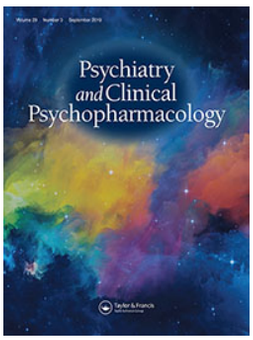

Psychiatry and Clinical Psychopharmacology

ISSN: 2475-0573 (Print) 2475-0581 (Online) Journal homepage: https://www.tandfonline.com/loi/tbcp21

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**To cite this article:** İsmail Akaltun, Tayfun Kara, Hamza Ayaydın, Behiye Alyanak, Hayati Beka & Ali Ağaçfidan (2019) The relation between serum *Toxoplasma gondii* IgG antibody in children and ADHD and its severity, Psychiatry and Clinical Psychopharmacology, 29:3, 326-331, DOI: 10.1080/24750573.2018.1449184

**To link to this article:** https://doi.org/10.1080/24750573.2018.1449184



Published online: 13 Mar 2018.

PSYCHIATRY AND CLINICAL PSYCHOPHARMACOLOGY
2019, VOL. 29, NO. 3, 326–331
https://doi.org/10.1080/24750573.2018.1449184



# The relation between serum *Toxoplasma gondii* IgG antibody in children and ADHD and its severity

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**ABSTRACT**

**AIM:** The purpose of our study was to investigate the relation between serum *Toxoplasma gondii* IgG antibodies in children and attention deficit hyperactivity disorder (ADHD) and its severity.

**METHOD:** 214 subjects, consisting of 107 children aged 6–18 and diagnosed with ADHD and 107 children with no ADHD or psychiatric pathology were included. Subjects underwent a detailed psychiatric examination based on DSM-V-TR diagnostic criteria, using a data form, the Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version (K-SADS-PL) for School-Aged Children (6–18), the DuPaul ADHD Rating Scale, Parent Rating Scale, the Conners Teacher Rating Scale (CTRS), and the Conners Parent Rating Scale (CPRS). Blood anti-Toxoplasma IgG antibody levels were investigated. The data obtained were then subjected to statistical analysis.

**RESULTS:** *T. gondii* IgG antibodies were positive in 8 (7.47%) of the case group and positive in 3 (2.8%) of the control group. No statistically significant difference was determined between the case and control groups in terms of *T. gondii* IgG positivity ($p = .215$). Higher levels of severe ADHD were determined in Toxoplasma IgG positive patients in the ADHD group compared to Toxoplasma IgG negative subjects, the difference being statistically significant ($p = .005$).

**CONCLUSION:** No significant differences were determined between the case and control groups in terms of *T. gondii* IgG positivity and ADHD. However, correlation was determined between ADHD severity and *T. gondii* IgG positivity.

**ARTICLE HISTORY**
Received 11 January 2018
Accepted 2 March 2018

**KEYWORDS**
Toxoplasma; infection; CNS; ADHD

## Introduction

Attention deficit hyperactivity disorder (ADHD) is a chronic condition with onset before 12 years and exhibiting symptoms of attention deficit, hyperactivity, and impulsivity [1]. Studies have shown that ADHD is more common in boys than girls. Community-based studies have revealed male:female ratios between 1:1 and 3:1, while clinically based studies suggest that the figures may be as high as 9:1 [2]. Interactions of genetic, biological, and environmental factors are today regarded as playing a role in the etiology of ADHD [3]. Dopamine is the neurotransmitter most linked to ADHD. The prefrontal cortex functions of dopamine are mediated by the D1/D5 and D4 receptors. Impairment of dopamine levels is known to give rise to hyperactivity, attention disorders, dyskinesia, tics, and self-harming behaviors [4]. In addition, attention and behavioral problems have been reported to be capable of occurring after bacterial or viral meningitis. The manner in which attention deficit appears in such conditions is unclear [5].

