Original Article

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Relationship of Toxoplasma Gondii Exposure with Multiple Sclerosis

Serdar Oruç[1], Fatima Karakaya[1], Hayri Demirbas[1], İnci Çeçen[1], Özge Yılmaz Küsbeci[1], Özlem Miman[2], Mehmet Yaman[1]

ABSTRACT

Objective: *Toxoplasma gondii infection is a very common parasitic disease in human. In Turkey, the rate of seropositivity was reported as 23.1% to 36%. Because of the high affinity of parasite into Central Nervous System (CNS), chronic toxoplasma infection has been found correlated with many neuropsychiatric disorders, including altered mental status, obsessive-compulsive disorder, cognitive impairment, epilepsy, headache and schizophrenia. In this study, we aimed to investigate whether T. gondii has any role in Multiple Sclerosis (MS) by measuring anti-T. gondii IgG antibodies.* ***Methods:*** *Fifty-two MS patients followed up and 45 controls with similar age and socioeconomic status were included in the study. Anti-T.gondii IgL antibodies of the patients and controls were studied in blood with micro-enzyme-linked immunosorbent assay (ELISA) technique.* ***Results:*** *Of 52 MS patients included in the study, 37 had RRMS, 10 PPMS and 5 SPMS. Mean age of onset of the disease was 31.7±10.4 (min; 14 and max; 53). Twenty three of 52 (44.2%) cases with MS and 11 of 45 (24.4%) healthy controls were positive for anti-T.gondii IgG antibodies. There was a statistically significant difference between the rates of positivity between the MS patient group and control group (p=0.042).* ***Conclusion:*** *This study shows a relation of chronic T. Gondii infection with MS. According to this study, experienced T.gondii infection may be one of the several environmental risk factors for MS.*

Key words: *Multiple Sclerosis, Toxoplasma gondii, chronic infection, autoimmunity.*

Multipl Sklerozlu Hastalarda Toxoplazmi Gondi Maruziyeti İlişkisi

ÖZET

Amaç: *Toxoplasma gondii enfeksiyonu insanda görülen çok yaygın bir paraziter hastalıktır. Türkiye'de seropozitiflik oranı% 23.1% 36 olarak bildirilmiştir. Kronik toxoplazma enfeksiyonu, parazitin Santral Sinir Sistemine'ne (SSS) yüksek afinitesi olduğu için; obsesif-kompulsif bozukluk, bilişsel bozukluk, epilepsi, baş ağrısı ve şizofreni dahil olmak üzere, birçok nöropsikiyatrik hastalıklar ile ilişkili bulunmuştur. Bu çalışmanın amacı, T. gondiyle ilişkili anti-T gondii IgG antikorlarını ölçerek Multipl Sklerozda (MS) her hangi bir rolü olup olmadığını araştırmaktır.* ***Yöntem:*** *Çalışmaya 52 MS hastası ve benzer yaş ve sosyoekonomik statüye sahip 45 kontrol hastası çalışmaya dahil edildi. Hasta ve kontrol grubu kanlarında (ELISA) tekniğiyle immunosorbent assay mikro-enzim-bağlantılı anti-T.gondii IgG antikorları incelendi. Çalışmaya dahil edilen 52 MS hastasının 37'si RRMS, 10'u PPMS ve 5'i SPMS idi.* ***Bulgular:*** *Hastalığın başlangıç yaş ortalaması 31.7±10.4 (min, 14 ve maksimum; 53) idi. 52 MS hastasının 23'ünde (% 44.2) ve 45 sağlıklı kontrol grubunun 11'inde (%24.4) anti-T.gondii IgG pozitifliği vardı. MS hasta grubu ve kontrol grubu (p= 0.042) arasındaki pozitiflik oranları karşılaştırıldığında istatistiksel olarak anlamlı fark vardı.* ***Sonuç:*** *Bu çalışma, MS ile kronik T. gondii enfeksiyonu arasındaki ilişkiyi göstermektedir. Bu çalışmaya göre T.gondii enfeksiyonu, MS için çeşitli çevresel risk faktörlerinden biri olabilir.*

Anahtar kelimeler: *Multipl skleroz, Toxoplasma Gondii, kronik enfeksiyon, otoimmünite*

Afyon Kocatepe University, Faculty of Medicine, Department of Neurology[1], Afyonkarahisar, Afyon Kocatepe University, Faculty of Medicine, Department of Microbiolgy[2]Afyonkarahisar, TURKEY

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Correspondence: *Mehmet Yaman*
Afyon Kocatepe University, Faculty of Medicine, Department of Neurology, 03200 Afyonkarahisar, TURKEY

E-mail: yaman.md@gmail.com

INTRODUCTION

Toxoplasma gondii infection is widespread in humans, it is estimated that up to 500 million people worldwide are infected with this ubiquitous parasite (1). In the United States and United Kingdom, 16% to 40% of the population may be infected, whereas in Central and South America and continental Europe, estimates of infection range from 50% to 80% (2). In Turkey, the rate of seropositivity was reported as 23.1% to 36% (3, 4).

