Prevalence of *Toxoplasma gondii* infection among individuals with severe mental illness in Nigeria: a case control study

Bawo O. James, Imafidon O. Agbonile, Modupe Okolo, Ambrose O. Lawani, Joyce O. Omoaregba

Department of Clinical Services, Federal Psychiatric Hospital, Uselu, Benin City, Edo State, Nigeria

Background: While the aetiology for most psychotic disorders is unknown, a strong association has been observed between *Toxoplasma gondii* infection and psychosis. The proportion of individuals with psychotic disorders who have current or past infection with toxoplasma has been varied. Reports from the African continent have however been scanty.

Methods: A case control study of patients with a psychotic disorder presenting for the first time to a regional psychiatric facility was undertaken and compared to age and sex-matched healthy controls. In addition to socio-demographic and clinical characteristics, seroprevalence (IgG and IgM) of *T. gondii* was undertaken using an immunoassay test kit.

Results: IgG seropositivity was significantly higher among cases (30.7% vs 17.85%, OR=2.04, 95% CI=1.12–3.74, $P<0.02$). In contrast, IgM seropositivity was significantly lower among the cases (7.14% vs 8.57%, OR=0.82, 95% CI=0.31–2.16, $P=0.82$). Cases who were IgG seropositive to *T. gondii* were more likely to be older ($P<0.001$) and female ($P<0.001$). There was no statistically significant difference in terms of *T. gondii* infection and, eaten poorly cooked meat (0.88), and diagnostic group ($P=0.53$). Though there was a trend towards exposure to cats, this failed to reach significance ($P=0.08$).

Conclusion: *T. gondii* (IgG) infection is common among individuals with severe mental illness sampled and significantly higher compared to controls.

Keywords: Toxoplasma gondii, Severe mental illness, Nigeria

Introduction

While the aetiology for most psychotic disorders remains unknown, the possible role of some infectious agents in inducing behavioural changes in animal and human models has gained increasing research interest in recent times. Of note is the infectious agent, *Toxoplasma gondii* (*T. gondii*).

T. gondii is a neurotropic intracellular protozoan parasite and a cause of toxoplasmosis.¹ It is ubiquitous and affects nearly a third of the world's population.² Though felines are its definitive hosts, human infection is commonly via ingestion of oocysts in water, or through tissue cysts in poorly cooked or raw meat. Contact with cats, cat faeces, or other pets such as dogs have been implicated in the transmission of the infection to humans.³

In a recent meta-analysis, *T. gondii* infection was nearly three times as likely to occur in patients with schizophrenia compared to apparently healthy

controls.⁴ The relationship between *T. gondii* and schizophrenia in particular or psychotic disorders in general is complex. The protozoan has been observed in animal studies to alter behaviour and increase 'pro-psychotic' phenomena,⁵ with the administration of antipsychotic agents to infected animals altering such behaviour.

Rates of *T. gondii* infection vary across the world. In sub-Saharan Africa high rates have been noted in East Africa⁶ and in Nigeria rates vary between 20% and 48% depending on the population sampled.^{7,8} Given the aetiological relationship between *T. gondii* infection and psychotic disorders, no study has examined this relationship in Nigeria, which is considered to be one of the most populous nations in the region.

This study sought to explore the prevalence of *T. gondii* infection among individuals with severe mental illness (psychotic disorders) presenting to a regional tertiary psychiatric facility in Benin-City, Nigeria and compare the same with a control group comprising health workers without a history of psychosis.

Correspondence to: Dr Bawo James, Department of Clinical Services, Federal Psychiatric Hospital, P.M.B 1108, Benin City, Edo State, Nigeria. Email: bawojames@yahoo.com

Methods

Study setting

The study was conducted at the Federal Psychiatric Hospital, Uselu, Benin City, Nigeria. The study was undertaken between October 2011 and December 2012. The facility is a 230-bed regional psychiatric facility that handles referrals and walk-in cases daily for a target population of 3–5 million people.

Study population

Individuals aged between 18 and 64 years presenting to the hospital for the first time and diagnosed as having a psychotic disorder (affective or non-affective) and provided written informed consent were recruited into the study. A control group, comprising health professionals and matched for age (± 4 years) and sex were also recruited. To be included in the study, controls must not have had a current or past history of a psychotic disorder. Each control was recruited among hospital staff at the study site. An advertisement was sent out on notice boards and interested participants had the nature of study explained to them. Each control subsequently signed an informed consent form. No stipend was provided, however controls were informed that they could know their status as it regarded not only the pathogen under study but also their hepatitis status which was done for gratis.