*Toxoplasma gondii* is a protozoal parasite that affects one in three of the world population and that is widespread in developing countries [6]. *T gondii*, the agent of toxoplasmosis, is an obligate intracellular parasite. It is generally asymptomatic in children and adolescents, or else involves self-limiting symptoms such as fever, lethargy, and lymphadenopathy [7,8]. Studies have revealed that latent toxoplasmosis causes behavioral changes in humans [9]. The idea that Toxoplasma may be associated with psychiatric diseases in humans is receiving increasing acceptance [10]. In addition, stimulation of the immune system has recently been shown to be associated with mental and behavioral changes in humans [6]. Studies supporting this thesis have reported greater incidences in individuals with toxoplasmosis of psychiatric diseases such as depression and suicidal tendencies [11,12], schizophrenia [13], bipolar disorder [14], and behavioral disorders [9]. One community-based study suggested that Toxoplasma IgG levels are associated

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with generalized anxiety disorder (GAD), with *T. gondii* seropositivity resulting in a two-fold increase in GAD [15]. It has been suggested that immune reactions, hypothalamus-pituitary-adrenal gland axis changes [6] and hormonal dysfunction occurring during Toxoplasma infection may play a role in the etiology of obsessive-compulsive disorder (OCD) [16]. One case report discussed the emergence of OCD following Toxoplasma infection in two children aged 11 and 14 [17]. *T. gondii* IgG antibody elevation has been observed in patients with OCD, and a potential relation between Toxoplasma infection and OCD has been proposed [18].

It has also been suggested that Toxoplasma affects behaviors requiring attention, such as causing a decrease in psychomotor performance and an increased involvement in traffic accidents [19–21]. Although some studies have shown that Toxplasma is associated with several psychiatric disorders, only one study has investigated the relation with ADHD. In a recently published study, Khademvatan et al. compared ADHD and control groups in terms of anti-toxoplasma antibodies and observed no significant difference [22]. However, that study did not examine the relation between Toxoplasma and severity of ADHD [22]. Investigation of the relation between Toxoplasma and ADHD, a frequently seen disorder in children, is urgently needed. The purpose of the present study was to investigate the relation between *T. gondii* and ADHD and its severity in children in the light of the current literature.

## Materials and methods

This study was performed in 2013–2014, One hundred seven children aged 6–18 under monitoring by the Istanbul University Medical Faculty Children's Mental Health and Disease Department, Turkey, with a diagnosis of ADHD were included as the case group. A further 107 children with no diagnosis of ADHD or other psychiatric pathology and under monitoring by the Istanbul University Medical Faculty Pediatric Clinic were enrolled as the control group. The study was approved by the Istanbul University, Istanbul Medical Faculty Ethics Committee (No. 1204, dated 05.08.2013). Written consent was obtained from those subjects under observation by these units, aged between 6 and 18 and willing to take part in the study and from their parents. The study aim was explained to the patients in the case group diagnosed with ADHD, and those individuals agreeing to be interviewed were included in the analysis. Inclusion criteria were (a) age 6–18 years, (b) no other psychiatric diagnosis in addition to ADHD in the ADHD group, (c) no diagnosis of generalized developmental disorder or intellectual disability (IQ < 70), (d) willingness to participate, and (e) no psychiatric diagnosis (in the control group). The control group consisted of healthy children over a 1-year period.

All children and adolescents in the case group meeting the inclusion criteria first underwent a detailed psychiatric examination based on DSM-V-TR diagnostic criteria. Before the evaluation took place, sociodemographic data were obtained from parents (age, sex, education, and premorbid characteristics). Presenting parents were interviewed, and face-to-face psychiatric interviews were also performed with children.

All participants were applied that part of the Turkish version [23] of the **Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime Version (K-SADS-PL-T)** concerned with ADHD. K-SADS-PL-T is applied through interview with parents and children, and the final evaluation is based on information obtained from all sources. In applying the inventory to the pre-adolescent period in this study, the parents were first interviewed. When adolescents were interviewed, the subject was interviewed first. In the event of an inconsistency between information from the different sources, the applicator used his own clinical judgment. K-SADS-PL was adapted by Kaufman et al. from K-SADS-P. Kaufman et al. reported (1997) that K-SADS-PL is a valid and reliable diagnostic tool [24].

**The DuPaul ADHD Rating Scale (ADHD-RS-IV Inventory Parent Version)**: This consists of 18 items, one for each of the 18 symptoms of ADHD in DSM-IV. This rating scale, developed by DuPaul et al. (1998), assesses the severity of symptoms during the preceding week. The scale is scored by experienced personnel in a research center based on interviews with parents and the patient, albeit separately [25].

