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Research Article

TOXOPLASMA GONDII AS A RISK FACTOR FOR SCHIZOPHRENIA

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ABSTRACT
Background: Toxoplasmosis is a parasitic disease caused by the protozoan Toxoplasma gondii. There are more than 500 millions of individuals worldwide who are Toxoplasma antibody positive. This parasite can be localized in central nervous system(CNS) and its tissue cysts can cause behavioral changes in host (patients). ***Methods:*** In this study, using ELISA method, toxoplasmosis antibody titer was measured. To measure IgG titer, we used Diapre ELISA kit. The statistical population was consist of 81 patients from a mental clinic in Tehran suburb. They were divided to 3 groups. Schizophrenic group, other mental disorders group and healthy group. ***Results:*** The frequency of contamination in schizophrenic patients was 74.5%, in other mental disorders was 45% and in healthy group was 27.5%. It was found that the frequency of toxoplasmosis in schizophrenic patients is higher than other groups. ***Conclusion:*** Toxoplasma effects on astrocytes glial cells and producing of neurotramsmiters, specially dopamine by secretion of Tyrosine hydroxylase to which schizophrenia is meaningfully related. As a result of this study the toxoplasmosis and schizophrenia are highly related therefore further studies on other mental disorders such as depression, paranoia and brain damages is recommended.

Keywords: *Toxoplasma Gondii, Schizophrenia, Astrocytes, Manipulation, Dopamine*

INTRODUCTION
Toxoplasmosis is a parasitic disease caused by the protozoan Toxoplasma gondii. The parasite infects most genera of warm-blooded animals, including humans, but the definite host is the felidae (cat family) (Torrey and Yolken, 2003).
Humans can become infected by any of several routes such as eating undercooked meat of animals harboring tissue cysts ,consuming food or water contaminated with cat feces or by contaminated environmental samples (such as fecal-contaminated soil or changing the litter box of a pet cat) ,blood transfusion or organ transplantation ,transplacentally from mother to fetus (Torrey and Yolken, 2003). Toxoplasma infection effects any person differently which depends on various factors such as genetic predisposition, the part of the brain affected, immune system, the virulence and dose of the infecting strain and timing (Suzuki, 2002).
Toxoplasma organisms have also been shown to impair learning and memory in mice and to produce behavioral changes in both mice and rats (Torrey and Yolken, 2003).
Schizophrenia is a chronic, debilitating, neuropsychiatric disorder of uncertain cause that affects approximately 1.1% of the world's population, regardless of racial, ethnic or economic background (Torrey and Yolken, 2003).
Schizophrenia typically begins in late adolescence or early adulthood and affects men and women equally. What precisely causes schizophrenia is not known, but current research suggests a combination of hereditary and environmental factors (Suzuki, 2002). Of special interests are studies showing that Toxoplasma-infected rats become less neophobic, leading to the diminution of their natural aversion to the odor of cats. It has been also shown that brain cysts in animals chronically infected with Toxoplasma alter the fine structure of exploratory behavior and risk/unconditioned fear, which may result in greater capture probability of infected rodents. These data also raise the possibility that selective pressures acted on Toxoplasma to broaden its transmission between intermediate hosts, in addition to definitive hosts (Torrey and Yolken, 2003; Pearlson *et al*., 1985).
Toxoplasmosis can also expand schizophrenia, bipolar disorders, parkinson, delusions and hallucinations (Kaiser and Burke, 1996; Elvevag and Goldberg, 2000).

Studies on schizophrenic patients have shown that they act similar to toxoplasmosis patients. Toxoplasma gondii effects on astrocytes glial cells and producing of neurotramsmiters, specially dopamine by secretion of Tyrosine hydroxylase to which schizophrenia is meaningfully related. Studies have shown that the parasite affects the character of infected person and causes anti social behaviors, moral indecency and susceptibility to schizophrenia and bipolar disorders in men and more sense of conscience in women (Elvevag and Goldberg, 2000).

These are examples of evolutionarily driven manipulation of host behavior by the parasite (Pearlson *et al*., 1985).

A series of ecologic studies suggest that Infection during pregnancy as a risk factor is consistent with the neurodevelopmental theory of schizophrenia. Later studies, which are more convincing, include individual assessment of infection, either via comparison of antibodies in adults with schizophrenia versus normal individuals, or, even more convincing, prospective studies in which the infection can be determined to have occurred during the pregnancy. There is consistent evidence that individuals with antibodies to Toxoplasma gondii have higher prevalence of schizophrenia (Kaiser and Burke, 1996).

