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The association between Parkinson disease and *Toxocara* infection/exposure: A case-control study

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Research Paper

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Abstract

Parkinson's disease (PD) is a prevalent neurological disorder and the second most common neurodegenerative disease. Research has explored the impact of infectious agents, such as the parasites, on neurological conditions, including PD. Given the limited studies worldwide and in Iran, this study aims to investigate the relationship between Toxocara infection and PD. This case-control study involved 91 PD patients and 90 healthy controls. After obtaining consent, serum samples and questionnaires were collected. All sera were examined using an ELISA test for IgG antibodies against *Toxocara canis*. Results were analyzed with SPSS, using chi-square tests, and odds ratios (OR), and confidence intervals (CI) were calculated via univariate and multivariate analyses. The prevalence of anti-*Toxocara* IgG was 33% (30/91) in PD patients and 33.3% (30/90) in the control group. Both univariate analysis (OR: 0.98; 95% CI: 0.52–1.82) and multivariate analysis (OR: 0.95; 95% CI: 0.49–1.83) indicated no statistically significant association. Additionally, univariate analysis (OR: 0.49; 95% CI: 0.16–1.5) and multivariate analysis (OR: 0.37; 95% CI: 0.09–1.43) suggested non-significant association between *Toxocara* infection and the severity of PD. Our findings do not support a statistically significant association between *Toxocara* infection and the PD. While the analysis suggested that *Toxocara* infection might reduce the severity of PD, these results were also not statistically significant. Further research with larger sample sizes and diverse populations is needed to fully understand the potential relationship between *Toxocara* infection and PD.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, characterized by the loss of dopamine-producing neurons in the substantia nigra and the accumulation of intraneuronal α-synuclein in Lewy bodies. This pathology results in various neurological symptoms, including resting tremor, bradykinesia, and rigidity (Alexoudi *et al.* 2018; Maiti *et al.* 2017; Poewe *et al.* 2017). PD prevalence is increasing in low- and middle-income countries, where it affects 1.51% of the world's population (Ou *et al.* 2021; Zhu *et al.*). Over the past two decades, the global incidence of PD has shown a remarkable annual percentage increase of 16.32% between 2004 and 2023 (Zhu *et al.*). Therefore, identifying the underlying causes of this disease can assist us in preventing this alarming increase.

Neuron degeneration in PD likely arises from a combination of genetic and environmental factors (Koprich *et al.* 2011; Shulman *et al.* 2011), although the exact causes remain unknown. Evidence suggests inflammation and mitochondrial dysfunction may contribute to dopaminergic neuron death (Johnson *et al.* 2019; Kannarkat *et al.* 2013). Notably, infections have been implicated in persistent microglia inflammation and potentially in PD development (Navarro-López *et al.* 2021; Zorina *et al.* 2023). Several studies have shown associations between PD and viral and bacterial infections such as HSV-1 (Bu *et al.* 2015; Hemling *et al.* 2003), EBV (Bu *et al.* 2015; Espay & Henderson, 2011), influenza (Cocoros *et al.* 2021), *Helicobacter pylori* (Shen *et al.* 2017), and HCV (Wijarnpreecha *et al.* 2018). However, definitive links between infectious agents and PD have yet to be established (Li *et al.* 2022). Parasitic infections play a major role in neurological disorders. Numerous studies have indicated that *Toxoplasma gondii* may play a role in PD (Bisetegn *et al.* 2023; Firouzeh *et al.* 2021; Nohtani *et al.* 2022; Virus *et al.* 2021). Despite limited direct evidence linking other parasites to PD progression, certain parasites share characteristics with *T. gondii* that might be relevant to PD progression. One such parasite is the *Toxocara* species.

