

Association between anti-*Toxoplasma gondii* antibodies and schizophrenia and psychotic bipolar in patients hospitalized in the psychiatric ward

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RESEARCH

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ABSTRACT

Background

Toxoplasmosis is caused by an intracellular parasite and is a worldwide disease. In laboratory, the parasites that cause the disease increases levels of dopamine in the brain tissue of treated mice. The evidence showed that dopamine releasing in the nucleus accumbens by activating the retro hippocampal region can disrupt the fornix section of brain as evolve to develop a psychosis in human.

Methods

This retrospective case-control study was conducted in patients with schizophrenia and psychotic bipolar referred to psychiatric clinic in Amir Kabir hospital, Arak. After psychiatric diagnosis of patients with schizophrenia and bipolar disorder, 2ml of blood samples were acquired from 76 patients and 75 controls without any psychotic illness or bipolar disorder and other mental illnesses with safety issues. The serum of samples was separated in laboratory

and was kept until the time of testing at -20°C. After collecting all the samples; Anti-*Toxoplasma* IgG on the case and control samples were analysed by ELISA. Results were analysed by SPSS software version 16 and were calculated by χ^2 tests.

Results

55.26 per cent of patients (42 persons) were infected with *Toxoplasma gondii* and in the control group 36 per cent (27 patients) were infected, that the different between them was significant ($p < 0/05$). Toxoplasmosis in psychotic men was more than psychotic women significantly ($p < 0/05$). *Toxoplasma gondii* infection in patients with schizophrenia with psychotic bipolar patients showed no significant difference.

Conclusion

Patients with schizophrenia and bipolar disorder showed significantly higher rate than healthy people against *Toxoplasma gondii* infection. Whether prevention of infection with these parasites is effective in reducing the risk of psychosis requires further investigation.

Key Words

Dopamine, schizophrenia, psychotic bipolar, *Toxoplasma gondii*

What this study adds:

1. What is known about this subject?

There is a changing trend in the susceptibility pattern of *Toxoplasma gondii* with emerging resistance to schizophrenia and bipolar disorder.

2. What new information is offered in this study?

Prevention of infection with this parasite is effective in reducing the risk of psychosis.

3. What are the implications for research, policy, or practice?

Studies should conduct in attempts to better define the relationship of *Toxoplasma* infection to schizophrenia.

Background

Toxoplasma gondii is an intracellular parasite that is widespread in mammals and birds with complex life cycle. The life cycle of this parasite are various forms,¹⁻³ active tachyzoites (acute form of the parasite), bradyzoites (cause chronic infection), Sporozoites which spread within oocysts. Cats are the definitive host of the *Toxoplasma gondii* since the sexual cycle of the parasite occurs in its gut and intermediate host of birds and mammals, including humans, which are done by asexual cycle (extraintestinal phase) develop parasites in their bodies.^{1,4}

Infection of human and other hosts by the parasite occur in three ways:

- Eating raw or undercooked meat containing tissue cysts (bradyzoites), that most infections are included.
- Eating contaminated food and water to the parasite oocysts
- Congenital transmission from mother to foetus, which in this case, only Tachyzoites of the parasite can cross the placenta.⁴⁻⁶ Most human infections with *Toxoplasma* are benign and in adults are usually asymptomatic disease and the sign of the disease may be similar to infectious mononucleosis with fever, chills, headache and also swollen lymph nodes.

But often acquired infections during pregnancy are very severe and only a small percentage of them full recovery. Chorioretinitis, encephalitis, hydrocephalus and microcephaly are consequences prevalent in infection that if observed in children can raise the risk of toxoplasmosis.^{4,6,7}

In chronic infections and dormant parasites in the brain, heart and skeletal muscles with the development of the immune system that are formed in the tissue cysts in body tissues, especially the brain that continue to survive and proliferate much more slowly than the acute phase. At this moment, different cells including astrocytes and neurons of the brain tissue may become infected. Tissue cysts may be persistent months or even years after infection in body tissues, especially nervous tissue.^{1,8}

Review of several studies that have been done suggest chronic infections that cause tissue cyst formation in the central nervous system would be cause changes in behaviour and general reaction of host.^{1,5,9-11}

According to studies that have been done in laboratory observed that the presence of the parasite in the brain tissue increases the level of dopamine in the brains of mice.^{2,12-15}

Dopamine is one of the key elements associated with psychotic disorders such as schizophrenia and bipolar disorder. Dopamine release in the nucleus accumbens in the activation area can be retrohippocampal Fornix causes dysfunction in the brain, resulting in the development of psychotic disorders.^{2,14}

Regarding the high prevalence of Toxoplasmosis, can be say that these parasites can play a role in abnormal social behaviour. Therefore, we can prevent the spread of this parasite and *Toxoplasma* infection prevention and by on time treatment of Toxoplasmosis reduces the rate of abnormal behaviours.