Instruments

Socio-demographic Questionnaire

A structured questionnaire was designed by the authors to capture socio-demographic variables of cases and controls as well as the clinical characteristics of the cases. Cat and dog exposure was determined by the statements 'Did you keep cats as pets as a child?' 'Did you keep dogs as pets as a child?' 'Have you ever come in contact with cat feces in your lifetime?'

Mini International Neuropsychiatric Interview (M.I.N.I.)

The M.I.N.I.⁹ was designed as a brief, structured interview for the major Axis I psychiatric disorders in DSM-IV and ICD-10. Validation and reliability studies have been performed for the M.I.N.I., with the results showing that the M.I.N.I. has acceptably high validation and reliability scores. Clinicians can use it after a brief training session, but lay interviewers require more extensive training. The M.I.N.I. has been extensively used in this geographical setting.^{10,11}

Brief Psychiatric Rating Scale (BPRS)

The Brief Psychiatric Rating Scale¹² is a clinician-rated scale that has been validated for use in this environment.¹³ The BPRS was used to assess severity of psychopathology. Ratings were made on a seven-point scale, ranging from not present (1) to extremely

severe (7). A simple summation of the scores obtained provides a total score, which is an index of illness severity.

Ethical approval

The study protocol was submitted, reviewed, and approved by the Ethics and Review Committee of the Federal Psychiatric Hospital, Uselu, Benin City. For each individual who satisfied the study inclusion criteria, the nature and purpose of the study was explained to the patient and/or the caregiver or healthy volunteer. Participants were informed that their participation was entirely voluntary and no untoward effect in terms of sub-optimal care would be given if they declined to participate. Respondents were also informed that the outcome of the laboratory investigations if positive, may inform a referral for further specialist review and care.

Procedure

For each individual who satisfied the study inclusion criteria, relevant socio-demographic and clinical data were captured using a pencil and paper questionnaire. The M.I.N.I. and the BPRS were subsequently interviewer administered to participants in the cases group.

Two millilitres of blood samples were collected from participants (cases and controls) into potassium-EDTA sample containers, mixed and allowed to stand for 2–5 minutes, after which samples were spun and plasma separated into plain sample containers.

The tests were run immediately and in cases where the assay could not be performed immediately, the samples were kept frozen till assay. OnSite® Toxo IgG/IgM Rapid Test-Cassette (Serum/Plasma/Whole blood) was used for assay. The OnSite® Toxo IgG/IgM Rapid Test is a lateral flow chromatographic immunoassay. The test cassette consists of:

1. a burgundy coloured conjugate pad containing recombinant *T. gondii* antigens conjugated with colloid gold (*T. gondii* conjugates) and rabbit IgG-gold conjugates,
2. a nitrocellulose membrane strip containing two test bands (M and G bands) and a control band (C band). The M band is pre-coated with monoclonal anti-human IgM for detection of IgM anti-*T. gondii* antibody, G band is pre-coated with reagents for detection of IgG anti-*T. gondii* antibody, and the C band is pre-coated with goat anti-rabbit IgG.

When an adequate volume of test specimen (in this case a drop i.e. 30 μ l–45 μ l of plasma and a drop of sample diluent) is dispensed into the sample well of the test cassette, the specimen migrates by capillary action across the cassette. IgM anti-*T. gondii* if present in the specimen will bind to the *T. gondii* conjugates. The immunocomplex is then captured on the membrane by the pre-coated anti-human IgM antibody, forming a burgundy coloured M band, indicating a *T. gondii* IgM positive or reactive test

result. IgG anti-*T. gondii* if present in the specimen will bind to the *T. gondii* conjugates. The immuno-complex is then captured by the pre-coated reagents on the membrane, forming a burgundy coloured G band, indicating a *T. gondii* IgG positive test result.

Absence of any T bands (M and G) suggests a negative or non-reactive result. The test contains an internal control (C band) which should exhibit a burgundy coloured band of the immunocomplex of goat anti rabbit IgG/rabbit IgG-gold conjugate regardless of the colour development on any of the T bands. Otherwise, the test result is invalid and the specimen must be retested with another device. The test cassettes are a product of CTK Biotech Inc., San Diego, California.

