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Original Article

Seroepidemiology of Chronic Toxoplasmosis in Multiple Sclerosis Patients in Northeastern Iran

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Abstract

Background: *Toxoplasma gondii* is a common intracellular parasite implicated in chronic infections that may contribute to the pathogenesis of multiple sclerosis (MS). The potential role of *T. gondii* in triggering or exacerbating neuroinflammatory processes has been suggested in several recent studies. We aimed to assess the seroprevalence of anti *T. gondii* IgG antibodies in MS patients compared to healthy individuals and to evaluate associated demographic, environmental, and lifestyle risk factors.

Methods: In this cross-sectional case-control study at the Comprehensive MS Center of Ghaem Hospital, Mashhad, Iran, 99 MS patients and 92 matched healthy controls were enrolled. Serum samples were tested for *T. gondii* IgG using ELISA, and data on demographics, pet ownership, diet, untreated water consumption, COVID-19 history, and MS symptoms (muscle weakness, bowel dysfunction, balance disorders, speech disturbances, and attack frequency) were collected. Multivariate logistic regression assessed associations between T. gondii seropositivity, clinical symptoms, and environmental factors.

Results: *T. gondii* seropositivity was significantly higher in the MS group (22%) compared to controls (8%) ($P = 0.013$). Pet ownership, particularly cat ownership, was identified as a significant risk factor (OR = 5.089, $P = 0.037$). No significant associations were found between seropositivity and raw or undercooked meat consumption, unwashed vegetable intake, or history of COVID-19. Additionally, among clinical symptoms in MS patients, muscle weakness and bowel dysfunction showed significant positive associations with *T. gondii* seropositivity.

Conclusion: The findings suggest a potential link between chronic *T. gondii* infection and MS, indicating that the parasite may play a role in modulating neuroinflammatory responses. Further longitudinal and multicenter studies are warranted to elucidate the underlying mechanisms and evaluate the impact of antiparasitic treatments in MS management.

Introduction

Toxoplasmosis, an infection caused by the intracellular protozoan *Toxoplasma gondii*, is a prevalent parasitic disease, with roughly one-third of the global population estimated to be affected. (1,2). The infection is typically acquired through ingestion of oocysts from contaminated food, water, or soil, as well as through consumption of raw or undercooked meat containing tissue cysts. While acute toxoplasmosis is often asymptomatic in immunocompetent individuals, chronic infection is characterized by the persistence of latent tissue cysts, primarily in the brain and muscles, where the parasite establishes a long-term host-parasite equilibrium. Although traditionally considered a benign or opportunistic infection, *T. gondii* has been increasingly implicated in neuroinflammatory and neurodegenerative disorders, including schizophrenia, epilepsy, Alzheimer's disease, and multiple sclerosis (MS) (3).

Multiple sclerosis (MS) is a long-lasting autoimmune condition and neurodegenerative disorder that involves inflammatory demyelination, axonal damage, and loss of neurons in the central nervous system (CNS) (3,4). Its etiology is complex and multifactorial, resulting from an intricate interplay of genetic predisposition, environmental influences, and immune dysregulation (4,5). Increasing attention has been given to infectious agents especially those that can cross the blood-brain barrier and trigger prolonged immune activation as potential contributors to the modulation of CNS immune responses and the development of MS (6). In this regard, *T. gondii* is a candidate of interest due to its neurotropic nature, capacity to persist in neural tissues, and influence on host immune regulation (7).

Several mechanisms have been proposed to explain how T. gondii infection might contribute to MS development or progression. One key hypothesis involves chronic neuroinflammation and immune dysregulation, as T. gondii infection has been shown to induce persistent low-grade inflammation in the CNS, triggering the release of pro-inflammatory cytokines such as IL-6, TNF-α, and IFN-γ, which are also implicated in MS pathogenesis (8). This sustained inflammatory state may exacerbate immune-mediated demyelination and neurodegeneration, thereby accelerating MS progression (9).

Another proposed mechanism is molecular mimicry, where antigens of *T. gondii* share structural similarities with myelin-related proteins, leading to cross-reactive immune responses. This phenomenon could result in the breakdown of self-tolerance, particularly in genetically susceptible individuals, thereby increasing the risk of autoimmunity and MS development (10). Additionally, *T. gondii* infection has been shown to alter gut microbiota composition, which plays a fundamental role in immune system regulation. Dysbiosis in the gut microbiome has been linked to MS susceptibility, and chronic parasitic infections like toxoplasmosis may further disrupt the gut-immune axis, affecting systemic inflammation and neuroimmune interactions (11).