Method

This study is a retrospective study to investigate the case and control groups. The target population is patients with schizophrenia and psychotic bipolar. The study population were patients with schizophrenia and psychotic bipolar that also referred to psychiatric clinics of Arak.

After obtaining ethics code and get a referral letter from university research unit and after psychiatric diagnosis in Amir kabir hospital, selected patients with schizophrenia and bipolar disorder and then, were obtained 2ml of blood samples for testing with safety issues.

Psychological tests were used, including assessment scale test positive symptoms (SAPS) and the Scale for Assessment of Negative Symptoms (SANS) to detect the experimental group and the control group. These questionnaires are studied positive and negative symptoms of schizophrenia. SAPS test discussed to check hallucinations, bizarre behaviour and paranoia and SANS test need to check and test the emotional indifference, apathy, social neglect and poverty verbal.

This questionnaire contains 30 questions and each question is graded from zero to 5 rating and so total points are from zero to 150.

The control group sampled with respect to matching with patient groups. After sampling the samples send to the laboratory and separate serum and serum samples refrigerated until examination at -20°C. Then, after

collecting the required number of samples, Toxoplasma IgG antibody was conducted by ELISA on samples and control by using the kit PT-Toxo IgG-96 (Pishtaz Teb- Iran) and done in accordance with the instruction as below. Standard kit was ready to use and requires no dilution.

1. The samples were diluted samples by using a ratio of 101 (10ml from samples and 1000ml of diluent sample).
2. 100ml from standards and 100ml of samples were cast as follows.
3. In 10 wells, first standards were cast in duplicate, respectively.
4. The rest of the wells were used for the samples.
5. After covering the wells, plates were incubated for 30 min at room temperature.
6. The contents of the wells were evacuated and the wells 5 times with washing solution were washed away.
7. 100ml ready to use conjugated enzyme solution was poured into the wells.
8. After covering the wells, plates were incubated for 30 min at room temperature.
9. The contents of the wells were evacuated and the wells 5 times with washing solution were washed away.
10. 100ml dye was added to the wells.
11. Plates were incubated for 15min at room temperature.
12. With the addition of 100 μ L of stopple solution to each well, the enzyme reaction was stopped.

Absorbance was read at 180nm by using ELISA reader BioTek- ELX 800; BioTek instruments, USA.

Cut off value was calculated as follows:

Cut off value = mean of standard 10

The index is calculated as follows that positive values of more than 1.1 and below 0.9 are considered negative and suspicious between these two values.

Cut off Index = sample OD/Cut off value

Results were analysed by SPSS software version 16 and were calculated by χ^2 tests

Results

Samples were collected from 76 patients in psychiatric ward in Amir Kabir hospital-Arak which 42 (55.26 per cent) men and 34 (44.74 per cent) were female. Also, 39 patients (51.31 per cent) with schizophrenia and 37 patients (68/48 per cent) were diagnosed with bipolar disorder (Table 1).

Toxoplasma IgG after testing by ELISA was observed. Forty two cases (55.26 per cent) of the patients were infected with *Toxoplasma gondiis*. The difference with the control group with 27 cases (36 per cent), using logistic regression test was significant ($p < 0.05$) (Table 2).

Also, in positive cases in the study group ($n=42$), 25 (59.52 per cent) men and 17 cases (50 per cent) women, were infected with toxoplasma gondii and had significant differences and Psychotic men with toxoplasma infection were higher in number ($p < 0.05$). While in the control group infection in men and women is approximately equal and not significant (Table 3). As well as, there were 39 patients with schizophrenia, that in them 22 patient (56.41 per cent) had toxoplasma and in the patients with bipolar psychosis, 20 of 37 cases had Toxoplasmosis (54.05 per cent). In this respect there isn't a significant difference (Table 4).

Discussion

In this study, the purpose wasn't to investigate the prevalence of toxoplasmosis, although the information obtained with the outbreak of toxoplasmosis in the control group matched in previous studies in population of Arak.

The study was conducted to investigate in patients with psychosis and bipolar disorder accompanied by the parasite *Toxoplasma gondii* in Arak. Toxoplasmosis in people with healthy immune systems usually was benign and parasite becomes microscopic cysts in the brain and other body parts eventually.

And only when combined with a weakened immune system or during pregnancy might be dangerous and risky. Review several studies that have been done suggest that chronic infections cause tissue cyst occurs in the central nervous system that cause changes in behaviour and general reaction in host.^{1,5,9-11}

According to studies in mice have been observed that the presence of this parasite in the brain tissue increases the level of dopamine in the brains of rats.^{2,12-15} Evidence suggests that dopamine is a key element related to psychotic disorders such as schizophrenia and bipolar disorder.