Data analysis

Data were analysed using the Statistical Package for the Social Sciences, version 17. Data were summarised using descriptive statistics. Continuous and categorical comparisons performed using the student *t*-test and chi-squared tests. Fisher exact tests were used where necessary. Level of significance was set at $P < 0.05$.

Results

Socio-demographic characteristics of cases and controls

A total of 140 patients (cases) who satisfied the inclusion criteria were recruited over the study period. A similar number of participants was also recruited among the control group. Among the cases, the mean age was 28.2 (3.3) years, with just over half being male (60%). A majority were unemployed (65.7%), and Christians (87.14%). Over a third were currently domiciled in an urban area, with over half (68.57%) indicating they spent their early life living in an urban area. A majority had at least 12 years of formal education (67.86%). In the control group, a similar proportion (60%) were of the male gender, with a mean age of 29.1 (2.6) years. Almost all participants in the control group were Christians (98.57%), employed, and all were currently domiciled in an urban area. See Table 1.

Illness characteristics of cases

The mean duration of untreated illness was 43.22 months (range 1–268 months). Males had a longer duration of untreated illness which was significantly longer than females ($t = 2.32$, $df = 138$, $P = 0.03$). A minority had co-morbid (22.8%) substance use. Similarly, a minority (18.4%) had a family history of mental illness. Using the MINI, nearly half (46.7%) presented with symptoms indicative of a non-affective psychosis. In terms of illness severity, the mean BPRS score for the whole sample was 46.72 (± 10.11). Male patients had a higher mean BPRS score compared to

females. This difference was not statistically significant ($t = 1.023$, $df = 138$, $P = 0.09$).

Prevalence and correlates of toxoplasmosis

Forty three patients (30.7%) were IgG positive compared to twenty five individuals (17.85%) in the control group. The odds were significantly higher among the cases compared to the control group (OR=2.04, 95% CI=1.12–3.74, $P = 0.02$). Ten (7.14%) of the cases were IgM positive, compared to twelve (8.57%) of controls. There was no significant difference in IgM seropositivity prevalence between both groups. Cases were less likely to be IgM positive compared to controls (OR=0.82, 95% CI=0.31–2.16, $P < 0.82$). Six patients (cases) reported a previous history of blood transfusion compared with thirteen controls. None in both groups admitted to injection drug use, and a minority 12.85% and 22.14% of cases and controls, respectively reported a history of exposure to cat faeces.

Patients (cases) who were older were significantly more likely to be exposed to *T. gondii* infection (29.32 vs 26.88 years, $t = 10.76$, $df = 278$, $P < 0.001$). There were no statistically significant differences between exposed and unexposed patients in terms of duration of untreated illness ($t = -0.107$, $df = 278$, $P = 0.09$) and illness severity as measured by the BPRS ($t = -0.244$, $df = 278$, $P = 0.91$).

Furthermore, there was no significant relationship between, dogs ($P = 0.92$), eaten poorly cooked or raw meat ($P = 0.88$), or diagnostic group ($P = 0.53$) and exposure to *T. gondii*. Though there was a trend towards seropositivity and exposure to cats or cat faeces, this just failed to reach statistical significance ($P = 0.08$) (Table 2). Female participants were significantly more likely to be positive for *T. gondii*

Table 1 Socio-demographic characteristics of patients

Variables	Cases Number (%)	Controls Number (%)
Gender		
Male	84 (60.0)	84 (60.0)
Female	56 (40.0)	56 (40.0)
Employment status		
Employed	48 (34.3)	122 (87.14)
Unemployed	92 (65.7)	–
Student	10 (7.14)	18 (12.86)
Religion		
Christian	122 (87.14)	138 (98.57)
Muslim	12 (8.57)	2 (1.43)
Others	6 (4.29)	–
Current residence		
Urban	100 (71.43)	140 (100)
Rural	40 (28.57)	–
Residence as a child		
Urban	96 (68.57)	78 (55.71)
Rural	44 (31.43)	62 (44.29)
Educational status		
Primary	33 (23.57)	–
Secondary	95 (67.86)	–
Tertiary	22 (15.71)	140 (100)

infection compared to males (OR: 4.6, 95% CI: 2.01–10.68, $P < 0.001$).

