Investigation of the relationship between schizophrenia and toxoplasmosis in Van province, Turkey

Original Article

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ABSTRACT

Background: Schizophrenia is a worldwide, serious neuropsychiatric disorder of unknown cause. Previous studies showed that infectious agents may play a role in its etiology. Among them, *T. gondii* was strongly hypothesized.
Objectives: The aim of this study was to determine the IgG and IgM seroprevalence of *T. gondii* in schizophrenia patients.
Subjects and Methods: The study was conducted on 190 patients diagnosed with schizophrenia in Van province, Turkey. Also included as the control group were 100 healthy individuals. Anti-*T. gondii* IgG and IgM antibody positivity was determined by enzyme-linked immunosorbent assay (ELISA) in blood samples taken from both groups.
Results: Anti-*T. gondii* IgG antibody was detected in 120 schizophrenic patients (63.2%), and in 100 (29%) healthy controls. Anti-*T. gondii* IgM antibody seropositivity was not detected in either group.
Conclusion: In line with the data obtained in the study carried out in Van province, it was concluded that individuals infected with *T. gondii* were more likely to develop schizophrenia. Further studies are recommended to prove the relationship between *T. gondii* and schizophrenia.

Keywords: Schizophrenia, toxoplasmosis, *Toxoplasma gondii*, Van.

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INTRODUCTION

The only species of *Toxoplasma* in the Apicomplexa group that can parasitize humans, other mammals and poultry is *T. gondii*. It was first described by Charles Nicole and Lovis Monceaux at the Pasteur Institute in Tunisia in 1908 by isolation from Ctenodactylus gundi, a North African rodent. The asexual and sexual life cycle of *Toxoplasma* was first established simultaneously by two research groups in 1970[1,2].

Toxoplasmosis is a systemic infection caused by *T. gondii* affecting mammals and avian species worldwide. Cats and other Felidae species are both intermediate, and final hosts of *T. gondii*. Intermediate hosts comprise many mammals including humans, and poultry[3]. It has serious clinical complications on human health and affects approximately 30%–60% of the population in both developed and developing countries[4]. The prevalence of *T. gondii* varies according to the lifestyle, socioeconomic status, and eating habits of the population in different geographical regions of the world[5]. The primary route of transmission of the parasite is through contact with the feces of infected felines, particularly domestic cats. Additionally, *T. gondii* can be transmitted through ingestion of improperly cooked infected meat, transplacentaly from mother-to-fetus, and from soil or water contaminated with oocysts[6]. When *T. gondii* infects pregnant women, it can cause a congenital syndrome that includes deafness, retinal damage, seizures, and mental retardation. It may cause severe central nervous system symptoms in immunocompromised individuals[7].

There are 2 forms of toxoplasmosis in humans. The first is caused by actively reproducing tachyzoite forms in the early acute phase of infection. In the second chronic or latent form, bradyzoites or tissue cysts are found in the muscles and brain[8]. Due to the high neurotropic effect of *T. gondii*, the most affected tissue in the body in the chronic process is the brain[4]. Toxoplasmosis is usually asymptomatic, but in immunocompromised patients, it can lead to severe clinical complications, such as retinochoroiditis, myocarditis, and meningoencephalitis, which can lead to death[6].

ELISA is widely used in the diagnosis of toxoplasmosis, especially in the search for IgG antibodies. However, an IgG titer alone, no matter the level, can not predict whether the infection occured in the recent or distant past but may be considered as ameasure of exposure to the infection. Avidity testing

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is required to make this distinction. Although IgM antibodies are detected earlier than IgG antibodies and decrease faster they are not an absolute marker of acute infection because they could persist for years after acute infection. Therefore, persisting IgM antibodies have no clinical significance[9].

Schizophrenia, usually starts in youthful individuals as a mental disorder with symptoms. The course and end may differ between individuals, resulting in different presentations that may be positive (hallucinations, illusions, thought and movement disorders) or negative (lack of emotional response, lack of excitement, anhedonia, no social interaction, planned activities, difficulty of maintaining chores)[10]. Schizophrenia with negative, positive, and cognitive symptoms is one of the most common and well-known psychotic disorders[11], affecting 1% of the world population[12]. According to the 2016 data of the World Health Organization, schizophrenic patients of every type and in every socioeconomic class comprise more than 21 million worldwide, while in Turkey it has reached approximately 500,000[11]. Although many factors are known to play a role in its etiology, the interaction between genetic predisposition and environmental stress is important. Interestingly, numerous epidemiological studies have shown that microorganisms may have a possible role in the etiopathogenesis of schizophrenia cases. As a result of the insufficiency of genetic studies on schizophrenia, the interest of researchers has focused on infectious risk factors. In many studies, the relationship between infectious agents and schizophrenia has been examined and its place in schizophrenia etiology has been discussed[4,13-15].

