ISSN: 2588-4115; Infection Epidemiology and Microbiology. 2024;10(3):245-252 10.52547/iem.10.3.245

# Association between *Toxoplasma gondii* Infection and Multiple Sclerosis

ARTICLE INFO

***Article Type***
**Original Article**

***Authors***
Samaneh Abolbashari, *PhD*[1]
Seyyd Mohammad Sadegh Mirzaei, *MD*[2]
Mahdieh Khoshakhlagh, *MSc*[4]
Zahra Sokhtanloo, *MSc*[5]
Ehsan Aryan, *PhD*[6]
Fariba Berenji, *PhD*[7]
Mojtaba Meshkat, *PhD*[8]
Reza Boostani, *MD*[9]
Zahra Meshkat, *PhD*[1]
Amin Hooshyar Chechaklou, *MSc*[1]
Mansoureh Bakhshi, *MSc*[1]
Aida Gholoobi, *PhD*[3,10*]

[1] Antimicrobial Resistance Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[2] Student Research Committee, Mashhad University of Medical Sciences, Mashhad, Iran
[3] Metabolic Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[4] Department of Biochemistry, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[5] Department of Biochemistry, Faculty of Science, Mashhad Branch, Islamic Azad University Mashhad, Iran
[6] Department of Microbiology and Virology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[7] Department of Medical Parasitology and Mycology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[8] Department of Community Medicine, Faculty of Medicine, Mashhad Medical Sciences, Islamic Azad University, Mashhad, Iran.
[9] Department of Neurology, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran
[10] Medical Genetics Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

**** Correspondence***
Metabolic Syndrome Research Center and Medical Genetics Research Center, Mashhad University of Medical Sciences, Mashhad, Iran, and Medical Genetics Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
E-mail: gholoubiad@mums.ac.ir

**How to cite this article**
Abolbashari S., Mirzaei M.S., Khoshakhlagh M.,Sokhtanloo Z., Aryan E., Berenji F., Meshkat M., Boostani R., Meshkat Z., Chechaklou A.H., Bakhshi M., Gholoobi A. Association between *Toxoplasma gondii* Infection and Multiple Sclerosis. Infection Epidemiology and Microbiology. 2024;10(3): 245-252.

***Article History***
Received: July 06, 2023
Accepted: June 11, 2024
Published: August 20, 2024

ABSTRACT

**Background:** Multiple sclerosis (MS) is an autoimmune inflammatory disease of the central nervous system. *Toxoplasma gondii* infection is one of the risk factors of MS. Knowing the correlation between *T. gondii* infection and MS could lead to a better understanding of the disease incidence. This study aimed to assess the correlation between *T. gondii* infection and the disease incidence in infected individuals. .
**Materials & Methods:** Serum samples of 38 MS patients referring to the neurology clinic of Ghaem hospital in Mashhad in 2019 were analyzed by Pishtazteb commercial kit for anti-*T. gondii* IgG and IgM antibodies using enzyme-linked immunosorbent assay (ELISA). The obtained data were analyzed with SPSS software Version 20.
**Findings:** Among the 79 tested individuals, 22 were positive, and 57 were negative for anti-*T. gondii* IgG antibodies. Among the negative cases, 29 (50.9%) had MS, and 28 (49.1%) were controls. Among the positive cases, nine (40.9%) patients had MS, and the remaining 13 (59.1%) were controls. The frequency of IgG antibody in the case and control groups was not significantly different ($p$= .427). Anti-*T. gondii* IgM antibody was negative in all samples. There was no significant difference between the types of MS regarding the frequency of anti-*T. gondii* antibodies ($p$= .402).
**Conclusion:** No significant difference was found in the frequency of anti-*T. gondii* IgG antibodies between the two groups. However, further studies with larger sample sizes are recommended to gain a better understanding of the relationship between anti-*T. gondii* IgG antibody positivity and MS incidence.

