

Research Article

The Role of Latent Toxoplasmosis in Alzheimer's Disease

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Abstract

Objectives: This study aimed to investigate whether there was any role of latent toxoplasmosis in Alzheimer's disease (AD).

Methods: Forty-four patients with the probable AD and 30 healthy individuals were included in this prospective study. The patient and healthy groups were matched by sex, age, dietary habits and socioeconomic status. *T. gondii* IgG antibody in all individuals was studied by enzyme-linked immune sorbent assay method.

Results: The present study consisted of 44 patients with the probable AD with 25 male and 19 female, and 30 healthy individuals with 19 male and 11 female. The mean age of the patients was 78.18 ± 8.95 years, and the control group was 74.33 ± 7.89 years. It was not found statistically significant difference in age and gender between patients and healthy individuals ($p=0.06$ and $p=0.58$, respectively). The percentages of *T. gondii* IgG antibody positivity were 71% for the patients with probable AD and 67% for the healthy individuals. The difference in *T. gondii* IgG antibody positivity between the Alzheimer and the healthy control group was not statistically significant ($p=0.73$).

Conclusion: These findings showed that there was no association between toxoplasmosis and AD. Thus, *T. gondii* infection could not be considered having any role in AD.

Keywords: Alzheimer's disease, toxoplasma gondii, toxoplasmosis

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Globally, the elderly population in the world is increasing day by day, and the number of older persons aged over 60 years is expected to more than 2 billion in 2050.^[1] Dementia appearing commonly in the elderly population and affecting their quality of life will become even more important. Therefore, Alzheimer's disease (AD) being the most common cause of dementia among older people will be threat awaiting the humanity in the future. AD being an irreversible, progressive brain disease is characterized by

the loss of cognitive functioning, behavioral abilities and the impairment of the person's daily life and activities.^[2] Although scientists have investigated what causes Alzheimer's disease for years, its etiology is still unclear. Until now, the relationship between various infectious species and AD have been investigated in many studies.^[3]

Toxoplasma gondii is a neurotropic protozoan and it remains as dormant in the form of tissue cysts in preferably brain and muscle.^[4,5] In the neuropathologic studies, it has

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been emerged various theoretical models explaining the pathogenic mechanism of *Toxoplasma* infection in the brain. These theories were that *T. gondii* could affect the neurons, glial cells, astrocytes, could lead the abnormal synthesis of the neurotransmitter, could cause neuroinflammation, and could alter host behavior.^[5,6]

It has been known that cerebral toxoplasmosis could lead to dementia in AIDS and immunocompromised patients.^[7] It was reported that two forms of *T. gondii*, bradyzoites and sporozoites, accumulate large amounts of crystalline storage polysaccharide granules analogou to amylopectin in the cytoplasm. So, this parasite may be partly responsible for producing of β -amyloid senile plaques.^[8] Based on these reports, this current study aimed to investigate whether any relation between *T. gondii* and AD.

Methods

Study Population

This prospective case-control study included 44 patients with the probable AD admitted to Mental Health Hospital in Elazig, Turkey between September 2013-December 2014. The clinical diagnosis was established according to the National Institute of Neurological and Communicative Disorder and Stroke and the Alzheimer's Disease and Related Disorders Association criteria. The Mini-Mental State Examination test was used to evaluate general cognitive functions. The patients who have histories of meningitis, encephalitis, head trauma, brain surgery, immunodeficiency disease, substance abuse, alcoholism and mental retardation were excluded from the study. The healthy group consisted of 30 healthy individuals. All individuals had no the history of psychiatric disease. The patient and healthy groups were matched by sex, age, dietary habits (drinking or eating uncooked/undercooked eggs, meat, or milk) and socioeconomic status. This study was evaluated and approved by the Firat University Ethical Committee (Reference number:24/03/05.09.2013).

Serological Analysis

The sera samples taken from all individuals were stored at -20°C for serological examination. The detection of *T. gondii* IgG was performed by the commercial enzyme-linked immunosorbent assay (ELISA) kit (Vircell, Granada, Spain) on the Triturus[®] system (Grifols, Parets del Valles, Spain).

Statistical Analysis

SPSS 21 (SPSS Inc, Chicago, IL, USA) was used for statistical analyses. The normality of distributions of variables was examined by the histograms and Kolmogorov-Smirnov test. The independent Student's t-test was used for comparisons

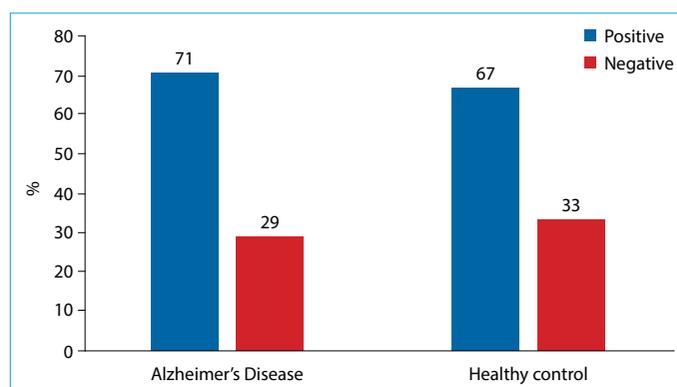


Figure 1. *T. gondii* IgG antibodies in the patients with the probable Alzheimer's Disease and healthy control.

of the variables in different groups. The Chi-square test was used to compare the nominal values between the groups. $p < 0.05$ was considered as a significant result.

