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# BMJ Open Toxoplasma gondii exposure and Parkinson's disease: a case-control study

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#### ABSTRACT

**Objectives:** To determine the association between Toxoplasma gondii infection and Parkinson's disease and to investigate whether T. gondii seropositivity is associated with the general characteristics of patients with Parkinson's disease.

Design: Case-control study.

Setting: Cases and controls were enrolled in Durango City, Mexico.

Participants: 65 patients with Parkinson's disease and 195 age- and gender-matched control subjects without Parkinson's disease.

#### Primary and secondary outcome measures:

Serum samples of participants were analysed for anti-T. gondii IgG and IgM antibodies by commercially available enzyme-linked immunoassays. Prevalence of T. gondii DNA was determined in seropositive subjects using PCR. The association between clinical data and infection was examined by bivariate analysis.

Results: Anti-T. gondii IgG antibodies were found in 6/65 cases (9.2%) and in 21/195 controls (10.8%) (OR 0.84; 95% CI 0.32 to 2.18; p=0.81). The frequency of high (>150 IU/mL) antibody levels was similar among cases and controls (p=0.34). None of the anti-T. gondii IgG positive cases and four of the anti-T. gondii IgG positive controls had anti-T. gondii IgM antibodies (p=0.54). The prevalence of T. gondii DNA was comparable in seropositive cases and controls (16.7% and 25%, respectively; p=1.0). Seroprevalence of T. gondii infection was associated with a young age onset of disease (p=0.03), high Unified Parkinson Disease Rating Scale scores (p=0.04) and depression (p=0.02). Seropositivity to *T. gondii* infection was lower in patients treated with pramipexole than in patients without this treatment (p=0.01). However, none of the associations remained significant after Bonferroni correction.

**Conclusions:** The results do not support an association between T. gondii infection and Parkinson's disease. However, T. gondii infection might have an influence on certain symptoms of Parkinson's disease. Further research to elucidate the role of T. gondii exposure on Parkinson's disease is warranted.

# Strengths and limitations of this study

- This study provides evidence for a better understanding on the association of Toxoplasma gondii infection and Parkinson's disease.
- This is the first study that adds molecular detection of T. aondii to assess its link with Parkinson's disease.
- Matching by age and sex was performed.
- This study provides clinical characteristics of Parkinson's disease associated with T. gondii infection.
- The seroprevalence of T. gondii infection was low.

#### INTRODUCTION

Protected by copyright, including for uses related to text and data mining Toxoplasma gondii (T. gondii) is an Apicomplexan parasite of medical importance.<sup>1</sup> Infections with *T. gondii* are common ۔ ح and occur worldwide.<sup>2</sup> The main routes of human infection with T. gondii include ingestion of water or food contaminated with parasite oocvsts shed by cats and consump-, and tion of raw or undercooked meat containing parasite tissue cysts.3 In rare cases, transmissimila sion of T. gondii may occur by blood transfusion or transplantation.<sup>4</sup> T. gondii spreads to a number of organs of the infected host and is able to cross biological barriers and enter into the brain, eye and placenta.<sup>5</sup> Primary infection with T. gondii during pregnancy may lead to infection of the fetus.<sup>6</sup> The clinical spectrum of T. gondii infection varies from asymptomatic to severe disease with lymphadenopathy, chorioretinitis and meningoencephalitis.<sup>3 6 7</sup>

Infection with T. gondii has been linked to number of neuropsychiatric diseases а including schizophrenia, Parkinson's disease and Alzheimer's disease, and the