**Keywords:** Multiple sclerosis, *Toxoplasma gondii*, Parasite, ELISA, Immunity

CITATION LINKS

[1] McCoy L, Tsunoda I, Fujinami RS. Multiple sclerosis... [2] Weiner HL. Multiple sclerosis is an inflammatory T-cell... [3] Manouchehrinia A, Tanasescu R, Tench CR, Constantinescu CS. Mortality... [4] Compston A, Coles A. Multiple... [5] Koch-Henriksen N, Sørensen PS. The changing... [6] Marrie RA. Environmental risk factors in multiple sclerosis... [7] Tahmasbi H, Manouchehri Naeini K, Masoumi-Ghajari S. Serological... [8] Mendez OA, Koshy AA. Toxoplasma gondii... [9] Hosseininejad Z, Sharif M, Sarvi S, Amouei A, Hosseini SA, Nayeri Chegeni T, et al. Toxoplasmosis... [10] Tenter AM, Heckeroth AR, Weiss LM. Toxoplasma gondii... [11] Suvisaari J, Torniainen-Holm M, Lindgren M, Härkänen T, Yolken RH. Toxoplasma gondii... [12] Alvarado-Esquivel C, et al. Toxoplasma gondii... [13] Xiao J, et al. Toxoplasma gondii... [14] Tedford E, McConkey G. Neurophysiological... [15] Parlog A, Schlüter D, Dunay IR. Toxoplasma gondii... [16] Koskderelioglu A, Afsar I, Pektas B, Gedizlioglu M. Is Toxoplasma... [17] Stascheit F, Paul F, Harms L, Rosche B. Toxoplasma gondii... [18] Gondi MS. Relationship of Toxoplasma gondii exposure... [19] Sabzevari M, Tavalla M. Seroepidemiological study... [20] Rahnama M, Asgari Q, Petramfar P, Tasa D, Hemati V, Solgi R. The role of... [21] Strachan DP. Hay fever, hygiene, and household... [22] Wendel-Haga M, Celius E. Is the hygiene... [23] Wagner A, et al. Immunoregulation... [24] Krause I, et al. Anti-infectious... [25] Pestehchian N, Etemadifarr M, Yousefi HA, Chiani M, Aslani N, Nasr Z. Frequency of... [26] Oruç S, et al. Relationship of... [27] Saberi R, et al. Is Toxoplasma gondii playing...

## Introduction

Central nervous system diseases that affect myelin could be classified into two categories: the former comprises conditions that could be acquired, while the latter pertains to myelin disorders. Multiple sclerosis (MS) is the most prevalent demyelinating disease affecting the central nervous system [1]. Among central nervous system disorders, MS is the most common permanent cause of disability in young adults (except trauma) [2], and life expectancy in patients with MS is 7 to 14 years lower than in the healthy population. In a recent meta-analysis study, the standard mortality rate (SMR) among individuals with MS was 2.8 times greater than that observed in the general population. Furthermore, this study revealed an elevated mortality risk among MS patients, particularly in cases with respiratory infections and diseases, suicide, and heart diseases [3]. Despite undergoing treatment, it's noteworthy that nearly two-thirds of individuals with MS experience mortality due to various infections and complications associated with these conditions [4]. MS is more prevalent among women compared to men. According to a comprehensive systematic review encompassing 28 epidemiological studies from 1955 to 2000, it was revealed that the estimated male-to-female ratio for MS increased from 1:1.4 to 1: 2.3 during this period [5].

Infection, particularly viral infection during childhood, is often considered as a significant risk factor for the development of MS. However, despite numerous efforts to identify the infectious agent responsible for MS through methods like virus isolation and detection of viral antigens or genomes in the brain and other tissues affected by MS, the reproducibility of these claims has not been demonstrated [6].

