gondii has been associated with several congenital CNS anomalies and more subtle delayed neurologic sequelae [16] In the CHDS cohort, the risk of schizophrenia among individuals who were exposed in utero to elevated maternal T. gondii immunoglobin G (IgG) antibody, based on assay of archived maternal sera, was more than twice that of comparison subject [17].

The main aim of this study was to compare the prevalence of T. gondii infection between individuals with schizophrenia and healthy controls in Egyptian choret samples.

MATERIALS AND METHODS

This study was carried out during 2011-2014 it comprised two groups: 100 patients with schizophrenia, and 100 healthy donors of a public blood bank faculty of Medicine Mansoura University, Clinical diagnoses were confirmed by means of the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)

SEROLOGICAL TEST FOR TOXOPLASMOSIS

5-mL blood sample was taken from each subject for serological analysis. The blood samples were centrifuged at 3000 rpm for 20 minutes to procure clear supernatants. The sera were kept at -20°C until the analysis.

The median age of the patients and controls was 37, 29 years (range 21-39 years). After receiving written consent from the patient and their family (at the psychiatry department, Mansoura University), blood samples were taken under sterile conditions by means of venipuncture. Commercially available enzyme-linked immunosorbent assay (ELISA) kits (Sigma-Aldrich) were used according to the manufacturer's instructions, and a microtiter plate reader Read O.D. at 450 nm using ELISA reader within 15 minutes. A dual wavelength is recommended with reference filter of 600–650 nm. was used to determine the IgG and IgM antibodies in serum samples.

STATISTICAL TESTS

The results were analyzed using Statistical Package for Social Sciences (SPSS) version 20. The serofrequency of Tg IgG and IgM antibodies were calculated by descriptive statistics (frequencies), and the differences between the groups were calculated using the chi-square or Fisher's exact test. The differences in medians were compared using the Mann-Whitney U test. The odd ratio (OR) and its 95% Confident Interval (CI) were used to estimate the strength of the association between Tg infection and schizophrenia.

RESULTS

In this study, the seroprevalence of anti-T. gondii IgG antibodies were evaluated in 200 subjects subdivided into two groups schizophrenia patients (n= 100) and control (n= 100). The demographic profiles of the controls (n=100) and patients with schizophrenia (n=100) were comparable in terms of age and gender, (Table 1). The mean ages of controls

and patients with schizophrenia were 29.2±4.9 years (range; 21-39 years) and 37.2±18.3 years (16-76 years), respectively, while the gender was 49 males, 51 females and 54 males, 44 females respectively.

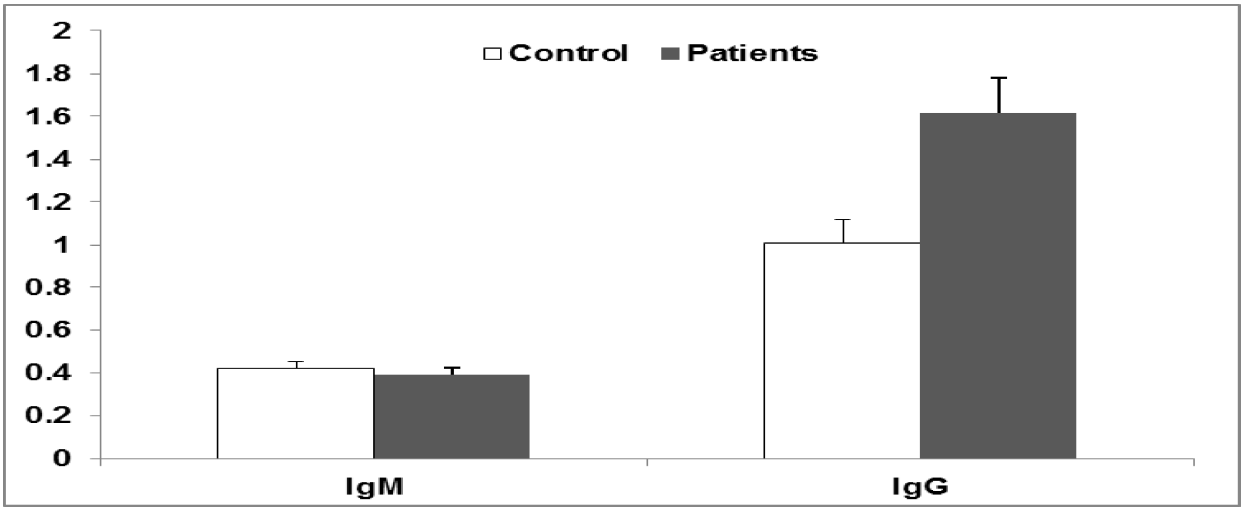
Table 1:

Demographic profile		Control (n= 100)	Schizophrenia (n= 100)
Age	Mean (SD)	29.2±4.9	37.2±18.3
	Range	21-39 years	16-76 years
Gender		49 M – 51 F	54 M – 44 F

Toxoplasma gondii IgG antibody was positive in (46%) and (21%) of patients with schizophrenia and controls, respectively, the IgM antibody was found in (7%) of patients with schizophrenia and (5%) in controls. A significant increase in the incidence of Toxoplasma gondii IgG positive antibody in patient group compared to control group (P= 0.004), no significant difference found in Toxoplasma gondii IgM positive antibody in comparing the patients group with control (Table 2).

Table 2:

	Schizophrenia	Control	P value
IgG positive	n (46) 46%	n (21) 21%	00.4
IgG Negative	n (54) 54%	n (79) 79%	N.S
IgM Positive	n (7) 7%	n (93) 93%	N.S
IgM Negative	n (5) 5%	n (95) 95%	N.S



DISCUSSION

In recent years, serological studies on patients with schizophrenia have been carried out showing that anti- T. gondii antibodies were higher in patients than in all the selected control groups. [18], [13] In our study, the seropositivity rate for anti-Toxoplasma IgG antibodies in schizophrenia patients (46%) indicates that chronic Toxoplasma infection in schizophrenia patients is greater than in controls (P =0.04). Concerning the question of whether the patients could have acquired Toxoplasma after the onset of the illness, perhaps by eating or drinking undercooked meat or eggs or unpasteurized milk. Anti- Toxoplasma IgM antibodies, which indicate an acute infection, were positive in only 7 individuals in the schizophrenia group and 5 individuals in the control groups.

The T. gondii strong tropism for the CNS has been shown analyzing both murine and human models. Brain cysts are formed in the whole brain, preferentially in cerebral hemispheres, hippocampus, amygdala [19], basal ganglia, cerebellum, cerebral cortex, brain stem [20], and olfactory bulb[21], and a variety of brain cells can be infected, including neurons, microglia and mainly astrocytes [22]. Encysted T. gondii bradyzoites are capable of inhibiting cellular apoptosis, so they can persist in host cells for long periods of time [23]. As cysts grow, the host cell degenerates and may rupture thereby releasing bradyzoites which can differentiate into tachyzoites and invade and kill surrounding cells, if unchecked by the immune system [24]. Other effects are more intriguing (1) alteration of neurotransmitter pathways involving production of proteins homologous to aromatic amino acid tyrosine hydroxylase (TH) and (to) dopamine (DOPA) 2 receptor (D2R) with increasing DOPA synthesis and tryptophan (TRP) degradation and decreasing serotonin synthesis [25]; (2) induction of the immune response [25], and (3) induction of endocannabinoids through the brain cannabinoid receptor type 1 (CB1R) activity on basal ganglia, substantia nigra, globus pallidus, caudate nucleus, and putamen [26].

IFN-γ, IL-12, TNF-α, IL-4 and IL-10, together with IL-1 and IL-1β, IL-2, IL-6, granulocyte macrophage colony-stimulating factor (GM-CSF) and IL-17 and IL-23 are variably expressed by microglia cells, astrocytes, infiltrating CD4+ and CD8+ T cells [27, 28], and may influence mood and behavior through their ability to modulate neurotransmission; thus, the idea that latent infection is clinically asymptomatic should be reconsidered [29]. Since tachyzoites induce more intense inflammatory cytokine-mediated response in host cells than do bradyzoites, proliferation of tachyzoites in the brain following cysts rupture might be related to the onset of schizophrenia [30] and other mental diseases. Indeed, a high specific IgG level in the absence or a low level of IgM was clearly demonstrated in serological studies, observed in the sera of patients with first-onset schizophrenia showing increased production of IL-6, IL-1β and of anti- T. gondii IgG, but not of anti-T. gondii IgM [31].