The organism is an obligate intracellular parasite and is found in 2 forms in humans. The actively proliferating trophozoites or tachyzoites are usually seen in the early, more acute phases of the infection. The resting forms or tissue cysts are primarily found in the muscle and brain, probably as a result of the host immune response (5). Tissue cysts containing bradyzoites may spontaneously rupture, releasing parasites that cause antibody titers to rise. A positive antibody titer reflects the persistence of parasites in the central nervous system (CNS) (6, 7).

Although up to 500 million people worldwide are infected with the protozoan parasite Toxoplasma gondii, a pattern of an asymptomatic chronic infection is prevalent in most immunocompetent individuals who harbor parasite cysts, especially in the CNS (8). There are a variety of reports that suggest that chronic toxoplasma infection may alter human behaviors, may cause obsessive-compulsive disorder, cognitive dysfunctions, cryptogenic epilepsy, headaches, and may lead to the onset of schizophrenia (7, 9-13). These effects of the parasite may be resulted either from the direct invasion of the parasite or immunologic damage caused by the parasite or both. IFN-γ, the main cytokine responsible for immunologic defense against T. gondii, is essential in all infected tissues, including the CNS. However, IFN-γ, activated microglia may cause tissue injury through the production of toxic metabolites, such as nitric oxide (NO), a potent inducer of CNS pathologies related to inflammatory neuronal disturbances (14). There has been long-standing interest in investigating possible associations between exposure to T. gondii and the development of severe CNS diseases.

Multiple Sclerosis (MS) is the most common inflammatory disorder of the CNS and a leading cause of disability in young adults. Strong evidence suggests that MS is an autoimmune disease directed against CNS myelin or oligodentrocytes. Pathologically, it is characterized by perivascular infiltrates of mononuclear inflammatory cells, demyelination, axonal loss and gliosis mainly in the white matter, with the formation of multiple plaques in the brain and spinal cord (15).

The cause of MS is still unknown. Genetic, environmental and immunological factors have been implicated in the etiology of this complex, multifactorial and heterogenous disease. There is wide acceptance that interactions between genes and environmental factors lead to tissue injury by autoimmune mechanism (16, 17). The main genetic susceptibility locus for MS was thought to reside specifically with the Human Leukocyte Antigen (HLA)- DRB1*1501 allele within the major histocompatibility complex (MHC) class II region. Environmental factors include geographical gradients, thus vitamin D and sunlight, smoking and some of the infective agents, especially Ebstein-Barr virus (EBV) (15, 17).

There is strong evidence on the correlation between EBV, Human endogenous retroviruses (HERV) and herpesviruses-6 (HHV-6) exposure and MS occurrence (18-20). Recently, several studies have been published, claiming an association between infective agents such as Acinetobacter species, Pseudomonas aeruginosa, Chlamiydia pneumoniae and MS (21, 22). According to the hygiene hypothesis which is now fully recognized, frequency of infective diseases in the childhood period is being decreased in developed countries because of the high standards of hygiene and widespread use of antibiotics and vaccines. As a result of this the immune system fails to develop properly, and when it is challenged later in life it is prone to the development of autoimmunity (23). Whereas infective diseases in the childhood period are more common in developed countries such as the countries in Africa and Asia, although MS is more infrequent in these regions. At the first glance, a contradiction may be seen between the above-mentioned thesis of many infective agents cause a risk for MS and hygiene hypothesis. However, period of life in which the infective agent has an impact is important (17).

On one hand, relationship between MS and infectious agents remain to be in question, while on the other hand the relationship between Toxoplasma gondii infection and CNS is strengthened. However, there are only few studies investigating the relationship between Toxoplasma gondii infection and MS. In this study, we aimed to investigate whether T. gondii has any role in MS by measuring anti-T. gondii IgG antibodies.

MATERIAL AND METHODS

Fifty-two patients followed-up in Afyon Kocatepe University, Medical Faculty, Department of Neurology, clinic of demyelinating diseases and definitively diagnosed with MS according to McDonald's criteria were included in this study (24). Forty-five healthy volunteers were set up and eveluated as the control group in the same socioeconomic status with the patient group. The study analyzed biomarkers measured on blood samples collected from either study or the members of the control group for another reason, and having no additive risk for the patient. Moreover, only a retrospective collection of follow-up information was done. Therefore, no explicit consent from the ethics committee was required. Clinical evaluation ascertained both personal and familial history and physical and neurological conditions of the participants. Inclusion criteria were as follows: Patients whom serum anti-T. gondii IgG antibodies were previously examined for screening and definitely diagnosed with MS and randomly selected healthy controls with similar age and socioeconomic status.