Discussion

This is one of very few reports from sub-Saharan Africa that report on the relationship between *T. gondii* infection and severe mental illness. The prevalence of 30.7% obtained for previous exposure to *T. gondii* in this study is within the range of 8% and 53% for similar studies reported in a meta-analysis.¹⁴ This proportion was much higher than the rate of 17.85% in the control arm. Furthermore, the rate of previous *T. gondii* exposure in individuals with severe mental illness was higher than rates obtained from seroprevalence studies from healthy populations in urban and rural districts in Nigeria.^{7,8}

This study found a significant risk of seropositivity for IgG among females. In a survey of women attending an ante-natal facility in Lagos, Nigeria, almost half of them were positive for *T. gondii* infection.¹⁵ This is a worrying find because most of the women we studied were within child bearing age. The risk of congenital anomalies and behavioural disorders in their offspring is a cause for concern. A report from the USA observed that the risk of schizophrenia was higher among adult offspring born to mothers exposed to toxoplasma compared to those who were not exposed.¹⁶

We did not identify any significant relationship between certain risk factors for toxoplasma infection such as exposure to cats and dogs kept as pets and a history of eating poorly cooked or raw meat. It is possible that patients who were interviewed while presenting for the first time had difficulty recalling events in their childhood or caregivers who assisted in providing some information failed to do so correctly. Among pregnant women in Lagos, no significant relationship was seen between *T. gondii* exposure and keeping pets.¹⁵ In Ethiopia, where consumption of raw or poorly cooked mutton is common, rates of toxoplasma infection are much higher.^{17,18}

In contrast to previous reports we did not observe any significant difference in rates of *T. gondii* infection among the diagnostic groups of non-affective psychosis (constituting exclusively of schizophrenia) and affective psychosis (comprising major

depression and bipolar disorders). In a recent study from Iran, toxoplasma infection rates were higher in the schizophrenia group compared to the depression and healthy groups, respectively.¹ Other studies often compare schizophrenia with affective disorders that are not severe. However, in our environment mild to moderate states of affective disorders rarely present to the facility where the study was conducted. Due to late presentations, most cases have become severe with psychotic symptoms in the clinical picture.

A smaller number of cases were seropositive to the IgM antibody for *T. gondii* indicating current infection. This proportion is similar to the study by Hamidinejat¹ and his colleagues from Iran. IgM is poorly consistent with psychotic states and in affected individuals, positivity lasts between 4 and 12 weeks.¹⁹ Perhaps, buttressing the inconsistency in the relationship between IgM seropositivity and psychosis was the fact that cases were significantly less likely to be seropositive compared to apparently healthy controls. One possible reason for the high rate of IgM seropositivity seen in the control arm may be the nature of their jobs which exposes them to infections.

A limitation of this study was the fact that we did not screen for the presence of other viral infections such as the Human Immunodeficiency Virus which increases susceptibility to infection or re-infection with the protozoan *T. gondii*. Secondly, controls were matched only for age and sex and not other socio-economic indices like employment status and educational qualifications. Thirdly, exposure to cats was prone to recall bias, since we determined this by asking cases and controls recall events over their lifetime. Lastly, we studied a non-homogenous sample of patients which included individuals with depression, psychosis, and bipolar disorder and may have limited the study power to detect differences in infection rates according to diagnostic groups.

Conclusion

This study finds that exposure to *T. gondii* infection was common among patients (cases) sampled, with rates significantly higher compared to apparently healthy controls. Current infection was significantly less common among cases compared to controls. *T. gondii* exposure was significantly more common in

Table 2 Risk factors for *Toxoplasma gondii* infection

Variables	Cases		Controls	
	Yes: number (%)	No: number (%)	Yes: number (%)	No: number (%)
Injection drug use	—	140 (100.0)	—	140 (100.0)
Kept cats as pets in childhood	18 (12.85)	122 (87.15)	31 (22.14)	109 (77.86)
Kept cats as pets in adulthood	9 (6.43)	131 (93.57)	18 (12.85)	112 (87.15)
Contact with cat faeces	9 (6.43)	131 (93.57)	16 (11.43)	124 (88.57)
Kept dogs as pets	23 (16.43)	117 (83.57)	42 (30.0)	98 (70.0)
Eaten raw or poorly cooked meat	77 (55.0)	63 (45.0)	100 (71.43)	40 (28.57)

females, and those with a lower level of education and older age. This study did not find strong evidence for an association between toxoplasma infection and pattern of severe mental illness in this environment.