Despite these proposed links, previous studies have reported conflicting results regarding the association between *T. gondii* infection and MS. Some studies suggest a higher prevalence of *T. gondii* in MS patients, while others report no significant correlation or even a protective effect (6,12–15). These discrepancies highlight the need for further investigation, particularly in different geographic and genetic populations, using robust study designs and advanced statistical modeling.

Furthermore, the potential mechanisms linking chronic toxoplasmosis to the pathogenesis of MS, such as neuroinflammation and the severity of clinical signs, are not yet fully understood. Additionally, the influence of host factors, including immunomodulatory treatments, on *T. gondii* seroprevalence in MS patients has not been extensively explored.

We aimed to address these gaps by investigating the prevalence of *T. gondii* in MS patients, while considering potential confounders, including demographic, clinical, and environmental factors.

Materials and Methods

Ethical Considerations

This study was approved by the Ethics Committee of Mashhad University of Medical Sciences (Approval Code: IR.MUMS.MEDICAL.REC.1399.267). Written informed consent was obtained from all participants before enrollment. Confidentiality of patient data was strictly maintained, and all study procedures were conducted in accordance with the Declaration of Helsinki.

Study Design and Population

This cross-sectional study investigated the seroprevalence of *T. gondii* IgG antibodies in MS patients compared to healthy controls at the Comprehensive MS Center of Ghaem Hospital, Mashhad, Iran.

A total of 99 MS patients and 92 age- and sex-matched healthy individuals without autoimmune or neurological disorders were included. MS diagnosis was confirmed based on the McDonald criteria, and eligible patients were aged 18–65 years, receiving routine treatment but not undergoing acute immunosuppressive therapy.

Exclusion criteria included recent *Toxoplasma* or other parasitic infections, intravenous corticosteroid use in the last month, pregnancy/lactation, and severe systemic diseases (e.g., malignancies, uncontrolled diabetes, end-stage renal disease) to avoid confounding effects on seroprevalence results.

Serological Testing

Serum samples were collected from all participants and tested for the presence of anti-*T. gondii* IgG antibodies using ELISA (Euroimmun, Germany). The cutoff index for positivity was determined according to the manufacturer's instructions. Samples were analyzed in duplicate to ensure reliability.

Data Collection and Variables

Demographic and clinical data were collected using structured questionnaires, which included information on various variables relevant to the study. Participants were asked to provide details regarding their age and sex, as well as their dietary habits, specifically the consumption of raw or undercooked meat and unwashed or contaminated vegetables and water. Additionally, a history of COVID-19 infection was recorded, with cases confirmed through self-reported positive PCR test results. For MS patients, data on current medication use were also documented, including Dimethyl Fumarate, Glatiramer Acetate, Interferon Beta, Rituximab, Teriflunomide, Fingolimod, and Natalizumab, to assess any potential association between treatment regimens and *T. gondii* seropositivity.

Clinical Symptoms in MS Patients

The questionnaire also included an assessment of common clinical symptoms associated with MS to investigate potential associations with *T. gondii* infection, including muscle weakness, bowel dysfunction, sensory impairments, speech disorders, balance disorders, and the number of MS attacks.

Statistical Analysis

Data analysis was performed using SPSS v26. Descriptive statistics were reported as mean ± SD for continuous variables and as frequency (%) for categorical variables. Associations between *T. gondii* IgG seropositivity and demographic, clinical, and environmental factors (e.g., MS diagnosis, gender, age, pet ownership, dietary habits, and clinical symptoms) were examined using multivariate logistic regression. Odds ratios (OR) with 95% confidence intervals (CI) were calculated, and a *P*-value < 0.05 was considered statistically significant.

Sample Size calculation

The sample size was determined using GPower software based on prior studies of the T. *gondii*/MS association (5,17). To achieve

70% power at a 95% confidence level, a minimum of 90 participants per group was required. To ensure sufficient power and account for potential dropouts, 191 participants were recruited (99 MS patients and 92 controls).

Results

Demographic Characteristics

This study included a total of 191 participants, comprising 99 MS patients (case group) and 92 healthy individuals (control group). Among the MS patients, 23 (23.2%) were male and 76 (76.8%) were female, indicating a higher prevalence of MS among women. In the control group, 29 (31.5%) were male and 63 (68.5%) were female.

