To 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.

INTRODUCTION

Toxoplasma gondii (T. gondii) is an Apicomplexan parasite of medical importance.¹ Infections with T. gondii are common and occur worldwide.² The main routes of human infection with T. gondii include ingestion of water or food contaminated with parasite oocysts shed by cats and consumption of raw or undercooked meat containing parasite tissue cysts.³ In rare cases, transmission of T. gondii may occur by blood transfusion or transplantation.⁴ 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.⁵ Primary infection with T. gondii during pregnancy may lead to infection of the fetus.⁶ The clinical spectrum of T. gondii infection varies from asymptomatic to severe disease with lymphadenopathy, chorioretinitis and meningoencephalitis.⁷

Infection with T. gondii has been linked to a number of neuropsychiatric diseases including schizophrenia, Parkinson’s disease and Alzheimer’s disease, and the
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.17 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±10.08 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. Sociodemographic data obtained included age and sex. Clinical data included Hoehn and Yahr stages.18 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, salorrhoea, constipation, weight loss, sleep disorders, erectile 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. 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 V7 (Centers for Disease Control and Prevention: http://www.cdc.gov/epiinfo/) and SPSS V.15.0 (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% 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 (<40 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 *T. 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, salorrhoea, 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 hypertension, smoking, diarrhoea, nausea and/or vomiting in the patients. Seropositivity to *T. gondii* infection was significantly (p=0.01) lower in patients receiving primipexole 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

**Table 1** Comparison of IgG seropositivity rates in cases and controls according to age groups

| Age groups | Subjects tested | Seropositive | p Value |
|------------|----------------|-------------|---------|
| ≤40 years  | 2              | 1           | 0.25    |
| 41–60 years| 12             | 1           | 1.00    |
| 61–80 years| 41             | 4           | 1.00    |
| >80 years  | 10             | 0           | 0.53    |

*p* Value
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.

### Table 2: Bivariate analysis of clinical data and infection with *Toxoplasma gondii* in patients with Parkinson’s disease

| Characteristic                        | Subjects tested | Prevalence of *T. gondii* infection | p Value |
|---------------------------------------|----------------|------------------------------------|---------|
|                                       | N              | N                                 | %      |
| 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    |         |
| Tremorogenic type                     |                |                                    |         |
| Yes                                   | 49             | 5                                  | 10.2    | 1.00    |
| No                                    | 16             | 1                                  | 6.3     |         |
| Rigid type                            |                |                                    |         |
| Yes                                   | 25             | 3                                  | 12      | 0.66    |
| No                                    | 40             | 3                                  | 7.5     |         |
| Hoehn and Yahr stages                 |                |                                    |         |
| 0                                     | 5              | 0                                  | 0       | 0.59    |
| 1                                     | 17             | 3                                  | 17.6    |         |
| 2                                     | 14             | 1                                  | 7.1     |         |
| 3                                     | 20             | 1                                  | 5       |         |
| 4                                     | 5              | 1                                  | 20      |         |
| 5                                     | 4              | 0                                  | 0       |         |
| Unified Parkinson disease rating scores |            |                                    |         |
| 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     |         |
| Dementia                              |                |                                    |         |
| Yes                                   | 23             | 3                                  | 13      | 0.65    |
| No                                    | 42             | 3                                  | 7.1     |         |
| Depression                            |                |                                    |         |
| Yes                                   | 35             | 6                                  | 17.1    | 0.02    |
| No                                    | 30             | 0                                  | 0       |         |
| Anxiety                               |                |                                    |         |
| 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    |         |
DISCUSSION

T. gondii is an intracellular parasite and can persist in neurons, modifying their function and structure.21 Cysts of T. gondii can be found throughout the brain,10 and this parasite alters dopamine metabolism.21 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 people20 and 13.3% in patients with liver disease22 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,23 20% in schizophrenic patients24 and 21.1% in inmates25 and waste pickers.26 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.24,25 and Oskouei et al.26

In contrast, our results conflict with those reported by Miman et al.13 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 al.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,28–30 a patient with acute myeloid leukaemia undergoing two allogenic stem cell transplantations,31 an immunocompromised female renal transplant recipient32 and a non-immunocompromised pregnant woman.33 Improvement of parkinsonism in an AIDS patient with cerebral toxoplasmosis was achieved after anti-T. gondii and antiretroviral therapies.34 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.35 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 with T. gondii is too low to compensate for the deficit of dopamine and to induce a clinical improvement in patients with Parkinson’s disease. Further research to elucidate the role of dopamine produced during T. gondii infection on neurons of patients with Parkinson’s disease is needed.

Interestingly, the frequency of T. gondii infection was higher in patients with onset of Parkinson’s disease at a young age than in those with a disease onset at older ages. It is not clear why T. gondii infection was associated with a young onset of Parkinson’s disease. This young onset of disease is less common than middle and late onsets, and patients with young onset have a long survival and suffer from depression more frequently than patients with older onset of disease.36 Remarkably, we found that seropositivity to T. gondii was associated with depression in the patients with Parkinson’s disease studied. To the best of our knowledge, this is the first report of an association between T. gondii exposure and depression in patients with Parkinson’s disease. Infection with T. gondii has been linked to depression in other population groups, such as women veterans37 and pregnant women.38 However, other studies including a meta-analysis of 50 studies of psychiatric patients and healthy controls,39 a cross-sectional internet study on a non-clinical population of 5535 subjects40 and the third National Health and Nutrition Survey in the USA41 have not found a correlation between T. gondii infection and depression.

Of note, seroprevalence of T. gondii infection correlated with high Unified Parkinson Disease Rating Scale scores. In a search for this association in the medical literature, no reports were found. This association suggests that T. gondii infection might have an influence on clinical characteristics of patients with Parkinson’s disease. It is possible that T. gondii does not associate per se with the presence of Parkinson’s disease because of the opposite relations with dopamine production—that is, T. gondii infection induces an increase in dopamine production whereas Parkinson’s disease is related to a decrease in dopamine production. However, infection with T. gondii might be involved in the appearance of symptoms found in patients with Parkinson’s disease such as depression. Further research on the influence of T. gondii infection on signs and symptoms of Parkinson’s disease should be conducted.

We also observed that seropositivity to T. gondii infection was significantly lower in patients treated with pramipexole than in those not receiving this treatment. This finding suggests a protective effect of pramipexole for T. gondii infection. It is not clear why pramipexole users had a low frequency of T. gondii infection. No anti-T. gondii activity of pramipexole has been reported. Further research to elucidate the negative association of pramipexole with T. gondii infection is needed.

This study has limitations. The sample size was small. Further studies with larger sample sizes should be conducted. The low number of cases seropositive for...
T. gondii did not allow us to perform multivariate analysis to determine the association between patient characteristics and seropositivity to T. gondii. In addition, the associations between clinical data and T. gondii seropositivity found in this study should be interpreted with care, since the statistical power of comparisons was low (<0.80) and no associations remained statistically significant after Bonferroni correction.

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 data, 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.

Funding This study was financially supported by Juarez University of Durango State.

Competing interests None declared.

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.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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REFERENCES
1. Arisue N, Hashimoto T. Phylogeny and evolution of apicomplexans and apicomplexan parasites. Parasitol Int 2015;64:254–9.
2. Dubey JP. The history of Toxoplasma gondii—the first 100 years. J Eukaryot Microbiol 2008;55:467–75.
3. Montoya JG, Lienfeld O. Toxoplasmosis. Lancet 2004;363:1965–76.
4. Barsoum RS. Parasitic infections in transplant recipients. Nat Clin Pract Nephrol 2006;2:490–503.
5. Harker KS, Ueno N, Lodoen MB. Toxoplasma gondii dissemination: a parasite’s journey through the infected host. Parasite Immunol 2015;37:141–9.
6. Dubey JP. Toxoplasmosis of animals and humans. Boca Raton, FL: 2nd edn. CRC Press, 2010.
7. Maenz M, Schütler D, Liesenfeld O, et al. Ocular toxoplasmosis: present, and new aspects of an old disease. Prog Retin Eye Res 2014;39:77–106.
8. Fabiani S, Pinto B, Bonuccelli U, et al. Neurobiological studies on the relationship between toxoplasmosis and neuropsychiatric diseases. J Neurol Sci 2015;351:3–8.
9. Michel PP, Hirsch EC, Hunot S. Understanding dopaminergic cell death pathways in Parkinson disease. Neuron 2016;90:675–91.
10. Kamerkar S, Davis PH. Toxoplasma on the brain: understanding host-pathogen interactions in chronic CNS infection. J Parasitol Res 2012;2012:569295.
11. McConkey GA, Martin HL, Bristow GC, et al. Toxoplasma gondii infection and behaviour—location, location, location? J Exp Biol 2013;216(Pt 1):113–19.
12. Miman O, Kusbeci OY, Aktepe OC, et al. The probable relation between Toxoplasma gondii infection and idiopathic Parkinson’s disease? Scand J Infect Dis 2010;42:604–8.
13. Celik T, Kamishi O, Babir C, et al. Is there a relationship between Toxoplasma gondii infection and idiopathic Parkinson’s disease? Neurosci Lett 2010;475:129–31.
14. Roth A, Roth B, Hoffken G, et al. Ocular toxoplasmosis in patients with idiopathic Parkinson’s disease: chance association or coincidence? Biomed Res Int 2013;2013:685196.
15. Osokuei MM, Hamidii F, Talebi M, et al. The correlation between Toxoplasma gondii infection and Parkinson disease: a case-control study. J Parasitol Res 2016;2016:872–8.
16. National Collaborating Centre for Chronic Conditions (UK). Parkinson’s disease: National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care. London: Royal College of Physicians (UK), 2006. (NICE Clinical Guidelines No 35).
17. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology 1967;17:427–42.
18. Roth A, Roth B, Hoffken G, et al. Application of the polymerase chain reaction in the diagnosis of pulmonary toxoplasmosis in immunocompromised patients. Eur J Clin Microbiol Infect Dis 1992;11:1177–81.
19. Alvarado-Esquibel C, Liesenfeld O, Burciaga-López BD, et al. Seroepidemiology of Toxoplasma gondii infection in elderly people in a northern Mexican city. Vector Borne Zoonotic Dis 2012;12:568–74.
20. Parlog A, Schütler D, Dunay IR. Toxoplasma gondii-induced neuronal alterations. Parasite Immunol 2015;37:159–70.
21. Alvarado-Esquibel C, Torres-Berumen JL, Estrada-Martínez S, et al. Toxoplasma gondii infection and liver disease: a case-control study in a northern Mexican population. Parasit Vectors 2011;4:75.
22. Alvarado-Esquibel C, Sánchez-Anguiano LF, Hernández-Tinoco J, et al. High seroprevalence of Toxoplasma gondii infection in female sex workers: a case-control study. Eur J Microbiol Immunol 2015;5:285–92.
23. Alvarado-Esquibel C, Urbina-Álvarez JD, Estrada-Martínez S, et al. Toxoplasma gondii infection and schizophrenia: a case-control study in a low Toxoplasma gondii seroprevalence Mexican population. Parasit Vectors 2011;4:151–5.
24. Alvarado-Esquibel C, Hernández-Tinoco J, Sánchez-Anguiano LF, et al. High seroprevalence of Toxoplasma gondii infection in inmates: a case control study in Durango City, Mexico. Eur J Microbiol Immunol 2014;4:76–82.
25. Alvarado-Esquibel C, Liesenfeld O, Márquez-Conde JA, et al. Seroepidemiology of infection with Toxoplasma gondii in waste pickers and waste workers in Durango, Mexico. Zoonoses Public Health 2008;55:306–12.
26. Noël S, Guillaume MP, Teilerman-Toppet N, et al. Movement disorders due to cerebral Toxoplasma gondii infection in patients with the acquired immunodeficiency syndrome (AIDS). Acta Neurol Belg 1992;92:148–56.
27. Suzuki K, Masuya M, Matsumoto T, et al. High-intensity signals in the basal ganglia from gadolinium-enhanced T1-weighted MRI as an

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early change in Toxoplasma encephalitis in an AIDS patient. *J Infect Chemother* 2010;16:135–8.

29. Lazo JE, Meneses AC, Rocha A, et al. [Toxoplasmic and chagasic meningoencephalitis in patients with human immunodeficiency virus infection: anatomopathologic and tomographic differential diagnosis]. *Rev Soc Bras Med Trop* 1998;31:163–71.

30. Ferer S, Baro M, Cárdenas M, et al. [Cerebral abscess caused by *Toxoplasma gondii* and AIDS. Report of a case with anatomicopathological study]. *Rev Med Chil* 1993;121:1037–42.

31. Pevná M, Vondrácek P, Palásek I, et al. [Toxoplasmosis of the central nervous systems after allogeneic stem cell transplantation]. *Cas Lek Cesk* 2010;149:184–8.

32. Weenink JJ, Weenink AG, Geerlings SE, et al. Severe cerebral Toxoplasma infection cannot be excluded by a normal CT scan. *Neth J Med* 2009;67:150–2.

33. Alapatt JP, Kutty RK, Jose B, et al. A case of cerebral toxoplasmosis in a pregnant non-immunocompromised patient. *Neurol Neurochir Pol* 2009;43:391–5.

34. Murakami T, Nakajima M, Nakamura T, et al. Parkinsonian symptoms as an initial manifestation in a Japanese patient with acquired immunodeficiency syndrome and *Toxoplasma* infection. *Intern Med* 2000;39:1111–14.

35. Lotharius J, Brundin P. Pathogenesis of Parkinson’s disease: dopamine, vesicles and alpha-synuclein. *Nat Rev Neurosci* 2002;3:932–42.

36. Mehanna R, Moore S, Hou JG, et al. Comparing clinical features of young onset, middle onset and late onset Parkinson’s disease. *Parkinsonism Relat Disord* 2014;20:530–4.

37. Duffy AR, Beckie TM, Brenner LA, et al. Relationship between *Toxoplasma gondii* and mood disturbance in women veterans. *Mil Med* 2015;180:621–5.

38. Groër MW, Yolken RH, Xiao JC, et al. Prenatal depression and anxiety in *Toxoplasma gondii*-positive women. *Am J Obstet Gynecol* 2011;204:433.e1–7.

39. Sutterland AL, Fond G, Kuin A, et al. Beyond the association. *Toxoplasma gondii* in schizophrenia, bipolar disorder, and addiction: systematic review and meta-analysis. *Acta Psychiatr Scand* 2015;132:161–79.

40. Flegr J, Hodný Z. Cat scratches, not bites, are associated with unipolar depression–cross-sectional study. *Parasit Vectors* 2016;9:8. doi:10.1186/s13071-015-1290-7

41. Peacock BD, Kruzon-Moran D, Jones JL. The relationship between *Toxoplasma gondii* infection and mood disorders in the third National Health and Nutrition Survey. *Biol Psychiatry* 2012;72:290–5.