Accumbens dopamine release in the nucleus due activate retro hippocampal area can cause problems in the area of the fornix brain and resulting in the development of psychotic disorders.^{12,13}

The Cetinkaya et al. conducted on 100 psychotic patients and healthy subjects in Turkey were observed that 66 per cent of patients with psychotic disorders of Toxoplasma antibody were positive whereas only 22 per cent of the healthy subjects were positive for this antibody. It was also observed that patients with psychotic disorders have a

higher level of *Toxoplasma* antibodies than healthy subjects.¹⁶

In another study that was conducted by kocazeybek et al. in 2009 in Turkey, the prevalence of intestinal parasites in people who have had dangerous driving offenses but had not studied the history of toxoplasmosis were examined and it was observed that 53.5 per cent of the evaluated patients affected by chronic toxoplasmosis while only 28 per cent were infected with in the control group ($p < 0.0001$).¹²

In a study by Flegr in the Czech Republic entitled the impact of *Toxoplasma* on human behaviour, it was observed that patients with infection compared with non-infected individuals differ in their behavioural pattern.¹³

He and her colleagues in another study in 2002 in the Czech Republic found that people with serious traffic accidents have more positive *Toxoplasma* than normal individuals and it also showed that people with chronic *Toxoplasma gondii* have 2.65 times negative *Toxoplasma* than those involved in dangerous accidents.¹⁷

Xiao et al. in a study in 2009 on 219 pregnant women with babies in America with schizophrenia or other psychotic disorders were brought into the world, found that mothers who are infected with toxoplasma type I significantly increases ($p = 0.03$) risk of psychotic disorders in their babies while there wasn't a significant correlation between *Toxoplasma* species and other psychotic disorders.¹⁸

In a study by Mortensen et al. in Denmark that was done on new-born babies with schizophrenia, were found significantly ($p = 0.045$) more *Toxoplasma* IgG antibody levels in new-born infants with schizophrenia than in controls (healthy babies).¹⁹

In a study by Amminger et al. in Australia entitled antibodies to germs in individuals at high risk of psychosis, 105 patients with psychotic disorders were studied and it was observed that high levels of IgG antibodies to *Toxoplasma gondii* in patients significantly associated with psychotic symptoms while this communication were not observed about herpes virus antibodies.¹⁴

A study by Yereli et al. was done in Turkey entitled “whether *Toxoplasma gondii* is a potential risk for car accidents?”. In this study, 185 patients were studied in the cities of Izmir and Manisa who has studied traffic accidents and observed that 34 per cent were infected with *Toxoplasma gondii* compared with 8 per cent of those in the control group and also observed that this disease dramatically increases the

traffic accidents.¹⁵

In case-control study by Sahneh saraee et al. in Qazvin entitled “Relationship between *Toxoplasma gondii* infections and schizophrenia”, there wasn't significant relationship between *Toxoplasma gondii* infection and incidence of schizophrenia.²⁰

In this study, the percentage of people with schizophrenia was 55.3 and 50.9 per cent of those in the placebo group were positive for *Toxoplasma* infection ($p > 0.05$).²⁰

In studies in Arak, a study was conducted on laboratory referred to Arak before marriage from 1026 people, 365 cases (57/35 per cent) were positive plasma of *Toxoplasma* antibodies²¹ and IgG titres in 38 per cent of pregnant women in another study were high care²² that is closely related to the results of our study and in our study of *Toxoplasma gondii* infection was observed in the control group was 36 per cent.

Conclusion

In our study, it was observed that patients with psychosis have higher prevalence of *Toxoplasma* than the general population. This finding is consistent with studies abroad. The important subject in this first study compared with previous studies was reached that psychotic toxoplasma infection in men than women had a higher percentage in psychotic population and this difference was statistically significant, while in the control group were infected men and women equally.

Based on the results of this study *Toxoplasma gondii* infection in patients with schizophrenia and *Toxoplasma gondii* infection in patients with bipolar psychosis was not statistically significant and requires further investigation.

Limitations of this study were the low schizophrenia and bipolar psychosis patient at time of research and impossibility of comparing the severity of symptoms and the severity of toxoplasmosis infection in them.

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PEER REVIEW

Not commissioned. Externally peer reviewed.

Table 1: Distribution age of experimental and control population

Age groups	20-29	30-39	40-49	50-59	More than 60	total
Experimental group	6	20	29	18	3	76
Control group	5	21	28	17	4	75

Table 2: Prevalence of *Toxoplasma gondii* in the experimental (psychotic) and control groups

Groups	Positive Toxoplasma	Negative Toxoplasma	P value
Experimental	42(55.26%)	34(44.7) 34%	$p<0.05$
Control	27(36%)	48(64%)	$p<0.05$

Table3: *Toxoplasma gondii* positive cases in experimental group (psychotic) and control based on gender

Groups	Male	Female	Male Toxoplasma positive	Female Toxoplasma positive	P value
Experimental	42	34	25(%)	17% (59.52)	$p<0/05$
Control	37	38	13(%)	14% (35.14)	$p>0/05$

Table 4: *Toxoplasma gondii* positive cases of the disease in patients with psychotic breakdown

P value	Positive Toxoplasma	total	patient
$p>0/05$	22% (56.41)	39	Schizophrenia
$p>0/05$	20% (54.05)	37	Bipolar psychosis