High antibody titers seem to be associated with higher inflammatory response and with first-episode schizophrenic status, and continuously high titers might favor a chronic course of the psychiatric disturbance. It was also described that individuals with schizophrenia with acute symptomatology display increased TH1-associated cytokine responses, returning to control levels during successful antipsychotic treatment [32, 33]. Regarding cytokine-mediated effects, it should be also underlined the role of IL-1β and IFN-γ in the astrocytes activation that, like microglia cells activation, inhibits tachyzoite replication through production of high nitric oxide (NO) levels [34]. In addition to cytokine-mediated effects, probably acting on specific receptors for cytokines present in many brain areas [35], it is also possible to hypothesize that antibodies against T. gondii cross-react with epitopes in neural tissue [36].

Furthermore recent experimental studies in rodents have analyzed CD8+T cells, playing a pivotal role in mediating long-term immunity to Toxoplasma. Indeed, a CD8+ T cell exhaustion could cause reactivation of latent disease during later phases of chronic toxoplasmosis. Of interest for the potentially correlation to this observation is the CD8+ T cell down regulation typically seen in schizophrenic patients [37].

If schizophrenia is a neurodevelopmental disorder, a hypothesis that is supported by converging evidence from several disciplines of research, then infection is a likely candidate risk factor, given that microbial pathogens have long been known to cause congenital brain anomalies. Rubella, herpes simplex virus, cytomegalovirus, toxoplasmosis, and other infections are potent disrupters of fetal neurodevelopment leading to abnormalities of brain and behavior, including mental retardation, learning disabilities, and hypoplasia of several brain regions [16]. Studies had documented that astrocytes and neurons of the brain could be infected by Toxoplasma gondii (Tg). The infection then stimulated the production of a variety of cytokines by microglia, astrocytes, and neurons which in turn initiated inflammatory responses[30] [38] The parasites formed cysts within the brain and produce an enzyme called tyrosine hydroxylase, which was needed for dopamine production [39]

Our finding support the previous findings that show significant increase in Toxoplasma gondii IgG antibodies in schizophrenia patients in comparison to control [13, 18, 39], A similar finding was demonstrated in an independent sample from Denmark in which T. gondii IgG was assayed in filter paper blood spots collected from offspring with schizophrenia and comparison offspring within 1 week of birth [40]. A Turkish study for 100 patients with schizophrenia, 50 with depressive disorder, and 50 healthy volunteers shows that the seropositivity rate for anti-Toxoplasma IgG antibodies among schizophrenia patients (66 %) was significantly higher than among patients with depressive disorder or healthy volunteers ($P < .01$). Suggesting a causal relationship between toxoplasmosis and the etiology of schizophrenia [41]. Recently Iranian study show positivity rate of anti-T. gondii IgG antibodies among individuals with schizophrenia (57.1%) was significantly higher than in healthy controls (29.2%) [42]. this finding raises the possibility that genetic variants that influence the susceptibility or immune response to certain infections may determine whether an individual exposed to the infectious agent has higher risk or not to schizophrenia and other neurodevelopmental disorder. There was no significant difference between Tg IgM antibody in patients with schizophrenia and controls. This finding was consistent with previous studies [43]. A positive correlation between toxoplasmosis and schizophrenia or any other psychiatric disease may lead to new approaches for the treatment of these diseases.

REFERENCE

[1] Brown, A.S., *Response to Vedeniapin Letter.* American Journal of Psychiatry, 2010. **167**(10): p. 1276-1276.

[2] Cotter, D.R., C.M. Pariante, and I.P. Everall, *Glial cell abnormalities in major psychiatric disorders: the evidence and implications.* Brain research bulletin, 2001. **55**(5): p. 585-595.