The aim of this study was to determine the seroprevalence of *T. gondii* in patients with schizophrenia and reveal the importance of toxoplasmosis as a risk factor in these patients.

SUBJECTS AND METHODS

This cross-sectional study was conducted on 190 patients diagnosed with schizophrenia for the first time and followed-up at the Community Mental Health Center between 20 December 2018 and 1 October 2020 in Van province, Turkey. Also included as the control group were 100 healthy individuals without schizophrenia. *T. gondii* IgG and IgM antibodies were investigated by ELISA method for the determination of chronic or latent toxoplasmosis, and for the detection of active infection, respectively.

Serum was separated from the blood samples of the patients and stored in a deep freezer at –80°C. Anti-*T. gondii* immunoglobulins G and M antibody levels (AL) in blood samples were determined using an enzyme-linked immunosorbent assay (ELISA) (Vircell SL, Granada, Spain). The serum samples were allowed to thaw at room temperature before testing in accordance with the manufacturer's instructions. An AL <9 was evaluated as negative, those between 9 and 11 as borderline, and >11 as positive (AL = [optical density (OD)/mean OD of cut off serum] × 10).

Statistical analysis: Minitab 14 package program was used for all statistical analysis. Z test and Fisher's exact tests were used to determine statistical significance and $P<0.05$ was considered significant.

Ethical considerations: Approval of the ethics committee with decision number 11 was obtained on 21.12.2018 from the Van Yuzuncu Yıl University Non-Invasive Ethics Committee. Informed consents were obtained from patients and controls

RESULTS

In this study, *T. gondii* IgG antibody was detected in 120 (63.2%) of the 190 schizophrenia patients, comprising 75/120 males (62.5%) and 45/70 females (64.3%). In the control group, anti-*T. gondii* IgG antibody was detected in 29 of 100 healthy controls (29%), comprising 15/44 males (34.1%) and 14/56 females (25%). Anti-*T. gondii* IgM antibody seropositivity was not detected in either group. In the patient and control groups, there were no statistically significant differences between, gender, and *T. gondii* positivity. However, a statistically significant relationship was found between schizophrenia and *Toxoplasma* IgG antibody positivity ($P = 0.001$) (Table 1).

Table 1. Comparative distribution of the prevalence of anti-*T. gondii* IgG antibody by gender and group.

Groups	Gender	Positive		Statistical analysis	
		No.	%	*P* values	
Patient	Female (n: 70)	45	64.3	= 0.8*	< 0.001**
	Male (n: 120)	75	62.5		
	Total	120	63.2		
Control	Female (n: 56)	14	25.0	= 0.8*	
	Male (n: 44)	15	34.1		
	Total	29	29.0		

* Comparison between the genders, ** Comparison between the patient and control groups.

DISCUSSION

The importance of toxoplasmosis in public health has been ignored for many years since it is largely asymptomatic. *T. gondii* has been mainly investigated in pregnant women and immunosuppressed patients. In recent years, parallel to technological developments in the field of health, it has been noted that infection with *T. gondii* may have different results. It is also clear that this parasite, which resides in brain tissue, has been associated with many outcomes that can change the behavior of humans and some animals[9]. The investigation of the potential effects of the infection on human behavior was based on behavioral manipulative studies of *T. gondii* among infected mice and cats. In these studies, the parasite induced behavioral changes in the host. It was observed that *Toxoplasma* impaired learning and memory in mice and caused changes in the behavior of both mice and rats. Due to these behavioral changes, it was noted that the rats became easy prey for hunting cats and thus, the parasite could continue to complete its life cycle[4].

Researchers found that mice infected with *T. gondii* had decreased instinctive fear of cat urine and impaired memory functions[16]. These studies with rodents led to the idea that the neurocognitive changes caused by the parasite may not be specific to mice alone, and that *T. gondii* may cause potential behavioral and/or neuropsychiatric disorders in humans. The relationship between *T. gondii* and behavioral states, such as psychiatric disorder, impulsivness, and impaired neurocognitive processes, has been investigated in humans, particularly in schizophrenics[17].

Some cases of acute toxoplasmosis in adults were associated with psychiatric symptoms such as hallucinations and delusions[18,19]. Two separate studies, considered that individuals who somehow had close relationships with cats during childhood, constituted a risk factor for schizophrenia and bipolar disorder diseases[20,21]. Although these findings may not be related directly to toxoplasmosis, they may be important indications that infectious agents play a role in the etiology of these diseases.