This study's goal was to investigate the relation between Toxoplasma gondii infection and schizophrenia. The results show a positive relation between them and the titer of Toxoplasma gondii antibodies in schizophrenic patients is meaningfully more than control group.

MATERIALS AND METHODS

In this study, statistical population is 51 schizophrenia patients. Blood serum of 20 patients with psychosis disorders were gathered for Control 1. For Control 2, blood serum of 40 patients were gathered from random clinical laboratories of Tehran.

All schizophrenic patients were from a mental clinic in Tehran suburb, all male, 18-75 years old. Their disease duration was estimated between 3 months to 10 years.

To analyze the titer of Toxoplasma gondii antibodies, 5 ml blood sample was gathered from each patiens and centrifuged in 3000 RPM for 5 minutes. Serums were diluted to 1:100 with the kit solution for serological testing of IgG anti-Toxoplasma antibodies.

In this study titer 1/20 and more is considered positive and indicates chronic infection in patients.

RESULTS AND DISCUSSION

Results

In this study 74.5% (38 persons of 51) schizophrenic individuals had IgG titer of 1/20 and more (Table 1).

Table 1: Frequency of toxoplasmosis contamination in schizophrenic patients

IgG	Frequency	Percentage
Negative	13	25.5
Positive	38	74.5
Total	51	100

45% (9 persons of 20) individuals suffering from other mental disorders had the antibody titer 50 IU/ml (1/20) or more.

In control individuals (healthy), contamination rate was 27.5% (11 persons of 40). (Table 2)

In schizophrenic patient, maximum percentage of toxoplasmosis was 44.73% (17 persons of 38) and IgG= 100-500 IU/ml.

Table 2: Comparison between IgG titer in control group 2 (healthy) and schizophrenics

Contamination rate	Sample	Positive samples	Contamination percentage
Schizophrenic individuals	51	38	74.5
Control 1	20	9	45.0
Control 2	40	11	27.5
Total	111	58	52.5

The frequency of IgG=500-900 IU/ml and IgG> 900 IU/ml was equal . each 13.15% (5 persons of 38). The frequency of IgG=50-100 IU/ml was 28.94% (11 persons of 38) (Table 3).

Table 3: Frequency according to IgG titer in schizophrenic individuals

Ab titer (IU/ml)	Positive samples	Percentage
50-100 (1/20-1/10)	11	28.94
100-500 (1/10-1/2)	17	44.73
500-900 (1/2- <1)	5	13.15
900-1000 (<1-1)	5	13.15
Total	38	100

According to t-test (P=0.0009), there is a correlation between schizophrenic group and control 2 group. It means that a high percentage of schizophrenic patients were contaminated by Toxoplasma gondii (Table 4).

Table 4: Comparison of average IgG titer in 3 groups of study

Groups	Sample	IgG Antibody average	Standard deviation (SD)
Group 1 (schizophrenic)	51	315.87	439.96
Group 2 (control 1) other mental disorders	20	207.27	283.99
Group 3 (control 2) healthy individuals	40	136.76	211.69

According to the Table 4, the IgG antibody average in schizophrenic patients is 315.87. This average in the control 1 (other mental disorders) is 207.27 and in the control 2 (healthy individuals) is 136.76. It means that the the IgG antibody titer in schizophrenic patients is higher than the control groups. Also the ratio of schizophrenia in the individuals with the maximum antibody titer to whom with negative antibody titer is 4.7.

Discussion

In 2007, Zafer Cetinkaya and Suleyman Yazar reached to same findings in a Turkish sample. They selected patients from the schizophrenia population and tested them with micro enzyme-linked immunosorbent assay (ELISA) for Toxoplasma gondii antibodies. They assumed that a positive antibody titer (IgG) reflects chronic infection and the presence of tissue cysts within the CNS or other body tissues (Cetinkaya and Yazar, 2007).

Studies show that Toxoplasma gondii uses macrophages and dendritic cells to reach to specific zones of brain (Trojan Horse) (Chao *et al*., 1993; Jones *et al*., 1986).

Some laboratorial studies on mouse brain show that Tachyzoites attack microglia, astrocycts and neurons and produce tissue cysts. Human studies also show these tissue cysts (Radke *et al*., 2006).