Exlusion criteria were as follows: Patients who had a lifetime history of neurological illness, Parkinson disease, Parkinson-plus syndrome, Alzheimer disease, head injury, substance abuse, schizophrenia, depression, epilepsia, migraine, brain surgery, earlier encephalitis/meningitis, clinical evidence of immunodeficiency, or other immunologic abnormalities (diabetes mellitus, leukemia, lymphoma, or other malignancies), and history of alcoholism.

Serological Analysis

The sera separated from whole blood shortly after collection were stored at -20˚C until analysis was completed. We used the micro-enzyme-linked immunosorbent assay (ELISA) technique for anti-T. gondii IgG antibody. The ELISA has become increasingly popular because of its high sensitivity and easy interpretation. The ELISA kit was provided by Euroimmun, the commercial manufacturer. The technique was carried out following the manufacturer's instructions. The immune status ratio (ISR) value of each specimen was calculated by dividing the sample absorbance by the calibrator value based on the manufacturer's guide. ISR ≤0.90 was interpreted as negative, ISR ≥1.10 as positive, and ISR of 0.91 to 1.09 as equivocal.

Statistical Analysis

All statistical analyses were done with the SPSS software (Statistical Package for the Social Sciences, version 18.0; SSPS Inc, Chicago, Illinois). All results are presented as mean±S.D. The rates of anti-T. gondii IgG antibody positivity and gender of the MS patients and the control group were compared by Chi-square test. Age means for each group were compared by 2 independent sample t tests. Results have been expressed as number of observations (n) and mean standard deviation (SD). A p value of less than 0.05 was considered as statistically significant.

RESULTS

Of 52 MS patients included in the study, 37 had relapsing-remitting MS, 10 primary progressive MS and 5 secondary progressive MS. Mean age of onset of the disease was 31.7±10.4 (min; 14 and max; 53). There was no statistically significant differences among the patients and controls with respect to age (38.6±12.4, 36.0±11.9 yo. respectively, p=0.315). There was also no statistically significant differences among the patients and controls with respect to sex (37 women and 15 men fort he patients, and 35 women and 10 for the controls, p= 0.457) and socioeconomic status. Twenty three of 52 (44.2%) cases with MS and 11 of 45 (24.4%) healthy controls were positive for anti-T.gondii IgG antibodies. There was a statistically significant difference between the rates of positivity between the MS patient group and control group (p=0.042)(Table 1).

DISCUSSION

There are several studies in the literature documenting the relationship between anti-toxoplasma antibody positivity and many neuropsychiatric disorders such as decrease of psychomotor skills, schizophrenia, cryptogenic epilepsy, headache and Alzheimer disease (7, 9-13). On the other hand, MS is relatively infrequent in the countries in which parasitic infection like Toxoplasma gondii is common (2). In our study, we found that the rate of seropositivity for anti-T.gondii IgG antibodies was greater in patients with MS than in control healthy subjects. This indicates the presence of chronic Toxoplasma infection in patients with MS.

In 1963, Poskanzer et al, noting the similarity between the epidemiology of MS with that of poliomyelitis, proposed that MS, like poliomyelitis, could be the rare neurological manifestation of a common enteric infection (25). This hypothesis was supported by early findings of

Table 1: Characteristics of the patient and control groups with seropositivity rates of anti-T.gondii IgG antibodies.

		MS (n:52)		Controls (n:45)		p value
		n	%	n	%	
Age		38.6±12.4		36.0±11.9		0.315*
Age of onset		31.7±10.4		-		
Gender	Female	37	71.2	35	77.8	0.457**
	Male	15	28.8	10	22.2	
Anti-T.gondii IgG antibodies	Positive	23	44.2	11	24.4	0.042**
	Negative	29	55.8	34	75.6	

*MS: Multiple Sclerosis. *T test, **Chi-square (x2) test*

creasing MS incidencewith increasing sanitation in Israil, and with increasing socioeconomic status in the Unitec States and U.K. (26-28). According to the hygiene hypotesis exposure to several infectious agents early in life is protective against MS, as in the poliomyelitis model, but there is not a specific agent responsible; rather, MS is an autoimmune reaction that is triggered in susceptible individuals in reponse to infection by multiple microorganisms, with risk increasing with age at infection (24, 29).