Results

The present study consisted of 44 patients with the probable AD with 25 male and 19 female, and 30 healthy individuals with 19 male and 11 female. The mean age of the patients was 78.18 ± 8.95 years, and the control group was 74.33 ± 7.89 years. It was not found statistically significant difference in age and gender between patients and healthy individuals ($p = 0.06$ and $p = 0.58$, respectively).

T. gondii IgG in 31 of 44 patients with the probable AD was positive and the seropositivity rate in the patients with the probable AD was 71%. *T. gondii* IgG in 20 of 30 healthy individuals was positive and the seropositivity rate in the healthy control group was found 67% (Fig. 1). It was statistically no difference in *T. gondii* IgG antibody positivity between the AD and healthy control group ($p = 0.73$).

Discussion

T. gondii, an intracellular protozoan parasite, infects humans through the ingestion of oocysts containing sporozoites and tissue cysts containing bradyzoites or congenital infection with rapidly replicating tachyzoites.^[5] After ingesting oocysts and cysts, released sporozoites and bradyzoites attack intestinal cells and convert to tachyzoites.^[9] The tachyzoites, actively proliferating, are generally seen in several tissues in the acute phases of the infection. After the tachyzoites disappear within weeks or months, remaining bradyzoites within tissue cysts appear in several tissues, preferably in the host muscle and brain.^[10] The tissue cysts maintain their presence in various tissues throughout the life of the host. If the immunosuppression in the host develops, reactivation of the infection may occur.^[11] Upon entry to the central nervous system, tachyzoites infect astrocytes, neurons, and mi-

croglia cells, possibly with different affinities. Once a chronic infection develops, the parasite is predominantly found in the bradyzoite form within the brain. Microscopic studies have showed that cysts were located throughout the brain, especially concentrated in the cerebral cortex, basal ganglia, hippocampus and amygdala.^[12] Due to *T. gondii* is a protozoan characterized by neurotropism and associated with congenital brain dysfunction, the studies investigating a possible association between *T. gondii* and behavioral changes or neuropsychiatric diseases arouse interest. The role of *T. gondii* as an etiological agent of Parkinson's disease and other neurodegenerative disorders has been discussed in various studies, while exposure to *T. gondii* has been claimed as a risk factor for the development of schizophrenia.^[6,13] Recently, new hypotheses reflecting the association of *T. gondii* and Alzheimer's disease have emerged.

In a study conducted on 34 individuals with AD and 37 healthy volunteers in Turkey, Toxoplasma IgG in 44.1% of patients with AD and 24.3% of healthy individuals were positive. It was reported that the rate of *T. gondii* IgG positivity in the patients with AD was statistically greater than the healthy group. In the study, it was suggested that *T. gondii* infection may be a part of pathogenetic mechanisms responsible for AD.^[14] In contrast, in an animal study was reported that the immunosuppression induced by *T. gondii* infection showed beneficial effects on the pathogenesis and progression of AD in mice.^[15] A study conducted on 75 patients with AD and 75 healthy volunteers, it was found that 61.3% of patients with AD and 62.6% of healthy individuals had positive for Toxoplasma IgG. The study found no difference in seropositivity between patients and controls.^[16] In another study conducted with the aim of investigating Toxoplasma IgG antibody titers in 105 patients with AD and 114 healthy individuals, it was no relation between latent toxoplasmosis and AD.^[17] This present study showed the rates of *T. gondii* IgG positivity were 71% in the patients with the probable AD and 67% in the healthy controls. As similar with the last studies, this study also found no relation between latent toxoplasmosis and AD.

Recently, it has been claimed that the genotype of the parasite was a risk factor for psychosis. The researchers found that the offspring of mothers with type I infection compared with the unaffected control mothers had a significantly increased risk for the development of psychosis.^[18] Strains of *T. gondii* have three major genotypes, which are types I, II, and III. Type I strain is predominantly isolated from outbreaks of acute toxoplasmosis, which could cause severe ocular disease. Type II strain is frequently isolated from patients with acquired immune deficiency syndrome, congenital infections and immunocompromised individuals with toxoplasma encephalitis. As a result, the parasite

genotype may be the association with different clinical outcomes. Additionally, in animal models have been shown that the parasite genotype has effects over the immune responses of infected hosts and cells.^[19] Based on these reports, a combination of *T. gondii* infection with genetic background or some other risk factors (e.g., aging, or cerebrovascular changes) may contribute to pathophysiology and pathogenesis of the neurodegenerative diseases.