*Toxoplasma gondii* is an obligate intracellular parasite protozoan [7]. While cats serve as the primary hosts of *T. gondii*, this parasite could also infect a broad spectrum of intermediate hosts, encompassing warm-blooded animals such as birds, rodents, and humans. *T. gondii* could establish latent infections in various tissues, including skeletal muscle, heart muscle, and central nervous system (such as brain, spinal cord, and retina), which may persist throughout an individual's life [8] It is estimated that 1.3% of the world's population is infected with this parasite [9], and numerous studies have been conducted on this parasite due to its association with abortion and congenital diseases in its intermediate hosts [10]. *T. gondii* undergoes two distinct stages of asexual replication within its intermediate hosts. During the initial stage, tachyzoites (also known as endozoites) quickly invade various host cells. Subsequently, the latest generation of tachyzoites initiates the second stage of growth, leading to the development of tissue cysts. Within these cysts, bradyzoites (also referred to as cystozoites) undergo slow proliferation [10].

Approximately one-third of the world's population carries *T. gondii*, but in healthy individuals, the immune system effectively suppresses the activation of the parasite, preventing the disease [7]. The majority of these individuals remain unaffected with asymptomatic healthy immune systems (10). *T. gondii* spreads extensively throughout the host's body and has the potential to infect the brain and cause psychiatric disorders such as depression, mixed anxiety and depression disorder, and schizophrenia [11-13]. Also, *T. gondii* induces comprehensive alterations in host neurons and neurological signaling pathways [14]. Persistent *T. gondii* infections could lead to adjustments in neuronal connections and synaptic plasticity [15]. Koskderelioglu et al. (2017) and Stascheit et al. (2017) in their studies identified an inverse relationship between this infection

and MS [16, 17]. Conversely, other studies have identified a notable and statistically significant connection between *T. gondii* seropositivity and MS [18-20]. Therefore, infections such as *T. gondii* could have a protective effect on MS.

**Objectives:** This article aimed to evaluate the serum status of MS patients in terms of anti-*T. gondii* antibodies.

## Materials and Methods

This prospective cross-sectional study was conducted in Mashhad, Iran in 2019. During the enrollment period at Ghaem hospital's neurology clinic, all patients who were diagnosed with MS (38 cases) and gave written consent to participate in the study were included. The diagnosis of MS generally involves a comprehensive approach, incorporating clinical evaluation, medical history assessment, neurological examination (including magnetic resonance imaging (MRI)), and various diagnostic tests. The primary goal of this process is to rule out other conditions that may present similar symptoms and to confirm the presence of distinctive features indicative of MS. The diagnosis of MS relies on the McDonald criteria, which integrate clinical, imaging, and laboratory findings to improve both accuracy and efficiency. The results of the MS group were compared with those of the control group, which comprised 41 serum samples collected from patients admitted to different wards of Ghaem hospital. The control group patients showed no signs of MS and were carefully matched with MS patients in terms of gender and age.

Once collected, serum samples were properly stored at -70 °C. They were later examined for IgG and IgM antibodies against *T. gondii* using the Pishtazteb IgG enzyme-linked immunosorbent assay (ELISA) kit from Iran following the instructions provided by the manufacturer. The antibody titers were expressed in international units per milliliter (IU/mL). The cut-off value was considered to be 10 IU/mL (at 450 nm). Participants with antibody titers lower than 10 IU/mL were considered negative, and those with antibody titers greater than 10 IU/mL were considered positive for *T. gondii* infection.

Chi-square and independent T tests were used to investigate the relationship between the frequency of anti- *T. gondii* antibodies and qualitative (such as MS, occupation, and gender) and quantitative (such as patients' age) variables, respectively.

## Findings

A total of 79 patients including 38 MS patients (case group) and 41 non-MS patients (control group) in the age range of 16-52 years were studied. The mean age of the two groups was not significantly different. The frequency distribution of sex in the case and control groups is shown in Table 1, which was not significantly different. The subjects were divided into three groups in terms of occupation: employed, unemployed, and student. The frequency distribution of jobs in the two groups was not significantly different (Table 1). In MS patients, the age of the disease onset was 14 to 44 years, and its mean was 28.95 years. Among 38 patients with MS, the disease was recurrent in 30 cases and progressive in eight patients. Also, the first signs of the disease onset are shown in Table 2.