On the other hand, many infection agent exposures experienced in the childhood period has been shown to create a risk for MS. The most important among them is EBV theory. There is strong evidence on the risk for MS increases in the persons exposed to EBV in the childhood period. Numerous studies report that the risk for MS is extremely low among the individuals with EBV seronegative (22). Similarly, the risk of MS has found higher in the persons with EBV seropositive, but had not history of mononucleosis and much higher in those had both EBV seropositive and history of mononucleosis (20, 25). Similarly, a correlation has been demonstrated between MS and both HERV and HHV-6 viruses. HERV has been isolated from CSF, serum and plasma of the patients with MS (18, 30). In this respect it is of interest that the presence of HERV sequences, and in particular those of the γ-retroviruses HERV-W/MSRV and of HERV-H/F, have ben found in association with MS (31, 32). In addition increased levels of antibody reactivity to specific γ-retroviral HERV Gag and Env epitopes have been found in serum and CSF from MS patients (19). Association of infections with HHV-6 to MS are weaker but serological parameters differ qualitatively from controls and it is possible that active, possibly chronically active, infections with these pathogens synergize with EBV to produce a dysregulated immune response (31, 33). Recently, Hughes et al, showed that antibodies to bacterial antigens from Acinetobacter species and Pseudomonas aeruginosa were significantly elevated in MS patients (21). Chlamydia pneumoniae has also attracted attention as relevant for MS. An initial study reporting that 97% of MS patients have positive PCR for Chlamydia pneumoniae in CSF compered with 18% of controls could not be reproduced (22).

The peripheral activation and subsequent migration in the CNS of autoreactive Th1 cells are said to be the initial events in MS, and these cells are probably important players in the long-term evolution of the disease at least in many cases (34). Nonetheless, the damage of the target tissue (central myelin and axons) is mediated by other components of the immune system and, particularly, by factors produced by the innate immunity (35). In fact, despite a pathogenic role of T cell-mediated adaptive immunity is advocated, the presence of activated infiltrated macrophages and resident microglial cells represent a common pathogenic denominator in most MS lesions and these cells strongly contribute to MS brain damage through a group of neurotoxic factors (34-38).

In our study, we found the rate of anti-T.gondii IgG antibodies' seropositivity high in the serums of MS patients than in controls. Target organ is brain in the persons with suppressed immune system, and it causes to encephalitis, which threatens the life. In healthy individuals, systemic infection by proliferating stage of the parasite, the tachyzoite, is efficiently controlled by the cellular immune response; however, the pathogen persists in its slowly replicating stage, the bradyzoite, in tissue cysts mainly within the brain. However, the role that brain

cells play during the onset of infection, and whether local inflammation depends on the parasite stage involved, are yet unclear (39). Neuropathologically, studies of T. gondii have shown that glial cells, especially astrocytes, are selectively affected in vitro (40). T. gondii invades the brain parenchyma and is frequently present in the subcortical white matter and basal ganglia (41). In vitro studies using mouse brain cells have shown that tachyzoites invade microglia, astrocytes, and neurons (42, 43). In humans, proliferating tachyzoites have been detected in glial cells in a patient who had developed toxoplasmic encephalitis. Tachyzoites induce more pronounced inflammatory cytokine responses in host cells (44). Among the cytokines produced in response to T. gondii infection, IFN-γ is the most important, because proliferation of tachyzoites is suppressed by IFN-γ, particularly through cell-mediated immune response (45, 46). The main source of, IFN-γ is T cells, which infiltrate into the brain after infection. , IFN-γ production by this lymphocyte population is essential for preventing the reactivation of infection. Microglia and blood-derived macrophages are the major non-T-cell populations that produce this cytokine in the brain of infected mice (44, 46). In the CNS, microglia, the resident innate immune cells play major role in the inflammatory process. Although they form the first line of defense for the neural parenchyma, uncontrolled activation of microglia may directly be toxic to neurons by releasing various substances, such as inflammatory cytokines (IL-1ß TNF-α, IL-6), NO, PGE2, and superoxide (47). As a result of these studies, effects of T. gondii infection on immune mechanisms, especially on the cellular immunity cannot be deniable.

In conclusion, MS is a complex disease that involves many pathogenic mechanism, such as inflammation, demyelination, and axonal damage. Heterogeneity, including vitamin D, sunlight exposure, smoking and infection is in question in terms of environmental factors, which is one of the main two components of etiology of the disease. This study shows a relation of chronic T. Gondii infection with MS. More detailed studies with larger study populations will be comprehensive. According to this study, experienced T.gondii infection may be one of the several environmental risk factors for MS.

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