Toxocariasis, a neglected zoonotic parasitic infection prevalent in low-income areas (Chen *et al.* 2018; Ma *et al.* 2020), is caused by *Toxocara cati* and *T. canis* in cats and dogs, respectively

(Quintero-Cusguen *et al.* 2021). This infection's global prevalence stands at 19% (Rostami *et al.* 2019). Humans, as accidental hosts, acquire the parasite's embryonated eggs through contaminated water, food, or soil (Choi *et al.* 2012; Morimatsu *et al.* 2006; Raissi *et al.* 2021). *Toxocara* larvae can migrate to various organs, including the brain. Larval migration in human toxocariasis can lead to severe clinical consequences, including internal organ damage (de Almeida Carvalho and Rocha 2014), vision loss (Fata *et al.* 2021; Zibaei *et al.* 2022), and neurological disorders (Chatzikonstantinou *et al.* 2022; Faure *et al.* 2021; Ma *et al.* 2018). Specifically, neurotoxocariasis has been associated with meningoencephalitis, dementia, schizophrenia, epilepsy, and Alzheimer's disease (Fan 2020; Fan *et al.* 2015a; Gale and Hedges 2020; Luna *et al.* 2018; Nicoletti 2020; Taghipour *et al.* 2021b; Taghipour *et al.* 2020). Despite the range of neurological disorders linked to toxocariasis, its connection with PD has received limited attention. A case-control study found a higher seroprevalence of *Toxocara* among PD patients (6%) compared to controls (0%), with no statistical significance (Çelik *et al.* 2013). Notably, animal studies have suggested altered neurotransmitter levels, including serotonin, GABA, monoamines, and dopamine, in *Toxocara*-infected subjects (Abdel Ghafar *et al.* 1996; Othman *et al.* 2010). Therefore, the potential for neuroinflammation and neural damage caused by *Toxocara* larvae in the brain could theoretically contribute to PD pathological processes.

Given the rising global prevalence of PD and the potential role infections may play in its pathogenesis, understanding the possible contribution of *Toxocara* infection to PD could provide valuable insights into its etiology. Investigating the links between this common parasitic infection and neurodegenerative disorders may lead to novel treatments and preventive strategies. Therefore, we conducted this study to evaluate this association in northern Iran.

Methods

Study site

Between June 5, 2022, and Julu 20, 2023, a case-control study was conducted at Rouhani Hospital, a referral hospital in Babol, Mazandaran province, northern Iran. This region experiences a hot, humid summer (20–35°C) and a mild, humid winter (13–20°C), with an annual precipitation exceeding 800 mm and a relative humidity over 70%. These conditions contribute to a high prevalence of parasitic diseases like Toxocariasis. Mazandaran province has a seroprevalence of over 23% (Aghamolaie *et al.* 2019; Fallah *et al.* 2021), which is two-fold higher than Iran's mean seroprevalence (9.3%, range of 6.3–13.1%) (Eslahi *et al.* 2020).

Study population and design

All participants provided written informed consent, and the research was approved by the Research Ethics Committee of Babol University of Medical Science, Babol, Iran (IR.MUBABOL.HRI.REC.1401.081). Patients presenting PD symptoms referred to the Ayatollah Rouhani Hospital's neurology department and clinic were included in the study. PD diagnosis relies on the clinical symptoms outlined by the Movement Disorder Society (MDS), which include tremor, hypokinesia, rigidity, and postural instability (Goetz *et al.* 2008). An expert neurologist confirmed the patient's clinical condition, encompassing the duration, primary clinical manifestations, and severity of the disease. UPDRS-MDS criteria were used to assess movement disorders according to the MDS movement disorder association. A modified Yahr & Hoehn classification system was utilized to categorize the disease's severity into three groups: 1–2 (mild), 3–5–2 (moderate), and more than 3 (severe). Brain imaging was performed to eliminate conditions such as brain tumors and cerebrovascular diseases. Patients with kidney and liver failure were excluded, as were those with neurologic disorders induced by neuroleptic drugs or toxins. Additionally, patients who did not provide consent or had incomplete information were excluded from the study. Healthy control subjects, matched in sex and age, were referred to the Rouhani Hospital's General Health Outpatient Clinic. A neurologist examined all subjects, finding no evidence of PD or cognitive disorders.

Covariates

Based on an examination of existing literature, covariates linked with reduced cognitive abilities were selected: age (years), gender (male or female), education (below high school, high school graduate, or some college or higher), place of residence (urban or rural), diabetes (yes/no), prevalent coronary heart disease (CHD) (yes or no), systolic blood pressure (mm Hg), alcohol consumption (never or any use), and family history of PD. Additionally, covariates related to *Toxocara* infection included contact with dogs, cats, and soil (yes/no).