The following information was obtained from investigations of the relationship between schizophrenia and toxoplasmosis in different countries. A study conducted by Esquivel *et al*.[22] in Mexico, reported 20% seroprevalence of *T. gondii* in schizophrenia patients, while it was 5.3% in the healthy individuals. Alipour *et al*.[23], estimated *T. gondii* seroprevalence in Iran as 67.7% in the schizophrenia patients, and 37.1% in the healthy individuals. Emelia *et al*.[24] reported in Malaysia, a seroprevalence of *T. gondii* in 61.1% schizophrenia patients, and 40.8% in the healthy individuals, and the seropositivity rate of anti-*T. gondii* IgG antibody in the schizophrenia patients was significantly related. In a study conducted by Khademvatan *et al*.[25] in Iran, the seroprevalence of *T. gondii* was reported to be higher in the schizophrenic women when compared to the healthy women and men. In their study conducted in the Netherlands, Ladee *et al*.[26] drew attention to the presence of uncommon schizophreniform features in those with chronic toxoplasmosis, acquired in childhood or early adulthood. The researchers noted that in some instances, a neurasthenic prodromal phase was followed by suspicious paranoia or paranoid delusions.

From Istanbul in Turkey, Yüksel *et al*.[27] recorded a seroprevalence of *T. gondii* of 60.7% in the schizophrenia patients, and 45.3% in healthy blood donors; while in Elazığ, Çetinkaya *et al*.[8] reported that the seroprevalence of *T. gondii* was 66% in the schizophrenia patients, and 22% in the healthy individuals. Cevizci *et al*.[28] in a similar study, reported that the seroprevalence of *T. gondii* was 33.3% in the schizophrenic patients, and 21.7% in the healthy individuals. In another study by Tamer *et al*.[29], the seroprevalence of *T. gondii* was reported to be 40% in schizophrenia patients, as compared to 13.5% in the healthy individuals.

Tanyuksel *et al*.[30] studied first-episode schizophrenia patients, and reported anti-*T. gondii* IgG positivity of 43.8% in the patients, while it was 32.5% in the healthy individuals. Also, Dogruman *et al*.[31] reported a prevalence rate of 47.7% in the schizophrenia patients, and 21.6% in the group of healthy individuals. A study conducted in the USA[32] examining 257 individuals with *T. gondii* antibodies, revealed 99 (38.5%) attempted suicides with high antibodies titers, and 119 (46.3%) had recurrent mood disorders. To investigate the relationship between toxoplasmosis and suicide attempts in Turkey, a conducted study, reported *T. gondii* positivity of 41% in the individuals who attempted suicide, versus 28% in the controls. This significant recorded difference showed that there may be a causal relationship between *T. gondii* positivity and the etiology of suicide attempts[33]. A meta-analysis of 42 studies conducted by Torrey *et al*.[34] covering the period from 1953-2007 revealed that those diagnosed with schizophrenia were nearly 3 times as likely to carry *T. gondii*. Additionally in a study conducted by Mortensen *et al*.[35] in Denmark, in which they matched the sera collected from 71 individuals with schizophrenia before the age of 18 with appropriate controls, *T. gondii* IgG antibodies were significantly higher than in the controls.

Our study is the first to investigate the relationship between schizophrenia and toxoplasmosis in the Van province. We found that 63.2% of 190 schizophrenia patients had anti-*T. gondii* IgG antibodies indicating previous exposure to infection. When the patients diagnosed with schizophrenia were compared with the control group, toxoplasmosis was observed at a higher rate and this difference was found to be statistically significant (P <0.005).

Conclusion: The data obtained in the current study, confirms that individual infection with *T. gondii* would likely lead to development of schizophrenia, and that toxoplasmosis was a causal contributor to schizophrenia. In addition, it was concluded that apparently healthy individuals with *T. gondii* positivity should be evaluated in terms of schizophrenia for early diagnosis and should be included in the possible risk group for schizophrenia. In order to reveal the relationship between schizophrenia and toxoplasmosis more precisely, it is necessary to conduct comprehensive studies on the interactions of the parasite with the human brain. It is believed that determining the role of *T. gondii* in schizophrenia will pave the way for new treatments, prevention, and control methods.

Authors` contributions: Ekici A, Yılmaz H and Ünlü AH conceived the study, and wrote the manuscript. Timuçin DK and Gürbüz E shared in the study design. Aydemir S performed the experiments and analyzed the data. All authors revised the manuscript.

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