According to the results, among the 79 tested individuals, 22 were positive, and 57 were negative for anti-*T. gondii* IgG antibodies. Among the negative cases, 29 (50.9%) had MS, and 28 (49.1%) were controls. Among the positive cases, nine (40.9%) patients had MS, and the remaining 13 (59.1%) were controls (Table 3). The statistical analysis results showed that the mean age of individuals with antibodies was higher

**Table 1)** Frequency distribution of sex and occupation in the two groups of case and control

| Factor | Case Group | | Control Group | | *P*-Value* |
|---|---|---|---|---|---|
| | Numbers | Percentage (%) | Numbers | Percentage (%) | |
| Sex | | | | | |
| Male | 9 | 39.1 | 14 | 60.9 | .3 |
| Female | 29 | 51.8 | 27 | 48.2 | |
| Occupation | | | | | |
| Employed | 17 | 44.73 | 25 | 61 | |
| Unemployed | 21 | 55.26 | 14 | 34.14 | .2 |
| Student | 0 | 0 | 2 | 4.87 | |

**Table 2)** Frequency and percentage of the first signs of patients with Multiple Sclerosis

| First Sign of Disease | Frequency | Percentage (%) |
|---|---|---|
| Impaired gait | 13 | 34.21 |
| Visual problems | 5 | 13.16 |
| Upper limb paraesthesia | 4 | 10.53 |
| Impaired gait and visual problems | 10 | 26.32 |
| Impaired gait and urinary problems | 2 | 5.26 |
| Impaired gait and upper limb paraesthesia | 2 | 5.26 |
| Visual problems and upper limb paraesthesia | 2 | 5.26 |
| Total | 38 | 100.0 |

than that of those without antibodies, and this difference was statistically significant (independent t-test; $p$= .020). There was no statistically significant difference in the frequency of antibodies between the case and control groups (Chi-square test; $p$= .427). Also, the difference in antibody seropositivity rate between the two sexes was not statistically significant (Chi-square test; $p$= .152). There was also no statistically significant difference in the frequency of anti-*T. gondii* antibodies and the disease course between the two MS types (Chi-square test; $p$ = .402). The frequency of anti-*T. gondii* antibodies by MS type, sex, and MS incidence is shown in Table 3.

## Discussion

According to the current study results, there was no significant difference in age and sex between the case and control groups. Although the frequency of anti- *T. gondii* IgG antibody was higher in the control group than in the MS group, no significant difference was observed between the control and MS group. Anti-*T. gondii* IgM antibody was also negative in all samples, indicating the absence of primary acute disease in both case and control groups. There was no statistically significant difference between the types of MS in terms of the disease course and the frequency of anti-*T. gondii* antibodies.

Numerous studies have explored the influential factors contributing to the development of autoimmune diseases. Among these factors, the increasing significance of infectious agents as factors involved in preventing, predisposing,

**Table 3)** Frequency distribution of anti-*T. gondii* antibodies in term of type, sex, and Multiple Sclerosis incidence

| Properties | | Toxoplasmosis IgG | | *P*-Value |
|---|---|---|---|---|
| | | Negative | Positive | |
| MS (%) | Yes | 50.9 | 40.9 | .42 |
| | No | 49.1 | 59.1 | |
| Sex (%) | Male | 24.6 | 40.9 | 0.152 |
| | Female | 75.4 | 59.1 | |
| Type of MS | Relapsing Remitting | 75.9 | 88.9 | 0.402 |
| | Progressive | 24.1 | 11.1 | |

or exacerbating various autoimmune conditions has been recognized. Numerous studies have demonstrated that frequent exposure to infectious agents during childhood could confer protection against allergic and autoimmune diseases, including MS. This phenomenon is often referred to as the hygiene hypothesis [21]. Recent studies have revealed a noteworthy inverse association between the occurrence of MS and the prevalence of *Trichuris trichiura*, a common human parasite often indicative of lower community health standards on a global scale. These findings provide contemporary support for the hygiene hypothesis within the context of individuals diagnosed with MS. Furthermore, owing to the immunomodulatory impact of worms on both innate and adaptive immune cells, several ongoing clinical trials are actively exploring the potential effects of these parasites on autoimmune diseases [22].