The mean age of MS patients was 38 years (SD = 9.05), while the mean age of the control group was 44.8 years (SD = 11.12). The mean age for males in the MS group was 40.2 years, and for females, it was 37.5 years. In the control group, the mean age for males was 46.1 years, and for females, it was 43.7 years. Statistical analysis showed no significant difference in age distribution between the case and control groups ($P = 0.2$).

Seroprevalence of Anti-Toxoplasma IgG in MS and Control Groups

The results of analysis indicate a significant association between *T. gondii* seropositivity and multiple sclerosis (MS). Among MS patients (n = 99), 22 individuals (22%) tested positive for *T. gondii* IgG antibodies, compared to only 8 individuals (8%) in the control group (n = 92), demonstrating a statistically significant difference ($P = 0.013$). This suggests a potential link between *T. gondii* infection and MS.

Risk Factors Associated with Toxoplasma Seropositivity

The prevalence of *T. gondii* seropositivity was higher in females (20 cases) than in males (10 cases), although this difference was not statistically significant ($P = 0.225$, OR = 1.750). Age was also not significantly associated with infection ($P = 0.635$, OR = 1.443), with the highest positivity observed in the 30–40 (n = 12) and 20–30 (n = 7) age groups, and no cases in the 10–20 group.

Cat ownership was a significant risk factor: among 22 pet owners, 15 (68.2%) were positive, compared to 24 of 161 non-pet owners (14.9%), yielding a statistically significant association ($P = 0.037$, OR = 5.089). In contrast, raw or semi-raw meat consumption (36.4% positive among 11 individuals vs. 14.4% among 180 non-consumers; $P = 0.110$, OR = 0.309) and vegetable consumption (18.3% vs. 13.3%; $P = 0.414$, OR = 0.697) were not significantly associated with seropositivity.

Among MS patients, untreated water consumption showed a borderline significant association with *T. gondii* positivity (30.4% positive among 46 consumers vs. 15.1% among 53 non-consumers; $P = 0.068$, OR = 0.336). Additionally, a history of COVID-19 infection was not significantly associated with *T. gondii* seropositivity (26.3% positive among 38 patients vs. 19.7% among 61 patients without COVID-19; $P = 0.536$, OR = 0.698) (Table 1).

Association between Toxoplasmosis and Clinical Symptoms in MS Patients

The logistic regression analysis revealed no significant association between *T. gondii* seropositivity and the number of MS attacks ($P = 0.598$, OR = 0.941) or disease duration ($P = 0.455$, OR = 1.035). Similarly, the use of immunomodulatory treatments did not affect *T. gondii* seropositivity ($P = 0.489$, OR = 0.924). Among neurological symptoms, only muscle weakness ($P = 0.045$, OR = 3.619) and bowel dysfunction ($P = 0.006$, OR = 5.6) showed significant associations with *T. gondii* infection, while balance, speech, vision, and sensory impairments did not reach statistical significance (Table 2).

Table 1: Association between Demographic, Environmental, and Lifestyle Factors with T. gondii Seropositivity in MS Patients and Control Group

Variable	Group	IgG Positive (%)	IgG Negative (%)	*P*-Value	Exp(B) (OR)	95% CI for OR
Group Comparison	MS Patients (99)	22	77	**0.013**	**2.40**	**(1.23 – 4.68)**
	Control Group (92)	8	84			
Gender	Male	10	42	0.225	1.750	(0.71 – 4.32)
	Female	20	119			
Age(yr	10-20	0	2	0.635	1.443	(0.31 – 6.64)
	20-30	7	22			
	30-40	12	56			
	40-50	5	42			
	50-60	5	34			
	>60	1	5			
Pet Ownership	Yes (22)	15	7	**0.037**	**5.089**	**(1.11 – 23.29)**
	NO (161)	24	137			
Meat Consumption	Raw/Semi-Raw (11)	4	7	0.110	0.309	(0.12 – 1.02)
	No history (180)	26	154			
Vegetable Consumption	With history (93)	17	76	0.414	0.697	(0.29 – 1.68)
	No history (98)	13	85			
Drinking Untreated Water in MS Patients	With history (46)	14	32	0.068	0.336	(0.10 – 1.14)
	No history (53)	8	45			
COVID-19 Infection in MS patients	With history (38)	10	28	0.536	0.698	(0.22 – 2.19)
	No history (61)	12	49			

Table 2: Association between Clinical Factors and T. gondii Seropositivity in Multiple Sclerosis Patients

Variable	Group	IgG Positive	IgG Negative	*P*-Value	OR	95% CI for OR
MS Attacks no	0	12	36	0.598	0.941	(0.75 – 1.19)
	1	2	14			
	2	0	6			
	3	1	7			
	4	4	2			
	5	1	2			
	6	0	2			
	7	1	0			
	8	0	1			
	10	1	6			
Disease Duration	1-5 years	11	40	0.455	1.035	(0.95 – 1.12)
	5-10 years	4	19			
	10-15 years	3	12			
	15-20 years	4	3			
	20-25 years	0	2			
	>20 years	0	1			
MS Medications	Dimethyl Fumarate	0	1	0.489	0.924	(0.74 – 1.15)
	Glatiramer Acetate	3	4			

Table 2: Continued …

	No Medication	3	6			
	Interferon Beta	1	4			
	Rituximab	4	22			
	Teriflunomide	3	3			
	Fingolimod	5	22			
	Natalizumab	2	6			
Muscle Weakness	No	3	28	**0.045**	**3.619**	**(1.02 – 12.8)**
	Yes	19	49			
Balance Disorders	No	13	38	0.947	0.980	(0.55 – 1.76)
	Yes	9	39			
Speech Disorders	No	19	62	0.163	3.253	(0.74 – 14.30)
	Yes	3	15			
Vision Impairment	No	15	59	0.477	0.627	(0.18 – 2.10)
	Yes	7	18			
Sensory Impairment	No	19	66	0.814	1.221	(0.24 – 6.22)
	Yes	3	11			
Bowel Dysfunction	No	5	48	**0.006**	**5.6**	**(** 1.52 to 20**)**
	Yes	17	29			

Discussion

This research assessed the presence of *Toxoplasma gondii* antibodies in patients with multiple sclerosis (MS) in comparison to a healthy control group. The results showed a notably higher rate of anti *T. gondii* IgG antibodies in the MS group (22%) than in the control group (8%, $P = 0.013$), indicating a potential link between chronic T. gondii infection and MS. These findings are in line with previous studies that have observed a greater prevalence of *Toxoplasma gondii* antibodies in individuals with MS, further supporting the hypothesis that chronic infections could influence MS pathogenesis.

Several studies have explored the link between *T. gondii* infection and MS, yielding inconsistent results. Studies reported higher seroprevalence rates (35.4% and 60.5%, respectively) among MS patients, which exceed the 22% prevalence observed in our study (6,17). In contrast, a study found no notable difference in the prevalence of *T. gondii* antibodies between patients with MS, which contradicts our findings (18). However, these discrepancies may be explained by factors such as geographical variations, environmental exposures, genetic predispositions, and differences in sample sizes. Supporting this explanation, a study emphasized that environmental and genetic factors significantly impact *T. gondii* infection rates, leading to variations in prevalence across different populations (19).

Additionally, a study observed a lower prevalence of *T. gondii* infection in MS patients compared to healthy controls, proposing that *T. gondii* might have a protective effect against MS (12). Similarly, a systematic review suggested a potential protective role of *T. gondii*, contrasting with our study's findings, which imply an association between toxoplasmosis and MS susceptibility(13).These conflicting results highlight the complexity of host-parasite interactions and the role of the immune system in neuroinflammatory diseases.

The analysis showed a strong association between pet ownership and *T. gondii* seropositivity, indicating a significantly higher infection risk (OR = 5.089), especially for cat owners. As the definitive host, cats shed *T. gondii* oocysts, contaminating the environment and promoting transmission through direct contact with feces or contaminated surfaces(20).

Chronic exposure to *T. gondii* may exacerbate neuroinflammation in MS patients, potentially influencing disease progression(21). Strict hygiene practices and routine screening for *T. gondii* in pet-owning MS patients are recommended to reduce infection risk.

Furthermore, a borderline association was observed between *T. gondii* seropositivity and consumption of untreated water, indicating that contaminated water sources could serve as a potential route of infection in this population. While this finding did not reach statistical significance, it aligns with existing literature emphasizing waterborne transmission as a major factor in *T. gondii* epidemiology (22).

Although we observed no statistically significant difference between the study groups regarding raw meat consumption and contaminated vegetable intake, further investigation into potential confounding factors is necessary. The lack of significance could be due to sample size limitations, as smaller cohorts may not detect subtle associations. A study also observed, the cultural and dietary habits of different populations can influence the likelihood of infection, suggesting that regional differences and individual behaviors may play an important role in determining exposure rates(23). These observations support our hypothesis that dietary patterns and hygiene practices are key factors in explaining the variability in T. gondii infection rates across studies.

Additionally, we found no significant association between prior COVID-19 infection and *T. gondii* seropositivity. While some studies suggest that SARS-CoV-2 infection may alter immune responses to chronic infections, our data do not support a direct interaction between COVID-19 and toxoplasmosis in MS patients (24–26).

In this study, no significant association was found between the use of MS medications and *T. gondii* IgG seropositivity. Given that some immunomodulatory drugs, such as fingolimod and natalizumab, exert immunosuppressive effects, an increased susceptibility to opportunistic infections might be expected(14,27). However, our results indicate that these medications do not significantly impact the prevalence of *T. gondii* infection. One possible explanation is that immune regulatory mechanisms in MS may overlap with immune alterations caused by chronic infections, potentially counteracting the expected effects of immunosuppressive therapy. Although immunosuppressive drugs generally increase susceptibility to infections, the immune changes associated with MS may interact in a way that mitigates their impact on *T. gondii* prevalence. Additionally, previous studies have shown that in some patients, immune responses against chronic infections remain active even under immunosuppressive therapy, which could explain the non-significant difference observed in this study (28,29). Moreover, genetic predispositions might influence susceptibility to both MS and chronic infections like *T. gondii* (30).

The findings of this study suggest a potential link between *T. gondii* infection and certain clinical manifestations in MS patients, particularly muscle weakness**,** bowel dysfunction**,** and speech disorders. Logistic regression analysis revealed significant associations between *T. gondii* IgG seropositivity and both muscle weakness and bowel dysfunction, suggesting that prior exposure to the parasite may contribute to or exacerbate these symptoms. Additionally, although the association between *T. gondii* seropositivity and speech disorders did not reach statistical significance, the relatively high odds ratio (OR = 3.253)suggests a potential link that warrants further investigation.

The underlying mechanisms of these associations remain unclear but could be related to the neurotropic nature of *T. gondii* and its ability to induce inflammatory and neuromodulatory changes in the central nervous system. The parasite is known to alter neurotransmitter levels, particularly dopamine and glutamate, which play essential roles in motor coordination and cognitive function. Dysregulation of these neurotransmitters has been implicated in

neurodegenerative and neuroinflammatory processes, potentially worsening neurological symptoms in MS patients. If *T. gondii* contributes to enhancing neuroinflammatory responses, it could accelerate damage to motor and speech-related brain regions, increasing the likelihood of neuromuscular dysfunction and speech impairments (7,31,32).

Conversely, sensory and balance impairments, as well as the number of MS attacks, did not show a significant correlation with *T. gondii* exposure. This lack of correlation could be attributed to factors such as the small sample size, variability in symptom severity, and compensatory immune mechanisms. It is important to recognize that MS progression is multifactorial, and other genetic, environmental, or immunological factors may play a more dominant role in shaping these clinical outcomes (33,34).

Future studies with larger cohorts and in different geographic regions are needed to confirm the generalizability of these findings. Additionally, the lack of data on other potential confounding factors, such as socioeconomic status limits the scope of our conclusions.

Conclusion

This study provides evidence for a potential link between *T. gondii* infection and multiple sclerosis (MS). Our results show a significantly higher prevalence of anti-*T. gondii* IgG antibodies in MS patients compared to the control group, suggesting that chronic infections may contribute to the pathogenesis of neuroinflammatory diseases. The observed association between *T. gondii* infection and symptoms such as muscle weakness and bowel dysfunction supports the idea that this parasite may influence the central nervous system through inflammatory or immunomodulatory mechanisms. However, no significant correlation was found with MS relapses or immunomodulatory drug use, indicating that the impact of *T. gondii* may be independent of disease activity.

Further longitudinal and multicenter studies are needed to confirm these associations and explore the underlying mechanisms. Additionally, genetic studies could provide valuable insights into susceptibility factors for MS and chronic infections.

Given the widespread prevalence of *T. gondii* in endemic regions, screening MS patients for this infection and examining the effects of antiparasitic treatments on disease progression could represent novel research directions and therapeutic strategies.

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Conflict of Interest

The authors declare that they have no conflicts of interest related to this research.

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