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neurobiological data of this link have recently been reviewed.<sup>8</sup> The actiology of Parkinson's disease is largely unknown; however, progressive impairment of voluntary motor control-which is a clinical feature of this disease -is caused by a loss of midbrain substantia nigra dopamine neurons.<sup>9</sup> Tissue cysts of *T. gondii* may be found in all brain areas,<sup>10</sup> and *T. gondii* may lead to neurological damage.<sup>11</sup> It therefore raises the question whether infection with T. gondii may lead to Parkinson's disease. On the other hand, infection with T. gondii may increase the production of dopamine in the brain.<sup>12</sup> Therefore, it also raises the question whether Parkinson's disease could be negatively associated with infection with T. gondii. However, the potential link of T. gondii infection and Parkinson's disease has been poorly investigated, and conflicting results about the association of T. gondii exposure and Parkinson's disease have been reported. Miman *et al*<sup>13</sup> found a significantly higher rate of anti-T. gondii IgG antibodies in patients with Parkinson's disease than in controls. In contrast, Celik et al<sup>14</sup><sup>15</sup> found similar seropositivity rates to T. gondii in 50 patients with idiopathic Parkinson's disease and 50 healthy volunteers. In addition, Oskouei et al<sup>16</sup> found similar prevalences of anti-T. gondii IgG antibodies in 75 patients with Parkinson's disease and 75 controls. Given these conflicting results, we assessed the association of T. gondii infection and Parkinson's disease in a cohort of patients attending public hospitals in Durango City, Mexico. In addition, we investigated the association of T. gondii seropositivity and the sociodemographic and clinical characteristics of patients with Parkinson's disease.

# MATERIALS AND METHODS

#### Patients with Parkinson's disease and controls

We performed a case-control study of 65 patients with Parkinson's disease (cases) and 195 control subjects. Diagnosis of Parkinson's disease was made using the UK Parkinson's Disease Society brain bank clinical diagnostic criteria.<sup>17</sup> Patients were enrolled in the departments of neurology at two public hospitals: the Hospital 'Santiago Ramón y Cajal' of the Institute of Security and Social Services for the State Workers, and the Hospital '450' of the Secretary of Health in Durango City, Mexico. Serum samples were obtained from January to December 2014. Inclusion criteria for the cases were patients with Parkinson's disease of either sex who voluntarily accepted to participate in the study. Exclusion criteria for the cases were presence of renal or liver diseases, gout, alcoholism, history of cerebrovascular disease or other neurological diseases, and use of acetylsalicylic acid or allopurinol. Cases were aged 39-95 years (mean 69.08±11.39 years) and included 30 men and 35 women. We used a convenience sampling to enrol cases. Inclusion criteria for controls were subjects from the general population of the same city without neurological disease, matched with cases by age and sex. We included

three controls per case. Controls were aged 38-91 years (mean  $68.56\pm10.08$  years) and included 90 men and 105 women. There was no difference in age between cases and controls (p=0.85).

#### Sociodemographic and clinical data of cases

We obtained the sociodemographic and clinical data of the patients with Parkinson's disease through face-to-face neurological consultations and with the aid of a questionnaire. Since the correlation of T. gondii infection with clinical features of Parkinson's disease is largely unknown, we explored the association between *T. gondii* seropositivity and a number of clinical characteristics directly or indirectly associated with Parkinson's disease. copy Sociodemographic data obtained included age and sex. Clinical data included Hoehn and Yahr stages,<sup>18</sup> Unified Parkinson Disease Rating Scale scores, age at onset of Parkinson's disease, duration of disease, presence of tremor or rigidity at disease onset, most affected body side, familial history of Parkinson's disease, presence of hyposmia, syncope, paraesthesias, dementia, impairments of memory and vision, depression, anxiety, sialorrhoea, constipation, weight loss, sleep disorders, erectile uses related dysfunction and orthostatic hypotension. In addition, information about the presence of obesity, dyslipidaemia, diabetes mellitus, arterial hypertension, smoking, diarrhoea, nausea and/or vomiting was obtained from each patient. Antiparkinsonian medication was also registered and included the use of levodopa, carbidopa, pramipexole, trihexyphenidyl, biperiden, amantadine, rasagiline, selegiline, azilect, rotigotine and bromocriptine. The occurrence of dyskinesia, urinary incontinence and motor fluctuations (ie, end-of-dose wearing-off, unpredictable off, delay on and no on) related to treatment was also recorded.