Several studies have been carried out on the relationship between *T. gondii* infection and the risk of developing autoimmune diseases as a result of the significant prevalence of *T. gondii* infection in the world. It is estimated that 1.3% of the world's population is infected with this parasite. In a study by Wagner et al. (2009) on mice, *T. gondii* infection was shown to trigger robust immunomodulatory responses that either prevented or diminished allergic reactions [23]. Another study found a lower prevalence of *T. gondii* seropositivity in patients with type I diabetes in comparison to the healthy population. This finding suggests a potential protective role of *T. gondii* in type I diabetes [24]. Conversely, *T. gondii* infection has been shown to be associated with an elevated risk of certain autoimmune conditions. For instance, a meta-analysis study conducted by Hosseininejad et al. (2018) discovered that toxoplasmosis was associated with an increased risk of rheumatoid arthritis [9].

So far, several studies have been conducted to investigate the association between toxoplasmosis and MS, but the results have been contradictory. In this study, the MS group comprised 38 individuals including 29 women and nine men, while the control group consisted of 41 individuals including 27 women and 14 men. The average age of patients in the MS group was 33.8 ± 8.9 years, and the control group had an average age of 32.0 ± 3.0 years. No significant difference in anti-*T. gondii* IgG antibody levels was observed between the MS and control groups. Additionally, all samples tested negative for anti-*T. gondii* IgM antibodies. In a study by Pestehchian et al. (2014), involving 50 patients with RRMS and a control group comprising 50 family members, the prevalence of anti-*T. gondii* IgG antibodies was found to be 36% among patients and 49% among their family

members. However, this disparity was not statistically significant. Furthermore, in their study, all samples tested negative for anti-*T. gondii* IgM antibodies. Additionally, there was no significant relationship between the duration of the disease and IgG antibody levels, which aligns with the outcomes of the present research [25].

In a 2017 study, researchers examined 115 patients with RRMS and compared them to a control group of 60 healthy individuals regarding anti-*T. gondii* IgG antibodies. The patient group had an average age of 41.16 ± 11.20 years, while the control group had a mean age of 39.52 ± 7.45 years. Notably, the study found that 55% of the control group tested positive for anti-*T. gondii* IgG antibodies, whereas only 33.9% of the MS patients showed positive results. Importantly, there was a statistically significant difference in the frequency of anti-*T. gondii* IgG antibodies between the two groups, highlighting the distinction between individuals with and without MS in this regard [16].

In a recent study by Oruç et al. (2016), which involved 52 MS patients and a control group consisting of 45 individuals matched in terms of age and socioeconomic status with MS patients, a significant disparity in the prevalence of anti-*T. gondii* IgG antibodies was observed between the two groups. Specifically, 44.2% of MS patients tested positive for these antibodies, while only 24.4% of subjects in the control group exhibited similar results. Their study results not only highlighted a marked difference between the MS and control groups regarding the frequency of anti-*T. gondii* IgG antibodies but also established a direct correlation between the presence of anti-*T. gondii* antibodies and the occurrence of MS [26]. The discrepancy in the results of this study and other comparable research may be attributed to the relatively small sample size and patient selection method employed in this investigation. The present study has limitations regarding the small sample size of MS patients and the small number of participating health institutions. In 2017, Saberi and colleagues conducted a comprehensive meta-analysis that incorporated findings from five studies exploring the potential connection between *T. gondii* and MS. Their analysis encompassed a total of 669 MS patients and 770 control individuals. The results revealed that 32.4% of MS patients and 39.1% of controls tested positive for anti-*T. gondii* IgG antibodies. Interestingly, despite the slightly higher prevalence of anti-*T. gondii* IgG antibodies among MS patients compared to the control group, this difference was not statistically significant, which aligns with the findings of the present study [27].