[3] Horacek, J., et al., *Latent toxoplasmosis reduces gray matter density in schizophrenia but not in controls: voxel-based-morphometry (VBM) study.* The World Journal of Biological Psychiatry, 2012. **13**(7): p. 501-509.

[4] Creese, I., et al., *Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs.* Journal of Neuropsychiatry and Clinical Neurosciences, 1996. **8**(2): p. 222-226.

[5] Richtand, N.M., et al., *Dopamine and serotonin receptor binding and antipsychotic efficacy.* Neuropsychopharmacology, 2007. **32**(8): p. 1715-1726.

[6] Jones-Brando, L., E.F. Torrey, and R. Yolken, *Drugs used in the treatment of schizophrenia and bipolar disorder inhibit the replication of Toxoplasma gondii.* Schizophrenia research, 2003. **62**(3): p. 237-244.

[7] Webster, J., et al., *Parasites as causative agents of human affective disorders? The impact of anti-psychotic, mood-stabilizer and anti-parasite medication on Toxoplasma gondii's ability to alter host behaviour.* Proceedings of the Royal Society of London B: Biological Sciences, 2006. **273**(1589): p. 1023-1030.

[8] Stibbs, H., *Changes in brain concentrations of catecholamines and indoleamines in Toxoplasma gondii infected mice.* Annals of tropical medicine and parasitology, 1985. **79**(2): p. 153-157.

[9] Xiao, J., et al., *MicroRNA-132 dysregulation in Toxoplasma gondii infection has implications for dopamine signaling pathway.* Neuroscience, 2014. **268**: p. 128-138.

[10] Torrey, E.F. and R.H. Yolken, *Toxoplasma gondii and schizophrenia.* Emerging infectious diseases, 2003. **9**(11): p. 1375.

[11] Wang, T., et al., *A potential association between Toxoplasma gondii infection and schizophrenia in mouse models.* Experimental parasitology, 2013. **135**(3): p. 497-502.

[12] Wang, H.-L., et al., *The effect of artemether on psychotic symptoms and cognitive impairment in first-episode, antipsychotic drug-naive persons with schizophrenia seropositive to Toxoplasma gondii.* Journal of psychiatric research, 2014. **53**: p. 119-124.

[13] Hamidinejat, H., et al., *Toxoplasma gondii infection in first-episode and inpatient individuals with schizophrenia.* International journal of infectious diseases, 2010. **14**(11): p. e978-e981.

[14] Garcia, S. and A. Bruckner, *Tissue protozoa (Toxoplasma gondii).* Diagnostic medical parasitology, 1997: p. 111-121.

[15] Cetinkaya, Z., et al., *Anti-Toxoplasma gondii antibodies in patients with schizophrenia—preliminary findings in a Turkish sample.* Schizophrenia bulletin, 2007. **33**(3): p. 789-791.

[16] Palazzi, D., J. Klein, and C. Baker, *Bacterial sepsis and meningitis.* Infectious Diseases of the Fetus and Newborn Infants. 6th ed. USA: Elsevier Saunders, 2006: p. 247-95.

[17] Brown, A.S., et al., *Maternal exposure to toxoplasmosis and risk of schizophrenia in adult offspring.* American Journal of Psychiatry, 2005. **162**(4): p. 767-773.

[18] Omar, A., et al., *Seropositivity and Serointensity of Toxoplasma gondii Antibodies and DNA among Patients with Schizophrenia.* The Korean journal of parasitology, 2015. **53**(1): p. 29.

[19] Melzer, T., et al., *Host cell preference of Toxoplasma gondii cysts in murine brain: a confocal study.* Journal of neuroparasitology, 2010. **1**.

[20] Ho, Y.-C., et al., *Clinical presentation and outcome of toxoplasmic encephalitis in patients with human immunodeficiency virus type 1 infection.* Journal of microbiology, immunology, and infection= Wei mian yu gan ran za zhi, 2008. **41**(5): p. 386-392.

[21] Prandota, J., *Possible link between Toxoplasma gondii and the anosmia associated with neurodegenerative diseases.* American journal of Alzheimer's disease and other dementias, 2014: p. 1533317513517049.

[22] Halonen, S., W. Lyman, and F. Chiu, *Growth and Development of Toxoplasma Gondil in Human Neurons and Astrocytes.* Journal of Neuropathology & Experimental Neurology, 1996. **55**(11): p. 1150-1156.

[23] Boothroyd, J.C., *Toxoplasma gondii: 25 years and 25 major advances for the field.* International journal for parasitology, 2009. **39**(8): p. 935-946.

[24] Frenkel, J., *Pathophysiology of toxoplasmosis.* Parasitology Today, 1988. **4**(10): p. 273-278.

[25] Henriquez, S., et al., *Neuropsychiatric disease and Toxoplasma gondii infection.* Neuroimmunomodulation, 2009. **16**(2): p. 122-133.

[26] Melamede, R., *Parasitic brain infection, endocannabinoids, and schizophrenia.* Medical hypotheses, 2009. **72**(2): p. 220-222.

[27] Kawanokuchi, J., et al., *Production and functions of IL-17 in microglia.* Journal of neuroimmunology, 2008. **194**(1): p. 54-61.

[28] Li, Y., et al., *Inducible IL-23p19 expression in human microglia via p38 MAPK and NF-κB signal pathways.* Experimental and molecular pathology, 2008. **84**(1): p. 1-8.

[29] Schwarz, M., *The immunological basis of glutamatergic disturbance in schizophrenia: towards an integrated view*. 2007: Springer.

[30] Carruthers, V.B. and Y. Suzuki, *Effects of Toxoplasma gondii infection on the brain.* Schizophrenia bulletin, 2007. **33**(3): p. 745-751.

[31] Wang, H.L., et al., *Prevalence of Toxoplasma infection in first-episode schizophrenia and comparison between Toxoplasma-seropositive and Toxoplasma-seronegative schizophrenia.* Acta Psychiatrica Scandinavica, 2006. **114**(1): p. 40-48.

[32] Kim, Y.-K., et al., *Th1, Th2 and Th3 cytokine alteration in schizophrenia.* Progress in Neuro-Psychopharmacology and Biological Psychiatry, 2004. **28**(7): p. 1129-1134.

[33] Bachmann, S., et al., *Psychopathology in first-episode schizophrenia and antibodies to Toxoplasma gondii.* Psychopathology, 2005. **38**(2): p. 87-90.

[34] Hopkins, S.J. and N.J. Rothwell, *Cytokines and the nervous system I: expression and recognition.* Trends in neurosciences, 1995. **18**(2): p. 83-88.

[35] Rice, J., et al., *Molecular mimicry: anti-DNA antibodies bind microbial and nonnucleic acid self-antigens*, in *Molecular Mimicry: Infection-Inducing Autoimmune Disease*. 2005, Springer. p. 137-151.

[36] Bhadra, R., et al., *Psychiatric disorders in toxoplasma seropositive patients—the CD8 connection.* Schizophrenia bulletin, 2013: p. sbt006.

[37] Prandovszky, E., et al., *The neurotropic parasite Toxoplasma gondii increases dopamine metabolism.* PLoS One, 2011. **6**(9): p. e23866.

[38] McConkey, G.A., et al., *Toxoplasma gondii infection and behaviour–location, location, location?* The Journal of experimental biology, 2013. **216**(1): p. 113-119.

[39] Khademvatan, S., et al., *Toxoplasma gondii Exposure and the Risk of Schizophrenia.* Jundishapur journal of microbiology, 2014. **7**(11).
[40] Mortensen, P.B., et al., *Toxoplasma gondii as a risk factor for early-onset schizophrenia: analysis of filter paper blood samples obtained at birth.* Biological psychiatry, 2007. **61**(5): p. 688-693.
[41] Leweke, F.M., et al., *Antibodies to infectious agents in individuals with recent onset schizophrenia.* European archives of psychiatry and clinical neuroscience, 2004. **254**(1): p. 4-8.