#### Detection of anti-T. gondii antibodies

Anti-*T. gondii* IgG antibodies were detected in the serum of participants using the commercially available enzyme immunoassay *Toxoplasma* IgG kit (Diagnostic Automation, Woodland Hills, California, USA). This test determines the presence and also the levels of IgG antibodies. A cut-off of 8 IU/mL of specific anti-*T. gondii* IgG antibody was used. All serum samples positive for anti-*T. gondii* IgG antibodies were further analysed for anti-*T. gondii* IgM antibodies by the commercially available enzyme immunoassay *Toxoplasma* IgM kit (Diagnostic Automation). All tests were performed following the manufacturer's instructions.

#### Detection of T. gondii DNA by PCR

Whole blood samples of cases and controls with anti-*T. gondii* IgG antibodies were further examined to detect *T. gondii* DNA by nested PCR. Whole blood extraction of DNA followed the protocol described by Iranpour and Esmailizadeh (http://www.protocol-online. org/prot/Protocols/Rapid-Extraction-of-High-Quality-DNA-from-Whole-Blood-Stored-at-4-C-for-Long-Period-4175.html). A PCR protocol with two pairs of primers directed

against the B1 gene of *T. gondii* was used, as previously described.<sup>19</sup> The amplified PCR products were detected using gel electrophoresis, stained with ethidium bromide and visualised under ultraviolet light.

#### **Statistical analysis**

We used the software Microsoft Excel 2010, Epi Info V.7 (Centers for Disease Control and Prevention: http:// SPSS V.15.0 wwwn.cdc.gov/epiinfo/) and (SPSS, Chicago, Illinois, USA) to analyse the results. For calculation of the sample size we used a 95% confidence level, power of 80%, 1:3 proportion of cases and controls and a reference seroprevalence of  $12.0\%^{20}$  as the expected frequency of exposure in controls. The result of the sample size calculation was 60 cases and 179 controls. To avoid bias, we excluded subjects with missing clinical data. Age values among the groups were compared with the paired Student's t-test. The Fisher exact test was used to evaluate the association between seropositivity to T. gondii and the characteristics of the patients. ORs and 95% CIs were calculated and a p value <0.05 was considered statistically significant. Bonferroni correction was applied for adjustment of multiple testing.

#### RESULTS

Anti-T. gondii IgG antibodies were found in 6/65 cases (9.2%) and in 21/195 controls (10.8%) (OR 0.84; 95%) CI 0.32 to 2.18; p=0.81). Of the six anti-T. gondii IgG positive cases, five (83.3%) had anti-T. gondii IgG antibody levels >150 IU/mL and one (16.7%) 12 IU/mL. In contrast, of the 21 anti-T. gondii IgG positive controls, 11 (52.4%) had anti-T. gondii IgG antibody levels >150 IU/ mL, one (4.8%) between 100 to 150 IU/mL and 9 (42.8%) between 8 and 99 IU/mL. The frequency of high (>150 IU/mL) antibody levels was similar among cases and controls (p=0.34). None of the six anti-T. gondii IgG positive cases had anti-T. gondii IgM antibodies whereas four (19.0%) of the 21 anti-T. gondii IgG positive controls had anti-T. gondii IgM antibodies. There was no difference in the rate of IgM seropositivity among cases and controls (p=0.54). Anti-T. gondii IgG antibodies were detected in four (11.4%) of 35 female cases and in seven (6.7%) of 105 female controls (OR 1.80; 95% CI 0.49 to 6.58; p=0.46), whereas anti-T. gondii IgG antibodies were detected in two (6.7%) of 30 male

cases and in 14 (15.6%) of 90 male controls (OR 0.38; 95% CI 0.08 to 1.81; p=0.35). The frequency of high (>150 IU/mL) anti-*T. gondii* IgG antibody levels was similar in male and female cases (2/30 (6.7%) and 3/35 (8.6%), respectively, p=1.00). Seroprevalence of *T. gondii* infection was similar among cases and controls of several age groups (table 1). One (16.7%) of the six cases seropositive to *T. gondii* IgG antibodies was positive for *T. gondii* DNA by PCR. We were able to test 20 of 21 controls seropositive to *T. gondii* IgG antibodies. Five (25%) of these 20 controls were positive for *T. gondii* DNA by PCR. The prevalence of *T. gondii* DNA was similar in cases and controls (p=1.0).