Sample collection and laboratory analysis

All participants underwent venipuncture, and their blood samples were immediately centrifuged for 5 minutes at 3500 rpm to separate serum. The sera samples were then aliquoted and transported on ice to the Laboratory of the Infectious Diseases and Tropical Medicine Research Center, Health Research Institute at Babol University of Medical Sciences, where they were stored at -20°C until analysis. Testing of the blood samples was conducted by expert technicians who were blinded to the individuals' health conditions. Analysis of anti-*Toxocara* IgG serum antibodies was performed using enzyme-linked immunosorbent assays (ELISAs) from NovaTec Immunodiagnostics, Dietzenbach, Germany, which boasted a diagnostic specificity and sensitivity of over 95%. Test results were reported as international units (IU), with values less than 9.0 IU/mL, 9.0–11.0 IU/mL, and more than 11.0 IU/mL classified as 'test-negative', 'suspicious', and 'test-positive' for anti-*Toxocara* IgG serum antibodies, respectively.

Statistical analysis

Stata statistical software (v.16 Stata Corp., College Station, TX, USA) was used for all analyses. To summarize participant characteristics, we used mean and standard deviations (SD) for continuous variables and proportions for categorical variables. Pearson's $\chi 2$ and Fisher's exact tests were used to examine between-group differences. The seroprevalence of *Toxocara* infections in cases and healthy controls was also presented as percentages with 95% confidence intervals (CI). Using approximate Bayesian logistic regression with penalized likelihood (PL) estimation via data augmentation, we examined the association between *Toxocara* seropositivity and PD and calculated the odds ratios (ORs) and 95% CI (Discacciati *et al.* 2015). Using the penlogit command, we added specific prior-data records to a data set automatically. Using these records, we generated a penalty function for the log-likelihood of a logistic model, which equals (up to an additive constant) a set of independent log

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prior distributions on the parameters of the model (Discacciati *et al.* 2015). Using directed acyclic graphs (DAGs), variables were adjusted based on a minimal sufficient adjustment set for potential confounders, including age, gender, and parent or relative history of PD (Knüppel, 2010). Statistical significance was defined as a P value of less than 0.05.

Results

The study comprised 91 patients with PD (35.2% female) and 90 healthy individuals (37.8% female) as controls. The mean ages for PD patients and healthy controls were 68.7 ± 10.1 and 68.4 ± 10.6 years, respectively. Among the PD patients, 20 individuals (22%) were younger than 60. Among them, 35 people (38.5%) were from urban areas and 56 people (61.5%) from rural areas. Forty-three individuals (47.3%) had no formal education. Thirty-one (34.1%) of the case group members had high blood pressure, 16 (17.6%) had diabetes, 3 (3.3%) were alcoholics, and 15 (16.5%) had a history of head trauma. Table 1 displays baseline characteristics of cases and controls.

Table 1. Demographic and Clinical characteristics of patients with Parkinson's disease and healthy controls

Variable		Case (n=91) n (%)	Control (n=90) n (%)	p-value
Gender	Male	59 (64.8)	56 (62.2)	0.715
	Female	32 (35.2)	34 (37.8)	
Age	≤ 60	20 (22)	21 (23.3)	0.828
	> 60	71 (78)	69 (76.7)	
Place of residence	Urban	35 (38.5)	38 (42.2)	0.606
	Rural	56 (61.5)	52 (57.8)	
Education	Illiterate	43 (47.3)	44 (48.9)	0.992
	Primary and secondary school	22 (24.2)	22 (24.2)	
	High school	17 (18.7)	16 (17.8)	
	College +	9 (9.9)	8 (8.9)	
Contact with dogs	No	78 (85.7)	82 (91.1)	0.257
	Yes	13 (14.3)	8 (8.9)	
Contact with cats	No	85 (93.4)	83 (92.2)	0.758
	Yes	6 (6.6)	7 (7.8)	
Regular Contact with soil	No	29 (31.9)	49 (51.4)	0.001
	Yes	62 (68.1)	41 (45.6)	
High blood pressure	No	60 (65.9)	41 (45.6)	0.006
	Yes	31 (34.1)	49 (54.4)	
Diabetes	No	75 (82.4)	59 (65.6)	0.010
	Yes	16 (17.6)	31 (34.4)	
History of head trauma	No	76 (83.5)	85 (94.4)	0.019
	Yes	15 (16.5)	5 (5.6)	
BMI	Low	1 (1)	4 (4.4)	0.518
	Normal	45 (49.5)	39 (43.3)	
	High	45 (49.5)	47 (52.3)	
Alcohol use	No	87 (96.7)	84 (92.3)	0.460
	Yes	3 (3.33)	7 (7.7)1111	
Family history of Parkinson disease	No	75 (82.4)	74 (82.2)	
	Yes	16 (17.6)	16 (17.8)	