**Conners Teacher Rating Scale (CTRS):** This scale was developed by Conners for the purpose of evaluating students' in-class behaviors [26]. Scores of 17 or above from items 7–9–17–18–20–21–22–25–26–27 and 28 indicate attention deficit, while scores of 17 or above from items 1–2–5–8–11–12–14–15–19–23 and 24 indicate hyperactivity. The scale has been adapted to Turkish culture [27].

**Conners Parent Rating Scale (CPRS):** This was developed to assess intrafamilial behaviors. Scores of 5 or above from items 1–6–18–25 and 31 indicate attention deficit, and scores of 7 or above from items 4–5–11 and 13 indicate hyperactivity. This four-point Likert-type scale was adapted into Turkish by Şener et al. (1998) [28].

Blood specimens were collected from the children included in the study, and anti-Toxoplasma IgG antibody levels were investigated using the Enzyme-Linked Immunosorbent Assay (ELISA) method. Five-milliliter specimens collected under sterile conditions were centrifuged at 1000 rpm for serum separation and were stored at -30° C until the time of assay. Serum Toxoplasma antibodies were measured in a 1:20 dilution based on National Committee on Clinical Laboratory Standards, and for ELISA tests, absorbance values >1.1

were regarded as positive. Absorbance values <0.9 were regarded as negative, while values between 0.9 and 1.1 were considered threshold. Repeat tests were performed after 2–3 weeks for cases assessed as threshold. Latent Toxoplasma infection (positive IgG, negative IgM) established by ELISA were confirmed using the Sabin–Feldman dye test (Abbott Laboratories Wiesbaden, Germany). A positivity index >16 was adopted for the Sabin–Feldman dye test [29].

At statistical calculation, we calculated that 107 individuals should be taken from each group for a 20% difference to be significant at 80% power at a 95% confidence level. Descriptive statistics were employed to express constant variables (mean, standard deviation, minimum, median, and maximum). The chi-square and Fisher Freman Halton tests were used to test relations between categoric variables. Statistical analyses were performed on MedCalc Statistical Software version 12.7.7 (MedCalc Software BVBA, Ostend, Belgium; http://www.medcalc.org; 2013) software. Statistical significance was set at 0.05.

## Results

Statistical calculation revealed that 107 individuals in each group would need to be enrolled for a 20% difference to be significant at a confidence interval of 95% and 80% power. The study group consisted of 107 children diagnosed with ADHD (86 boys, 80.3%, and 21 girls, 19.6%) aged 6–17, and 107 healthy children (57 boys, 53.2%, 50 girls, 46.7%). The mean age of the subjects with ADHD was 10.84 years, while the mean age of the control group was 10.71. Comparison of serum *T. gondii* IgG antibodies between the children constituting the case and control groups revealed positivity in 8 (7.47%) of the 107 ADHD cases and in 3 (2.8%) of the 107 control subjects. Serum *T. gondii* IgM antibodies were negative in all cases in both groups. No statistically significant difference was observed between the case and control groups in terms of *T. gondii* IgG positivity ($p = .215$) (Table 1).

Statistically significant differences were observed in terms of gender between the ADHD Toxoplasma IgG (+) and control groups, and between the ADHD Toxoplasma IgG(−) and control groups (chi-square $p < .05$). The proportion of males was higher and that of females was lower among ADHD Toxoplasma IgG +/− subjects compared to the control group. Statistically significant variation was determined in the case group between the ADHD Toxoplasma IgG (+) and IgG (–) groups and the control group in terms of presence of ADHD in at least one parent and sibling (chi-square, $p < .05$). However, so statistically significant difference was observed between the Toxoplasma IgG (+) and Toxoplasma IgG(−) groups in terms of ADHD in at least one parent and sibling (Table 2).

When Toxoplasma IgG(+) and IgG(−) subjects in the case group were compared in terms of ADHD subtypes and severity, significant variation was determined in the severe ADHD compound subtype ($p < .05$). The level of Toxoplasma IgG(+) subjects with severe compound-type ADHD was higher than that of Toxoplasma IgG(−) subjects (Table 3).

Mean inventory scores were compared in terms of Toxoplasma IgG (+) and IgG (–) status. Statistically significant variation was determined at all two-way comparisons (Mann–Whitney *U* test, $p < .05$). Mean ADHD inventory scores in Toxoplasma IgG (+) subjects were significantly higher compared to those in Toxoplasma IgG (−) subjects (Table 4).

**Table 1.** A comparison of case and control group Toxoplasma IgG results.

| | Total n | Toxoplasma IgG (+) | Toxoplasma IgG (–) | $p^a$ |
|---|---|---|---|---|
| Case group | 107 | 8 (7.47%) | 99 (92.53%) | 0.215 |
| Control group | 107 | 3 (2.8%) | 104 (97.2%) | |

[a]Fisher's exact chi-square test.

## Discussion and conclusion

Clinical studies and animal experiments have shown that compromise of dopamine and noradrenalin use can result in ADHD. Animal studies have shown that impulsive and hyperactive behaviors may derive from impairments in the catecholamine system [30]. Impairment of the dopaminergic system is thought to be significant in operant reward mechanisms and working memory, and to be problematic in attention deficit and hyperactivity [31,32]. Additionally, it has been suggested that functional impairments in the dopaminergic system can lead to inattention, hyperactivity, schizophrenia, anxiety disorders, OCD, tic disorders, dyskinesias, and behaviors such as self-mutilation. Several studies have indicated that ADHD is associated with minimal brain damage, the dopaminergic system and other neurotransmitters [33]. *T. gondii* infects approximately 30% of the world population; however, it only causes marked clinical symptoms in humans in a small group with immune suppression [6]. The parasites are known to cause pathological and immunological reactions and to be capable of affecting behavioral functions by altering neurological mechanisms in the host in the light of their own survival requirements. Experimental studies have shown impairment of psychomotor functions in mice infected with *T. gondii* [34]. Studies supporting this thesis have reported greater incidences in individuals with toxoplasmosis of psychiatric diseases such as depression and suicidal tendencies [11,12], schizophrenia [13], bipolar disorder [14], GAD [15], OCD [18], and behavioral disorders [9]. *T. gondii* being found to be linked to several psychiatric diseases, and some of the neurotransmitters associated with these diseases also being associated with ADHD,

**Table 2.** A comparison of sociodemographic characteristics in terms of case and control group Toxoplasma values.

| | Case group, ADHD+ | | ADHD− | | | |
|---|---|---|---|---|---|---|
| | Toxoplasma IgG(+) | Toxoplasma IgG(−) | Control | $p^1$ | $p^2$ | $p^3$ |
| (*n*) | 8 | 99 | 107 | | | |
| Sex (F/M)[a] | 0 (0.0)/ 8 (100.0) | 21 (21.2)/ 78 (78.8) | 50 (46.7)/ 57 (53.3) | 0.322/ 0.322 | **0.027/ 0.027** | **<0.001/ <0.001** |
| Age (mean years ± SD)[b] | 9.8 ± 2.6 | 10.9 ± 2.1 | 10.7 ± 2.1 | 0.164 | 0.252 | 0.495 |
| Mother's age (mean years ± SD)[b] | 38.6 ± 3.6 | 38.8 ± 3.3 | 39.2 ± 3.3 | 0.870 | 0.622 | 0.385 |
| Father's age (mean age ± SD)[b] | 41.1 ± 2.7 | 41.9 ± 3.6 | 42.1 ± 3.8 | 0.540 | 0.467 | 0.699 |
| Mother's education(mean years ± SD)[b] | 5.5 ± 5.52 | 5.4 ± 3.3 | 5.6 ± 3.1 | 0.938 | 0.934 | 0.654 |
| Father's education(mean years ± SD)[b] | 8 ± 4 | 7.8 ± 3.2 | 7.7 ± 3.2 | 0.987 | 0.802 | 0.822 |
| Number of siblings (mean ± SD)[b] | 1.5 ± 1.3 | 1.1 ± 1 | 1.1 ± 1 | 0.289 | 0.287 | 1.00 |
| Parents living together[a] | 6 (75.0) | 91 (91.9) | 98 (91.6) | 0.343 | 0.359 | 0.861 |
| Parents separated[a] | 2 (25.0) | 8 (8.1) | 9 (8.4) | 0.343 | 0.359 | 0.861 |
| Family with ADHD in at least one parent[a] | 2 (25.0) | 8 (8.1) | 2 (1.9) | 0.343 | **0.015** | 0.082 |
| No ADHD[a] | 6 (75.0) | 91 (91.9) | 105 (98.1) | 0.343 | **0.015** | 0.082 |
| Family with ADHD diagnosed in at least one sibling[a] | 3 (37.5) | 25 (25.3) | 5 (4.7) | 0.736 | **0.005** | **<0.001** |
| No ADHD[a] | 5 (62.5) | 74 (74.7) | 102 (95.3) | 0.736 | **0.005** | **<0.001** |
| Family with ADHD diagnosed within sibling and at least one parent | 3 (37.5) | 25 (25.3) | 5 (4.7) | 0.736 | **0.005** | **<0.001** |
| No ADHD | 5 (62.5) | 74 (74.7) | 102 (95.3) | 0.736 | **0.005** | **<0.001** |

[a]Chi-square *p*, [b]Mann–Whitney *U p*.
ADHD IgG+ vs. ADHD IgG −[1], ADHD IgG+ vs. Control[2], ADHD IgG− vs. Control[3]. Variables with $p < .05$ are in bold.

gave rise to a need to investigate the relationship between this parasite and ADHD. In addition, some mechanisms suggesting a possible relation between *T. gondii* and ADHD are as follows: (a) The *T. gondii* genome is known to contain two aromatic amino acid hydroxylases potentially capable of directly affecting dopamine and/or serotonin biosynthesis [6]. (b) The ability of Toxoplasma cysts to produce damage by settling in the brain and, additionally, to cause changes in the dopaminergic and neurotransmitter systems suggests that Toxoplasma may be involved in the etiology and severity of ADHD and (c) Higher testosterone levels have been determined in men with latent toxoplasmosis compared to controls [35,36]. Testosterone has been shown to be linked to dopamine release [37,38]. Inflammatory cytokines that increase dopamine release NO, IL-2, and IL-6 [39–43] are important against *T. gondii* infection [44,45]. (d) *T. gondii* infection has been reported to be capable of causing various psychiatric diseases by producing changes in such regions of the brain as the amygdala and the hippocampus [46–49]. (e) One study showed that miR-132 is upregulated following infection with *T. gondii* and is associated with changes in dopamine receptor signaling [50]. Prandovszky et al. reported that *T. gondii* orchestrates a significant increase in dopamine release in neural cells. The rate-limiting enzyme for DA synthesis (tyrosine hydroxylase) has also been found in intracellular tissue cysts in brain tissue with antibodies specific for the parasite-encoded tyrosine hydroxylase [51].

Our comparison of *T. gondii* IgG antibody levels in the children comprising the case and control groups revealed positivity in eight (7.47%) of the 107 children with ADHD and in three (2.8%) of the control group. *T. gondii* IgM antibody levels were negative in all cases in both groups. Of the children diagnosed with ADHD based on clinical data and on DSM-V diagnostic criteria, severe ADHD was present in six of the eight Toxoplasma IgG positive patients, and moderate or mild ADHD in two, while severe ADHD was diagnosed in 20 of the 99 Toxoplasma IgG negative patients, and moderate or mild ADHD in 79. We determined no statistically significant difference between our case and control groups in terms of *T. gondii* IgG or IgM positivity. However, a statistically significant relation was determined between IgG positivity and severity of ADHD. In their recently published study, Khademvatan et al. compared ADHD and control groups in terms of anti-Toxoplasma antibodies' seropositivity

**Table 3.** A comparison of Toxoplasma IgG positivity and severity of attention deficit and hyperactivity disorder severity in the case group.

| | IgG(+) | IgG(−) | *p* |
|---|---|---|---|
| ADHDc severe (*n*) | 6 (75%) | 20 (20.2%) | 0.002 |
| ADHDh severe (*n*) | – | – | – |
| ADHDa severe (*n*) | – | – | – |
| ADHDc moderate (*n*) | – | 36 (33.3%) | – |
| ADHDh moderate (*n*) | – | 8 (7.4%) | – |
| ADHDa moderate(*n*) | 1 (16.6%) | 7 (6.5%) | 0.725 |
| ADHDc mild(*n*) | – | 18 (16.8%) | – |
| ADHDh mild(*n*) | – | 4 (3.7%) | – |
| ADHDa mild(*n*) | 1 (16.6%) | 6 (5.6%) | 0.637 |
| Total (*n*) | 8 | 99 | |

Notes: Fisher Freeman Halton test, ADHD: Attention deficit hyperactivity disorder, ADHDc: combined type, ADHDh: hyperactivity subtype, ADHDa: attention deficit subtype.