With respect to clinical characteristics of patients, seroprevalence of T. gondii infection was higher in patients with an onset of Parkinson's disease at a young age  $(\leq 40 \text{ years})$  than in those with a disease onset at older ages (p=0.03). Table 2 shows a selection of clinical characteristics of patients with Parkinson's disease and their correlation with Т. gondii seropositivity. Seroprevalence of infection with T. gondii was also higher in patients with higher Unified Parkinson Disease Rating Scale scores (88-136) than in those with lower scores (p=0.04). Seropositivity to T. gondii was observed in six (17.1%) of 35 patients suffering from depression but in none of 30 patients without depression (p=0.02). Other clinical characteristics of patients including Hoehn and Yahr stages, duration of disease, presence of tremor or rigidity at disease onset, most affected body side, familial history of Parkinson's disease, presence of hyposmia, syncope, paraesthesias, dementia, impairments of memory and vision, anxiety, sialorrhoea, constipation, weight loss, sleep disorders, erectile dysfunction, and orthostatic hypotension did not show an association with T. gondii seropositivity. In addition, T. gondii exposure was not associated with the presence of obesity, dyslipidaemia, diabetes mellitus, arterial training, hypertension, smoking, diarrhoea, nausea and/or vomiting in the patients. Seropositivity to T. gondii infection was significantly (p=0.01) lower in patients receiving pramipexole than in patients not treated with this drug (table 2). Seroprevalence of infection was similar in patients regardless of the use of other antiparkinsonian medications including levodopa, carbidopa, trihexyphenidyl, biperiden, amantadine, rasagiline, selegiline, azilect, rotigotine and bromocriptine. The presence of

	Cases			Controls			
	Subjects tested N	Seropositive		Subjects tested	Seropositive		
		N	%	N	Ν	%	p Value
Age groups							
≤40 years	2	1	50	6	0	0	0.25
41–60 years	12	1	8.3	22	1	4.5	1.00
61–80 years	41	4	9.8	144	17	11.8	1.00
>80 years	10	0	0	23	3	13	0.53

Table 2 Bivariate analysis of clinical data and infection with Toxoplasma gondii in patients with Parkinson's disease							
	Subjects tested	Prevalence of <i>T. gondii</i> infection					
Characteristic	N	N	%	p Value			
Age at Parkinson onset							
<40 years	4	2	50	0.03			
>40 years	61	4	6.6				
Duration of disease							
≤10 years	57	5	8.8	0.56			
>10 years	8	1	12.5				
Tremorigenic type							
Yes	49	5	10.2	1.00			
No	16	1	6.3				
Rigid type		-	10				
Yes	25	3	12	0.66			
No	40	3	7.5				
Hoenn and Yahr stages	5	0	0	0.50			
1	5 17	0	17.6	0.59			
1 2	17	3 1	7 1				
2	20	1	5				
3 4	5	1	20				
5	4	0	0				
Unified Parkinson disease ra	ating scores	Ŭ	v				
0–87	55	3	5.5	0.04			
88–136	10	3	30				
Constipation							
Yes	29	4	13.8	0.39			
No	36	2	5.6				
Syncope							
Yes	6	1	16.7	0.45			
No	59	5	8.5				
Paraesthesias							
Yes	12	3	25	0.07			
No	53	3	5.7				
Weight loss							
Yes	27	4	14.8	0.22			
No	38	2	5.3				
Vee	00	0	10	0.65			
No	20	2	71	0.05			
Depression	42	3	7.1				
Yes	35	6	17 1	0.02			
No	30	0	0	0.02			
Anxiety		Ŭ	v				
Yes	30	4	13.3	0.40			
No	35	2	5.7				
Vision impairment							
Yes	22	3	13.6	0.39			
No	43	3	7				
Dyskinesia							
Yes	21	3	14.3	0.37			
No	44	3	6.8				
Use of pramipexole							
Yes	43	1	2.3	0.01			
No	22	5	22.7				

dyskinesia, urinary incontinence and motor fluctuations (end-of-dose wearing-off, unpredictable off, delay on and no on) did not correlate with *T. gondii* infection.