References

- Hamidinejat H, Ghorbanpoor M, Hosseini H, Alavi SM, Nabavi L, Jalali MH, *et al.* *Toxoplasma gondii* infection in first-episode and inpatient individuals with schizophrenia. *Int J Infect Dis.* 2010;14:e978–81.
- Fekadu A, Shibre T, Cleare AJ. Toxoplasmosis as a cause for behaviour disorders – overview of evidence and mechanisms. *Folia Parasitol.* 2010;57(2):105–13.
- Carruthers VB, Suzuki Y. Effects of *Toxoplasma gondii* infection on the brain. *Schizophr Bull.* 2007;33(3):745–51.
- Torrey EF, Bartko JJ, Yolken RH. *Toxoplasma gondii* and other risk factors for schizophrenia: an update. *Schizophr Bull.* 2012;38(3):642–7.
- Webster JP, Lamberton PH, Donnelly CA, Torrey EF. Parasites as causative agents of human affective disorders? The impact of anti-psychotic, mood stabilizer and anti-parasite medication on *Toxoplasma gondii*'s ability to alter host behaviour. *Proc Biol Sci.* 2006;273(1589):1023–30.
- Negash T, Tilahun G, Medhin G. Seroprevalence of *Toxoplasma gondii* in Nazareth Town, Ethiopia. *Cent Afr J Med.* 2007;53(9–12):47–51.
- Uneke CJ, Duhlińska DD, Ngwu BA, Njoku MO. Seroprevalence of *Toxoplasma gondii* infection in Kwal, a rural district of Plateau-Nigeria. *Afr J Med Med Sci* 2007;36(2):109–13.
- Kamani J, Mani AU, Egwu GO, Kumushe HA. Seroprevalence studies of human infection with *Toxoplasma gondii* and the associated risk factors in Maiduguri, Borno State, Nigeria. *Ann Trop Med Parasitol.* 2009;103(4):317–21.
- Sheehan DV, Lecrubier Y, Sheehan HK, Amorim P, Janavs J, Weiller E, *et al.* The Mini International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry.* 1998;59 (Suppl 20):22–33.
- Adewuya AO, Ologun YA, Ibigbami OS. Post-traumatic stress disorder after childbirth in Nigerian women: prevalence and risk factors. *BJOG.* 2006;113:284–8.
- Adewuya AO, Afolabi MO, Ola BA, Ogundele OA, Ajibare AO, Oladipo BF, *et al.* Post-traumatic stress disorder (PTSD) after stigma related events in HIV infected individuals in Nigeria. *Soc Psychiatry Psychiatr Epidemiol.* 2009;44(9):761–6.
- Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychol Rep.* 1962;10:799–812.
- Ohaeri JU, Otote DI. Subtypes and factors of schizophrenia in an acutely ill Nigerian sample. *Psychopathology.* 2003;36:181–9.
- Torrey EF, Bartko JJ, Lun ZR, Yolken RH. Antibodies to *Toxoplasma gondii* in patients with schizophrenia: a meta-analysis. *Schizophr Bull.* 2007;33(3):729–36.
- Akinbami AA, Adewunmi AA, Rabiun KA, Wright KO, Dosunmu AO, Dada MO, Adeyemo TA. Seroprevalence of *Toxoplasma gondii* antibodies amongst women at the Lagos State University Teaching Hospital, Nigeria. *Niger Postgrad Med J.* 2010;17(2):164–7.
- Brown AS, Schaefer CA, Quesenberry CP Jr, Liu L, Babulas VP, Susser ES. Maternal exposure to toxoplasmosis and risk of schizophrenia in adult offspring. *Am J Psychiatry.* 2005;162:767–73.
- Negash T, Tilahun G, Medhin G. Seroprevalence of *Toxoplasma gondii* in Nazaret town, Ethiopia. *East Afr J Public Health.* 2008;5(3):211–4.
- Shibre T, Alem A, Abdulahi A, Araya M, Beyero T, Medhin G, *et al.* