

Toxoplasma gondii infection in patients with schizophrenia

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Abstract

Background and objective: Schizophrenia is a complex chronic neuropsychiatric disease of the central nervous system, believed to have multiple etiologies. Toxoplasma gondii has emerged as an interesting candidate as a possible cause of some cases of schizophrenia. As there is scarce information about the seroprevalence of T. gondii infection in psychiatric patients in Erbil; we investigated the seroprevalence of T.gondii in schizophrenic patients and compared with that obtained from control individuals in Erbil correlated with inflammatory marker C-reactive protein.

Methods: This case control study included 93 schizophrenic patients seeking medical advice at Hawler Psychiatric Hospital and private clinics with 93 non psychiatric control were screened for the presence of anti-toxoplasma IgG, IgM (by ELISA test) and C-reactive protein using qualitative methods. A questionnaire was used to collect socio-demographic and behavioral data among the respondents.

Results: In chronic cases anti-Toxoplasma gondii IgG antibodies were seropositive in 30/93 (32.3%) of the schizophrenic patients and 4/93(4.3%) of control (P <0.001). The seropositive rate of IgM antibodies was 9.7% and 1.1% among schizophrenic patients and control, respectively (P = 0.006). The result of C-reactive protein positivity among patients and control was 23.6% and 3.22%, respectively (P <0.001).

Conclusion: Our results delineate that association might exist between Toxoplasma gondii infection and schizophrenia etiology.

Keywords: Toxoplasmosis, Toxoplasma gondii, Schizophrenia, C-reactive protein.

Introduction

Toxoplasma gondii is an obligate intracellular protozoan parasite belong to phylum Apicomplexa.¹ Toxoplasma gondii is a protozoan parasite found worldwide,² that infects all kinds of mammals, including cats, livestock, and human beings. In its life cycle, cats and other felids are the definitive hosts and the other warm-blooded vertebrates are intermediate hosts.³ Human infections with Toxoplasma gondii occur mainly by ingesting food or water contaminated with oocyst or eating undercooked or raw meat containing tissue cyst.⁴ The role of coccidian protozoa Toxoplasma gondii represents one of the most enigmatic and unexplained questions in the field of pathophysiology of

schizophrenia. Toxoplasma gondii is a very successful parasite, infecting approximately 30% of the human population.⁵ The congenital toxoplasmosis is linked to severe neuropsychiatric and ophthalmological symptoms.⁶ A variety of brain cells including astrocytes and neurons can be infected. It is proposed that neurotropic cysts of toxoplasma exert an effect on animal behavior, either directly or via release of metabolic products. Long standing infection in humans has been linked to cerebral tumor formation and personality shift.⁷ Schizophrenia is a progressive neuropsychiatry disease of uncertain cause that approximately affects 1% of the adult population in USA and Europe. There is a clear inheritable

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component, but familial incidence is sporadic and schizophrenia does occur in families with no history of the disease.⁸ Schizophrenia is widely believed to have a neurobiological basis. The most notable theory is the dopamine hypothesis, which posits that schizophrenia is due to hyperactivity in brain dopaminergic pathways.⁹ Some researchers have found an association between some cases of schizophrenia and toxoplasmosis. Toxoplasmosis can lie dormant in the nervous system and migrate to the brain over many years. Some cases of acute toxoplasmosis in adults are associated with psychiatric symptoms such as delusions and hallucinations.¹⁰ *Toxoplasma gondii* genome is known to contain two aromatic amino acid hydroxylases that potentially could directly affect dopamine and/or serotonin biosynthesis.⁹ However, stimulation of the immune response has also recently been associated with mood and behavioral alterations in humans, and compounds designed to alter mood, such as fluoxetine, have been demonstrated to alter aspects of immune function. Herein, the evidence for *Toxoplasma gondii* induced behavioral changes relevant to schizophrenia and depression is reviewed.¹¹ The activity of the immune system is likely to play an important role in many of the observed effects of *Toxoplasma* infection. Thus, the impairment of the immune system has been suggested to be at least partly responsible for the observed association between toxoplasmosis and schizophrenia.¹² Many of the observed behavioral effects of toxoplasmosis might be a result of the increased level of dopamine in the brain tissue in response to IL-2 produced by immune cells in the sites of local inflammation in the infected brain.^{13,14} *Toxoplasma gondii* has been identified as a candidate infectious agent related to schizophrenia.⁸ A study has revealed that newborns who have antibodies to *Toxoplasma gondii* have an increased risk of later being diagnosed with schizophrenia.¹⁵ Apart from that, environmental

factors such as infections with *Toxoplasma gondii* is found to be more frequent in individuals with schizophrenia than in psychiatrically healthy controls.¹⁶ To investigate possible associations between *Toxoplasma gondii* infection and schizophrenia, we assessed the seroprevalence of anti-*Toxoplasma gondii* IgG and IgM antibodies in individuals with schizophrenia and disease free group as control subjects; together with the assessment and evaluation of role of inflammatory marker C-reactive protein (CRP).

Methods

Studied groups

Serum samples were collected from 93 patients (36 females and 57 males) admitted to Hawler Psychiatric Hospital in Erbil. Diagnosis was made by psychiatrists and confirmed by diagnostic and statistical manual of mental disorders, fourth edition (DSM-IV).¹⁷ The mean (\pm SD) age was 34 ± 53 . On clinical ground and laboratory investigations were carried out, 20 were recently diagnosed as acute schizophrenic cases. The other 73 patients were under antipsychotic therapy (chronic cases).

A matched age and gender control group consisted of 93 healthy volunteers was chosen who had no history of schizophrenia. They were also tested for toxoplasmosis as a control. The patient and controls were living in the urban and rural region in and near Erbil city.

Serological technique

Five millimeters of blood was taken from 93 schizophrenic patients and 93 controls under sterile conditions. Serum sample were obtained by centrifugation at (3000 rpm for 10 min) of blood collected from the participants and kept at -20°C pending ELISA tests. Serum samples were assayed for latex agglutination test, anti-*T.gondii* IgG and IgM antibodies with a commercially ELISA kit and qualitative method for C-reactive protein. All tests were performed following the instructions of the manufacturer. 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.

Ethical Consideration

This study was approved by the Research Ethics Committee of Hawler Medical University/College of Medicine, Erbil. All participants were provided with written informed consent after the study purpose and procedures were explained.

Statistical analysis

Statistical analysis was done by using statistical package for the social sciences (version 19.0). The relative proportions were calculated with a confidence interval of 95%. Possible associations were identified using the Chi-square and Fisher's exact statistical tests at a significant level $P \leq 0.05$.

Results

The baseline of control and schizophrenic patients regarding the type of clinical presentation as acute or chronic is shown

in Table 1. In males, 13/57 (22.8%) and 44/57 (77.2%) of cases were diagnosed as acute and chronic cases, respectively. In female, 7/36 (19.4%) and 29/36 (80.6%) were diagnosed as acute and chronic case, respectively. The control schizophrenia free subjects included 49 males and 44 females with age range apparently compatible with schizophrenia cases. The results of serologic finding are summarized in Table 2 using Toxoplasma latex test and anti-Toxoplasma IgM and IgG by means of ELISA test. Thus 44.1% and 12.9% of cases and control showed Toxoplasma seropositivity when using direct Toxoplasma latex test and the result was highly significant ($P < 0.001$). ELISA anti-toxoplasma IgM test on the other hand revealed seropositivity in 9.7% and 1.1% of cases and control, respectively ($P < 0.006$). Meanwhile ELISA anti-toxoplasma IgG was positive in 32.3% and 4.3% of schizophrenic patients and control group, respectively ($P < 0.001$). The difference between anti-toxoplasma IgM and IgG was highly significant ($P < 0.001$).

Table 1: Base line characteristic of schizophrenic patients and control group

Group	Schizophrenic patients				Control	
	Total No (%)	Acute Cases No (%)	Chronic Cases No (%)	Age (Mean±SD)	Total No (%)	Age (Mean±SD)
Male	57	13(22.8%)	44(77.2%)	34±53	49	33±68
Female	36	7(19.4%)	29(80.6%)	35±23	44	34±25
Total	93	20(21.5%)	73(78.5%)		93	

Table 2: Anti-Toxoplasma antibodies seropositivity in schizophrenic patients and control group

Group	Toxoplasma latex			Anti-Toxoplasma IgM (ELISA)		Anti-Toxoplasma IgG (ELISA)	
	Total No.	+ve No (%)	-ve No (%)	+ve No (%)	-ve No (%)	+ve No (%)	-ve No (%)
Schizophrenic	93	41 (44.1%)	52 (55.9%)	9 (9.6%)	84 (90.3%)	30 (32.3%)	63 (67.7%)
Control	93	12 (12.9)	81 (87.1)	1(1.1%)	92(98.9%)	4 (4.3%)	89 (95.7%)

Toxo-latex agglutination $P < 0.001$
 Anti-Toxoplasma IgM (ELISA): $P = 0.006$ (acute cases)
 Anti-Toxoplasma IgG (ELISA) : $P < 0.001$ (chronic cases)
 Anti-Toxoplasma IgM and IgG (ELISA) : $P < 0.001$

Table 3 reveals the number and percent distribution of patients and control seropositive and negative for inflammatory marker namely CRP using qualitative method. Thus CRP seropositive sera was detected in 23.7% and 3.2% of schizophrenic cases and control, respectively (P <0.001). The difference between schizophrenia and control groups highly significant for CRP (P <0.001).

Table 3: C_ reactive protein positivity in control and schizophrenic patients

Group	C-reactive protein status	
	+Ve (%)	-Ve (%)
Schizophrenia	22 (23.7%)	71 (76.3%)
Control	3 (3.2%)	90 (96.8%)

Discussion

Toxoplasma gondii is highly neurotropic that affecting both neurons and glia in brain.¹⁸ These later cells are also target in the pathophysiology of schizophrenia¹⁹⁻²¹ that subsequently affecting brain neurotransmitters. This study possibly could be the first in Iraqi Kurdistan region that seek the association between T. gondii and schizophrenia as a possible etiologic parasitic factor in some cases. The present study has demonstrated anti-T. gondii seropositivity in schizophrenic patients when compared with control group using Toxoplasma latex; anti-T. gondii IgM by ELISA (P< 0.006) and anti-T. gondii IgG. On clinical ground anti-T. gondii IgM and IgG seropositive cases might reflect possibly acute and chronic schizophrenic cases respectively.² The findings of our study replicate the results of same recent studies that have shown a higher significant anti-T. gondii IgG antibodies in schizophrenic when compared with control.^{11,2,10,18,22} However, they disagree with other studies who report no significant difference between patients and control for anti-T. gondii IgG.^{3,23} For anti-T. gondii IgM, the results of the present study

disagree with other studies who report no significant difference between schizophrenic patients and control.^{1,3,18,24} T. gondii has emerged as a prime candidate etiologic factor in some cases of schizophrenia for a variety of reasons.¹⁹ Of these, (i) many studies have reported a higher prevalence of T. gondii antibodies in sera of schizophrenic patients compared with control, (ii) some peoples with adult toxoplasmosis develop psychotic symptoms similar to those of schizophrenia, (iii) epidemiologically the existence of many similarities between toxoplasmosis and schizophrenia, (iv) antipsychotic drugs can also inhibit T.gondii, (v) elevated level of dopamine is commonly seen in schizophrenic patients that coincide with elevated level of dopamine experimental animal infected with T. gondii (vi) schizophrenic patients when compared with control have had a greater exposure to cats in children.²⁵ Since 25 original studies in 1953,^{19,20} 54 similar studies have been reported for the line between T. gondii and psychoses. Of these 54 studied, 42 have been reviewed in 2007 included a meta-analysis of 23 of them in which the odds ratio of having T. gondii with a diagnosis of schizophrenia was 2.73.^{16,19} It is well known that schizophrenic patients have abnormal neurotransmitters namely dopamine, glutamate and gamma-Aminobutyric acid (GABA).^{18,19} The link between T. gondii and dopamine, is the fact that T. gondii harbor two genes that encode forms of tyrosine hydroxylase; the enzyme vital in the generation of dopamine in the brain.^{9,19} Epidemiologically, there are at least seven areas of similarity between toxoplasmosis and schizophrenia; of these, age of onset and gender, beside two epidemiologic dissimilar aspects. In this study male was higher than female as schizophrenia incidence or prevalence. Our results agree with other studies.^{19,26} Schizophrenia may be associated with inflammatory reaction and CRP as one of the inflammatory marker is a nonspecific serum protein that reflect persistent

a highly significant difference exist between schizophrenic patients (23.7%) and healthy control (3.2%) seropositivity for the inflammatory marker CRP ($P \leq 0.001$) using qualitative method. Our results agree with other studies.²⁷⁻³⁰ Antipsychotic effects on CRP have received little attention as different antipsychotics drugs may have differential effects on CRP level particularly after three months of treatment.³¹ Elevated serum level of CRP in schizophrenia are associated with the severity of cognitive impairment but not of psychiatric symptom.²⁶ This is in contrast with a study which reported that patient with elevated CRP had a significantly more severe psychiatric symptom.²⁹ Of antipsychotic, haloperidol significantly increased CRP level during the first three months of treatment. After three months of treatment, CRP level using haloperidol was 92.7% higher than those in risperidone patients.³¹ Thus, the contribution of various antipsychotic (via increasing CRP level) to coronary heart disease may differ in their influence on metabolic syndrome by increasing the risk of obesity; directly increasing lipid level and directly increasing glucose level.³¹⁻³³

Conclusion

The high seropositivity of anti-*T. gondii* IgM and IgG among schizophrenic patient reflects a possible role of this parasite in the pathophysiology and etiology of schizophrenia; supported with increased inflammatory marker of CRP.

Conflicts of interest

The author reports no conflicts of interest.

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