None of the associations between clinical data and *T. gondii* seropositivity remained significant after Bonferroni correction.

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### DISCUSSION

T. gondii is an intracellular parasite and can persist in neurons, modifying their function and structure.<sup>21</sup> Cysts of *T. gondii* can be found throughout the brain,  $10^{10}$  and this parasite alters dopamine metabolism.<sup>21</sup> Thus, it raises the question whether infection with T. gondii has any link with a dopamine-related neurological disease. There is controversy concerning the association of T. gondii infection and Parkinson's disease. The number of reports about this association is very small. We therefore sought to determine the association between T. gondii seropositivity and patients with Parkinson's disease in the northern Mexican city of Durango. This age- and gender-matched case-control seroprevalence study showed similar frequencies of T. gondii infection in cases and controls. Similarly, we did not find differences in the frequency of high levels of anti-T. gondii IgG antibodies, IgM seropositivity rates and prevalence of T. gondii DNA among cases and controls. The 9.2% seroprevalence found in patients with Parkinson's disease is comparable to the 12% seroprevalence of T. gondii infection reported in elderly  $people^{20}$  and 13.3% in patients with liver disease<sup>22</sup> in the same Durango City. In contrast, the seroprevalence found in patients with Parkinson's disease is lower than seroprevalences reported in other population groups in Durango City including 15.4% in female sex workers,<sup>23</sup> 20% in schizophrenic patients<sup>24</sup> and 21.1% in inmates<sup>25</sup> and waste pickers.<sup>26</sup> Therefore, the results of our study do not support an association between T. gondii infection and Parkinson's disease. The lack of association between T. gondii infection and the presence of Parkinson's disease is consistent with similar results reported by Celik et al<sup>14</sup><sup>15</sup> and Oskouei et al.<sup>16</sup>

In contrast, our results conflict with those reported by Miman *et al*<sup>13</sup> who found a significantly higher seroprevalence of anti-T. gondii IgG antibodies in patients with Parkinson's disease than in controls. Other studies have also linked toxoplasmosis with Parkinson's disease. For instance, in 1992 Noël *et a* $\ell^{27}$  reported hemichorea and parkinsonism in two AIDS patients with cerebral toxoplasmosis. Basal ganglia, which are involved in the control of voluntary motor movements, can be affected in cerebral toxoplasmosis, as reported in patients with AIDS,<sup>28–30</sup> a patient with acute myeloid leukaemia undergoing two allogenic stem cell transplantations,<sup>31</sup> an immunocompromised female renal transplant recipient<sup>32</sup> and a non-immunocompromised pregnant woman.<sup>33</sup> Improvement of parkinsonism in an AIDS patient with cerebral toxoplasmosis was achieved after anti-T. gondii and antiretroviral therapies.<sup>34</sup> Infection with T. gondii has been associated with elevated levels of dopamine within dopaminergic cells,12 whereas an important feature of Parkinson's disease is the loss of dopamine-producing neurons.<sup>35</sup> However, the interaction of T. gondii and neurons in patients with Parkinson's disease is largely unknown. It raises the question whether dopamine production during infection

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#### CONCLUSIONS

The results obtained in a cohort of patients in Durango, Mexico do not support an association between *T. gondii* infection and Parkinson's disease. However, the results suggest that *T. gondii* infection might influence the symptoms of Parkinson's disease. Further research to elucidate the role of *T. gondii* exposure on the clinical characteristics of Parkinson's disease is therefore needed.

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**Contributors** CA-E designed the study protocol, performed the laboratory tests and data analysis and wrote the manuscript. EMM-H, JMS-P, LAR-C and AAS-C obtained the blood samples and clinical dat, and performed the data analysis. JH-T, OA-C, LFS-A, FXC-J and OL performed the data analysis and wrote the manuscript. All authors read and approved the final version of the manuscript.

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Patient consent Obtained.

**Ethics approval** This study was approved by the Ethics Committees of the General Hospital of the Secretary of Health and the Institute of Security and Social Services for the State Workers, Durango, Mexico.

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