It has been shown that Auto antigen-1, is an important factor for bradyzoits growth in human fibroblast cells (Powell *et al*., 1978). Studies show that glial cells, mostly astrocytes, are infected selectively. Also in postmortem studies, many glial abnormalities have been found in schizophrenic brain like decreased numbers of astrocytes (Creuzet *et al*., 1998). Several in-vitro and clinical studies have shown that cysts can be found in astrocytes and there are evidences of an interaction between astrocytes and Toxoplasma gondii tissue cysts. In a study observing astrocytes in brains infected with virulent Type I Toxoplasma gondii strain, parasites were seen to be colocalized with astrocytes and were found beside neuronal nuclei. Hence, encysted Toxoplasma gondii are ideally positioned for neuromodulation with infection of neurones (Halonen *et al*., 1996). Due to these studies, Toxoplasma gondii infects varieties of host cells that could affect signaling path in brain (Carruthers, 2007). Toxoplasma gondii manipulation of intermediate host behaviour could be due to the parasite localizing in specific brain regions and the most likely brain regions are those associated with fear processing and the main region is amygdale. Although

it has been showed an increased cyst density in the amygdale regions but there are other studies which have found cysts in numerous brain regions such as cortex, diencephalon and thalamus, hippocampus, olfactory bulbs and basal ganglia. It was suggested that Toxoplasma gondii may have a gene or genes that increase predation of the intermediate host by the parasite's definitive host for the survival of genes and the parasite. These genes may affect Toxoplasma gondii localization in the brain to achieve the behavioral manipulation (Fischer *et al*., 1996). Electron microscopic observations of mouse brain shows that most of the tissue cysts locate inneurons, axons and dendrites. Also it's been found that tissue cysts in human with Toxoplasmic encephalitis reproduce in glial cells. These cysts have been also seen in purkinje cells in cerebellum (Bertoli *et al*., 1995). There are various studies that indicate schizophrenia, like Parkinson and sclerosis, is a chronic central nervous system disease which starts in early stages of brain development and this aspect of schizophrenia pathogenesis is consistent with the ability of Toxoplasma gondii to infect the perinatal brain (Rentakallio *et al*., 1997). Clinical studies also show that adults who have schizophrenia or bipolar disorder, have been exposed greater to cats in childhood (Torrey and Yolken, 1995). Some studies show that Toxoplasma gondii infection has been effective on host's behavior (Da Gama *et al*., 2004). Toxoplasmosis changes some of the chemical messages in the brain, and these changes can have an enormous effect on behaviour. Studies have shown there is a direct statistical link between incidences of schizophrenia and toxoplasmosis infection (Rentakallio *et al*., 1997). The relation between toxoplasmosis and schizophrenia is due to the secretion of an enzyme which ruins astrocytes in brain. This is exactly what happens in schizophrenic patients. In 2009, a study in university of Leeds discovered how the toxoplasmosis parasite may trigger the development of schizophrenia and other bipolar disorders. They have found out that The parasite infects the brain by forming a cyst within its cells and produces an enzyme called tyrosine hydroxylase, which is needed to make dopamine. Dopamine's role in mood, sociability, attention, motivation and sleep patterns are well documented and schizophrenia has long been associated with dopamine, which is the target of all schizophrenia drugs on the market. Toxoplasma infections can also affect the level of dopamine, norepinephrine and other neurotransmitters which are widely known to be affected in schizophrenic patients. Dopamine is a neurotransmitter which has important role in controlling brain beavioral, perceptional and dynamic functions. An abnormal increase in level of dopamine could lead to some mental disorders like mania and schizophrenia because all medicine's target is dopamine. The parasite synthesizes the tyrosine hydroxylase that converts the amino acid tyrosine to l-DOPA, the precursor of dopamine. The host cell must supply DOPA decarboxylase for convertion of the parasite-produced l-DOPA to dopamine. Mainly neurons would be affected and selective behavioral change can be seen because neurons have transport and packaging mechanism of dopamine. According to the studies, many schizophrenic patiens, are positive Anti Toxoplasma IgG therefore Toxoplasma gondii could be one of the etiologic factors of schizophrenia (Carruthers, 2007).

Conclusion

There have been several other investigations and studies, based on the relation between Toxoplasma gondii and schizophrenia.

This study focuses on the role of Toxoplasma gondii infection as the cause of schizophrenia in some cases. The results of our study and statistical population show a meaningful relation between toxoplasmosis and schizophrenia.

It seems that positive correlation between toxoplasmosis and schizophrenia or any other psychiatric disease may lead to new approaches for the treatment of these diseases.

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