## Conclusion

Some studies have suggested a potential correlation between *T. gondii* infection and MS, while others have found no significant association. Some epidemiological studies have reported a higher prevalence of *T. gondii* antibodies in individuals with MS compared to the general population. These studies have suggested that exposure to the parasite may be a risk factor for developing MS. On the other hands, in some regions with a high prevalence of *T. gondii*, the incidence of MS is also higher. However, this correlation is not consistent across all populations. In conclusion, the correlation between *T. gondii* infection and the incidence of MS is a complex and ongoing area of research. While some studies have suggested a potential link, the evidence is not definitive, and more research is needed to understand the underlying mechanisms and whether there is a causal relationship between *T. gondii* infection and MS. In this study, although the frequency of anti-*T. gondii* IgG antibodies in

the control group was higher than in the MS group, no statistically significant difference was observed between the control and MS groups. Anti-*T. gondii* IgM antibody was negatively measured in all samples, indicating the absence of active disease in both case and control groups. Although the results of this study contradict the health hypothesis, more studies with larger sample sizes are needed to better understand the relationship between anti-*T. gondii* IgG antibody seropositivity and the incidence of MS. Continued investigations on this topic are necessary to provide further insights into the pathogenesis of MS and potential preventive strategies.

**Acknowledgments**

This study was supported by the research deputy of Mashhad University of Medical Sciences based on the MD thesis of Seyyed Mohammad Sadegh Mirzaei.

**Ethical permissions:** The protocol of this research was confirmed by the Ethics Committee of Mashhad University of Medical Sciences (Code: IR.MUMS.fm.REC.1396.549).

**Conflicts of interests:** In this study, all authors declare that there is no conflict of interest.

**Authors' contributions:** ZM, SA, and AGH contributed to the study design and clarity, AHC, MB, and MSM contributed to data collection, FB and MM contributed to data analysis and interpretation, ZS and MKH contributed to the writing of the original article, EA and RB contributed to the approval of the final version of the article.

**Funding:** This research was financially support by Mashhad University of Medical Sciences (Grant No. 960725).

**Consent to participate:** All patients provided written informed consent prior to participation in the study.

## References

1. McCoy L, Tsunoda I, Fujinami RS. Multiple sclerosis and virus induced immune responses: Autoimmunity can be primed by molecular mimicry and augmented by bystander activation. Autoimmunity. 2006;39(1):9-19.
2. Weiner HL. Multiple sclerosis is an inflammatory T-cell–mediated autoimmune disease. Arch Neurol. 2004;61(10):1613-5.
3. Manouchehrinia A, Tanasescu R, Tench CR, Constantinescu CS. Mortality in multiple sclerosis: Meta-analysis of standardised mortality ratios. J Neurol Neurosurg Psychiatry. 2016;87(3):324-31.
4. Compston A, Coles A. Multiple sclerosis. Lancet. 2008;372(9648):1502-17.
5. Koch-Henriksen N, Sørensen PS. The changing demographic pattern of multiple sclerosis epidemiology. Lancet Neurol. 2010;9(5):520-32.
6. Marrie RA. Environmental risk factors in multiple sclerosis aetiology. Lancet Neurol. 2004;3(12):709-18.
7. Tahmasbi H, Manouchehri Naeini K, Masoumi-Ghajari S. Serological survey of human Toxoplasma gondii infection in northern and central regions of Iran. Biol J Microorganisms.2013;1(4):15-20.
8. Mendez OA, Koshy AA. Toxoplasma gondii: Entry, association, and physiological influence on the central nervous system. PLoS Pathog. 2017;13(7):e1006351.
9. Hosseininejad Z, Sharif M, Sarvi S, Amouei A, Hosseini SA, Nayeri Chegeni T, et al. Toxoplasmosis seroprevalence in rheumatoid arthritis patients: A systematic review and meta-analysis. PLoS Negl Trop Dis. 2018;12(6):e0006545.
10. Tenter AM, Heckeroth AR, Weiss LM. Toxoplasma gondii: From animals to humans. Int J Parasitol. 2000;30(12-13):1217-58.
11. Suvisaari J, Torniainen-Holm M, Lindgren M, Härkänen T, Yolken RH. Toxoplasma gondii infection and common mental disorders in the Finnish general population. J Affect Disord. 2017;223:20-5.
12. Alvarado-Esquivel C, Sanchez-Anguiano LF, Hernandez-Tinoco J, Berumen-Segovia LO, Torres-Prieto YE, Estrada-Martinez S, et al. Toxoplasma gondii infection and mixed anxiety and depressive disorder: A case-control seroprevalence study in Durango, Mexico. J Clin Med Res. 2016;8(7):519-23.
13. Xiao J, Prandovszky E, Kannan G, Pletnikov MV, Dickerson F, Severance EG, et al. Toxoplasma gondii: Biological parameters of the connection to schizophrenia. Schizophr Bull. 2018;44(5):983-92.
14. Tedford E, McConkey G. Neurophysiological changes induced by chronic Toxoplasma gondii infection. Pathogens. 2017;6(2):19.
15. Parlog A, Schlüter D, Dunay IR. Toxoplasma

gondii-induced neuronal alterations. Parasite Immunol. 2015;37(3):159-70.
16. Koskderelioglu A, Afsar I, Pektas B, Gedizlioglu M. Is Toxoplasma gondii infection protective against multiple sclerosis risk? Mult Scler Relat Disord. 2017;15:7-10.
17. Stascheit F, Paul F, Harms L, Rosche B. Toxoplasma gondii seropositivity is negatively associated with multiple sclerosis. J Neuroimmunol. 2015;285:119-24.
18. Gondi MS. Relationship of Toxoplasma gondii exposure with multiple sclerosis. Eur J Gen Med. 2016;13(1):58-63.
19. Sabzevari M, Tavalla M. Seroepidemiological study of Toxoplasma gondii in patients with multiple sclerosis in Ahvaz, southeastern Iran. Med Lab J. 2017;11(3):6-9.
20. Rahnama M, Asgari Q, Petramfar P, Tasa D, Hemati V, Solgi R. The role of Toxoplasma gondii infection among multiple sclerosis patient compared to ordinary people in south of Iran: A case-control study. Mod Care J. 2020;17((3:e105090.
21. Strachan DP. Hay fever, hygiene, and household size. Br Med J. 1989;299(6710):1259.
22. Wendel-Haga M, Celius E. Is the hygiene hypothesis relevant for the risk of multiple sclerosis? Acta Neurol Scand. 2017;136(Suppl 201):26-30.
23. Wagner A, Förster-Waldl E, Garner-Spitzer E, Schabussova I, Kundi M, Pollak A, et al. Immunoregulation by Toxoplasma gondii infection prevents allergic immune responses in mice. Int J parasitol. 2009;39(4):465-72.
24. Krause I, Anaya JM, Fraser A, Barzilai O, Ram M, Abad V, et al. Anti-infectious antibodies and autoimmune-associated autoantibodies in patients with type I diabetes mellitus and their close family members. Ann N Y Acad Sci. 2009;1173(1):633-9.
25. Pestehchian N, Etemadifarr M, Yousefi HA, Chiani M, Aslani N, Nasr Z. Frequency of blood-tissue parasitic infections in patients with multiple sclerosis, as compared to their family members. Int J Prev Med. 2014;5(12):1578-81.
26. Oruç S, Karakaya F, Demirbas H, Çeçen İ, Küsbeci ÖY, Yaman M, et al. Relationship of Toxoplasma gondii exposure with multiple sclerosis. Eur J Gen Med. 2016;13(1):58-63.
27. Saberi R, Sharif M, Sarvi S, Aghayan SA, Hosseini SA, Anvari D, et al. Is Toxoplasma gondii playing a positive role in multiple sclerosis risk? A systematic review and meta-analysis. J Neuroimmunol. 2018;322:57-62.