**Table 4.** A comparison of scale scores in terms of Toxoplasma positivity/negativity in the case group.

| | ADHD (Case group) | | |
|---|---|---|---|
| | ToxoplasmaIgG (+) | ToxoplasmaIgG (−) | *p* |
| Total ADHD | *8* | *99* | |
| CPRS (hyperactivity) | 10.25 ± 1.4 | 7.6 ± 1.3 | <0.001 |
| CPRS (attention deficit) | 11.1 ± 1.4 | 7.5 ± 1.4 | <0.001 |
| CTRS (hyperactivity) | 25.4 ± 1.3 | 19.2 ± 1.5 | <0.001 |
| CTRS (attention deficit) | 25.5 ± 1.7 | 18.8 ± 1.3 | <0.001 |
| Dupaul (attention deficit) | 22.3 ± 1.6 | 15.2 ± 1.4 | <0.001 |
| Dupaul (hyperactivity/ impulsivity) | 23 ± 1.4 | 15.1 ± 1.3 | <0.001 |

Notes: Mann–Whitney *U p*, CTRS: Conners Teacher Rating Scale, CPRS: Conners Parent Rating Scale, Dupaul: The DuPaul ADHD Rating Scale.

and, in agreement with our study, observed no significant difference [22]. However, that study did not evaluate the relation between Toxoplasma and severity of ADHD [22]. Our findings show that while Toxoplasma cannot cause ADHD, it can exacerbate the severity of existing ADHD. This shows that the capacity of Toxoplasma to create minimal damage in the brain and changes in neurotransmitters, particularly the dopaminergic system, may be associated with exacerbation of ADHD. A marked association has been shown between ADHD and traffic accidents, taking part in high-risk dangerous sports and substance use [20]. investigated the relation between Toxoplasma and traffic accidents and observed an almost three-fold greater level of involvement in accidents among pedestrians or drivers with Toxoplasma infection [20]. Kocazeybek et al. reported a similar conclusion regarding the involvement in traffic accidents of subjects with Toxoplasma infection [52]. These studies suggested that Toxoplasma infection may give rise to anomalies such as decreases in motor performance reflexes, concentration and learning capacity [20,52]. Exacerbation of ADHD may increase such risky behavior. Toxoplasma may therefore have exacerbated existing ADHD in drivers involved in traffic accidents by increasing inattention and impulsive behavior.

Several studies have emphasized the importance of the genetic component in the emergence of ADHD [53,54]. In our study, we sought to exclude the genetic effect in ADHD symptom severity. When the ADHD IgG(+) vs. the control groups and the ADHD IgG(−) vs. control groups were compared in terms of genetic effect we observed, in agreement with the previous literature, that ADHD was more common in first-degree relatives of subjects with ADHD. However, when the ADHD IgG(+) and ADHD IgG− groups were compared in terms of genetic effect, no significant difference was determined in terms of ADHD in first-degree relatives. In addition, all ADHD scale scores (attention deficit/hyperactivity) were significantly higher in the ADHD IgG(+) group than in the ADHD IgG(−) group. ADHD scores being higher in the ADHD IgG(+), while there was no difference in terms of genetic effect between these two subgroups, suggested that Toxoplasma infection exacerbates the severity of ADHD independently of the genetic effect.

In conclusion, no correlation was observed in this study between Toxoplasma seropositivity and ADHD. However, a relation was observed between Toxoplasma seropositivity and severity of ADHD. Much is still unknown about the relationship between agent and host. However, clarification of the effects of Toxoplasma and the disease at the molecular and pathophysiological levels, and the development of protective measures, will probably reduce the severity of ADHD. Long-term cohort studies investigating the relation between time of diagnosis, stage, and areas of involvement of toxoplasmosis and all psychiatric diseases, including severity of ADHD, are now needed.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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