There were some limitations in the study: First, the sample size was small. Second, there was not an information about the time first exposed to toxoplasmosis. Lastly, it could not be analyzed the genotypes of the strains of *T. gondii*.

Conclusion

T. gondii antibody seroprevalence was found similar in the patient and healthy control groups. This study showed that there was not the association between toxoplasmosis and AD. Thus *T. gondii* infection could not be considered as a risk factor for the development of AD.

Disclosures

Ethics Committee Approval: This study was evaluated and approved by the Firat University Ethical Committee (Reference number: 24/03/05.09.2013).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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References

1. World population ageing 2013. United Nations, Department of Economic and Social Affairs, Population Division 2013.
2. Mayeux R, Stern Y. Epidemiology of Alzheimer disease. Cold Spring Harbor perspectives in medicine 2012;2.
3. Honjo K, van Reekum R, Verhoeff NP. Alzheimer's disease and infection: do infectious agents contribute to progression of Alzheimer's disease? Alzheimer's & dementia: the journal of the Alzheimer's Association 2009;5:348–60.
4. Park MH, Kwon YJ, Jeong HY, Lee HY, Hwangbo Y, Yoon HJ, et al. Association between Intracellular Infectious Agents and Schizophrenia. Clinical psychopharmacology and neuroscience: the official scientific journal of the Korean College of Neuropsychopharmacology 2012;10:117–23.
5. Karabulut N. Toxoplasma and Schizophrenia. Türk Mikrobiyol Cem Derg 2013;43:39–44.
6. Fabiani S, Pinto B, Bruschi F. Toxoplasmosis and neuropsychiatric diseases: can serological studies establish a clear relationship? Neurological sciences: official journal of the Italian

- Neurological Society and of the Italian Society of Clinical Neurophysiology 2013;34:417–25.
7. Freidel S, Martin-Solch C, Schreiter-Gasser U. [Alzheimer's dementia or cerebral toxoplasmosis? Case study of dementia following toxoplasmosis infection]. *Der Nervenarzt* 2002;73:874–8.
 8. Prandota J. Metabolic, immune, epigenetic, endocrine and phenotypic abnormalities found in individuals with autism spectrum disorders, Down syndrome and Alzheimer disease may be caused by congenital and/or acquired chronic cerebral toxoplasmosis. *Research in Autism Spectrum Disorders*. 2011;5:14–59.
 9. Karabulut N, Bilgic S, Gurok MG, Karaboga F. Is there any role of latent toxoplasmosis in schizophrenia disease? *Journal of the Chinese Medical Association: JCMA* 2015;78:533–7.
 10. Cetinkaya Z, Yazar S, Gecici O, Namli MN. Anti-Toxoplasma gondii antibodies in patients with schizophrenia—preliminary findings in a Turkish sample. *Schizophrenia bulletin* 2007;33:789–91.
 11. Pedersen MG, Stevens H, Pedersen CB, Norgaard-Pedersen B, Mortensen PB. Toxoplasma infection and later development of schizophrenia in mothers. *The American journal of psychiatry* 2011;168:814–21.
 12. Kamerkar S, Davis PH. Toxoplasma on the brain: understanding host-pathogen interactions in chronic CNS infection. *Journal of parasitology research* 2012;2012:589295.
 13. Torrey EF, Bartko JJ, Yolken RH. Toxoplasma gondii and other risk factors for schizophrenia: an update. *Schizophrenia bulletin* 2012;38:642–7.
 14. Kusbeci OY, Miman O, Yaman M, Aktepe OC, Yazar S. Could Toxoplasma gondii have any role in Alzheimer disease? *Alzheimer disease and associated disorders* 2011;25:1–3.
 15. Jung BK, Pyo KH, Shin KY, Hwang YS, Lim H, Lee SJ, et al. Toxoplasma gondii infection in the brain inhibits neuronal degeneration and learning and memory impairments in a murine model of Alzheimer's disease. *PloS one* 2012;7:e33312.
 16. Mahami-Oskouei M, Hamidi F, Talebi M, Farhoudi M, Taheraghdam AA, Kazemi T, et al. Toxoplasmosis and Alzheimer: can Toxoplasma gondii really be introduced as a risk factor in etiology of Alzheimer? *Parasitol Res* 2016;115:3169–74.
 17. Perry CE, Gale SD, Erickson L, Wilson E, Nielsen B, Kauwe J, et al. Seroprevalence and Serointensity of Latent Toxoplasma gondii in a Sample of Elderly Adults With and Without Alzheimer Disease. *Alzheimer disease and associated disorders* 2016;30:123–6.
 18. Xiao J, Buka SL, Cannon TD, Suzuki Y, Viscidi RP, Torrey EF, et al. Serological pattern consistent with infection with type I Toxoplasma gondii in mothers and risk of psychosis among adult offspring. *Microbes and Infection* 2009;11:1011–8.
 19. Carruthers VB, Suzuki Y. Effects of Toxoplasma gondii infection on the brain. *Schizophrenia bulletin* 2007;33:745–51.