Table 2. Univariable and multivariable analyses to assess whether there is an association between Parkinson's disease (PD) and seropositivity to *Toxocara* spp. in elderly people

Participants	Seropositive for toxocariasis n (%)	seronegative for toxocariasis n (%)	Univariate analysis ORs (95% CIs)	Multivariate analysis ORs (95% CIs)
Case	30 (33)	61 (67)	0.98 (0.52–1.82)	0.95 (0.49–1.83)
Control	30 (33.3)	60 (66.7)	Reference	Reference
Mild PD	9 (40.91)	13 (59.09)	Reference	Reference
Moderate PD	11 (36.67)	19 (63.33)	0.83 (0.27–2.58)	0.58 (0.15–2.30)
Severe PD	10 (25.64)	29 (74.36)	0.49 (0.16–1.5)	0.37 (0.09–1.43)

A total of 60 out of 181 participants (33.15%, 95% CI: 26.3–40.5%) were seropositive for anti-*Toxocara* IgG based on the ELISA test. Among the 91 PD patients, 30 (32.9%, 95% CI: 23.4–43.6%) tested positive for anti-*Toxocara* IgG. Comparatively, 30 out of 90 control participants (33.3%, 95% CI: 23.7–44.0%) were also seropositive. To further investigate the potential predictive value of *Toxocara* infection on PD, we performed univariate and multivariate logistic regression analyses. As shown in Table 2, with the control group serving as the reference, the ORs for univariate and multivariate analyses were 0.98 (95% CI: 0.52–1.82) and 0.95 (95% CI: 0.49–1.83), respectively. These findings indicate no statistically significant association between *Toxocara* infection and PD.

To assess the potential association between *Toxocara* infection and the severity of PD, we analyzed the data based on the modified Yahr & Hoehn classification system. Of the 91 PD patients, 22 were classified as mild, 30 as moderate, and 39 as severe. After adjusting for confounding variables in a multivariate analysis (Table 2), we observed a trend suggesting that individuals with *Toxocara* infection had a 63% lower chance of experiencing severe PD compared to those without the infection. However, this association did not reach statistical significance.

Discussion

Our case-control study investigated the potential associations between *Toxocara* infection/exposure and PD risk in the elderly, and the severity of the disease in an endemic area in northern Iran. Results revealed a similar prevalence of *Toxocara* infection/exposure among PD patients (33%) and controls (33.3%). In multivariate logistic regression analyses, there was no statistically significant association between *Toxocara* infection/exposure and PD. Additionally, *Toxocara* infection seropositivity was lower among patients with mild PD than among those with moderate to severe PD, but there was no significant association between seropositivity and severity. Previously, only one study examined the association between PD and toxocariasis. According to Celik *et al.*, although the seroprevalence of *T. canis*

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was higher in patients with IPD (6.0%) than in controls (0%), no statistical differences were found (Çelik *et al.* 2013).

Toxocara larvae can invade the brains of humans, and while case descriptions of cerebral toxocariasis are historically rare, improved diagnosis and greater awareness have contributed to increased detection. Despite this, cerebral or neurological toxocariasis (NT) remains a poorly understood phenomenon. Furthermore, our understanding of cognitive deficits due to toxocariasis in human populations remains particularly deficient. Recent data describe an enhanced expression of biomarkers associated with brain injury, such as GFAP, AβPP, TGF-β1, NF-L, S100B, tTG, and p-tau, in mice receiving even low doses of *Toxocara* ova (Fan *et al.* 2015b). The lack of a significant association between *Toxocara* infection and PD in this study raises questions about the underlying mechanisms involved in PD pathogenesis. Several viruses and bacteria have been linked to increased PD risk (Bopeththa and Ralapanawa 2017; Bu *et al.* 2015; Cocoros *et al.* 2021; Dourmashkin *et al.* 2012; Espay and Henderson 2011; Harris *et al.* 2012; He *et al.* 2015; Hemling *et al.* 2003; Laurence *et al.* 2019; Sasco and Paffenbarger 1985; Shen *et al.* 2017; Vlajinac *et al.* 2013; Wijarnpreecha *et al.* 2018). There is, however, a different aspect to the relationship between parasitic infections such as *T. gondii* and *Toxocara*. *Toxoplasma* infection has been associated with many different aspects, including an increase in PD progression (Firouzeh *et al.* 2021) or a reduction in PD complications (Nohtani *et al.* 2022). According to Bayani *et al.*, in a meta-analysis (Bayani *et al.* 2019), there was no statistically significant association between PD and toxoplasmosis. Similarly to *Toxoplasma*, *Toxocara* infection has been shown to have different effects on dopamine levels in vivo. Compared to uninfected mice, Othman *et al.* demonstrated significantly reduced levels of dopamine, serotonin, monoamines, and GABA in a murine model (Othman *et al.* 2010). However, Fan has shown that outbred ICR mice infected with *Toxocara* have elevated levels of dopamine (Fan 2020). The study hypothesized that mice infected with *Toxocara* would exhibit increased expression of tyrosine hydroxylase, an enzyme that plays a crucial role in dopamine production. *Toxocara* infection/exposure may also contribute to the development of Schizophrenia, a disease characterized by an increased production of dopamine (Taghipour *et al.* 2021a). It is important to further explore the possibility of dopamine-related PD occurring in *Toxocara* infection in light of the difference in dopamine expression between the two animal studies.

When the T-helper 2 (Th2) response is triggered by helminth infections such as *Toxocara* spp, it differs from that triggered by microbial pathogens. Th2 increases cytokine levels in the body such as IL-4, IL-5, and IL-13 (Maizels 2013). Moreover, *Toxocara* induces downregulated cytokines, including TGF-β and IL-10 (Allen and Maizels 2011). These cytokines are associated with suppression of the Th1 immune reaction along with decreased IL-17, IFN-γ, and TNF-α levels which are critical for PD progression (Di Lazzaro *et al.* 2024). Pro-inflammatory cytokines can be neuroprotective, but a sustained or excessive release can damage neurons (Othman *et al.* 2010). It has been shown that in *Toxocara*-infected mice's brains, nitric oxide and pro-inflammatory cytokines are significantly increased (Othman *et al.* 2010). Early in the course of PD, pro-inflammatory cytokines are expressed more frequently, and later in the course, a Th2- and Th17-mediated response is found (Di Lazzaro *et al.* 2024). IL-5, IL-10, and IL-17 levels were lower in patients with a more recent onset of disease and higher in patients with a more extensive disease (Di Lazzaro *et al.* 2024). Based on these facts, more studies are needed to investigate the immune response and inflammatory effects of *Toxocara* spp on PD, especially at different stages of PD progression and infection with *Toxocara*. Nevertheless, it is important to remember that not all PD patients exhibit consistent signs of an inflammatory cytokine imbalance. Furthermore, chronic inflammation is not necessarily associated with PD (Acioglu *et al.* 2022; Zheng *et al.* 2022). In conclusion, there is no way to prove that every instance of PD is associated with elevated inflammatory processes and concomitant chronic infection.

Several limitations should be considered when interpreting the findings of this study. The relatively small sample size and the single-center design may limit the generalizability of the results. Additionally, the cross-sectional nature of the study prevents the establishment of causality between *Toxocara* infection and PD. Future research endeavors could involve larger, multicenter studies with longitudinal designs to validate these findings and explore potential causal relationships. Moreover, investigating the mechanistic pathways underlying the observed associations and considering other potential confounding variables could provide a more comprehensive understanding of the relationship between *Toxocara* infection and PD.

In conclusion, this study did not find a statistically significant association between *Toxocara* infection and Parkinson's disease. However, the trend suggesting a potential protective effect against severe PD with increasing *Toxocara* infection warrants further investigation. These findings contribute to the ongoing discourse on the role of infectious agents in neurodegenerative diseases and highlight the need for additional research to elucidate the mechanisms underlying these complex relationships. Ultimately, understanding the interplay between infections and neurodegenerative disorders may offer novel insights into disease prevention and treatment strategies.

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Data availability statement. All relevant data are within the manuscript and further data that support the findings of this study are available from the corresponding author upon reasonable request.

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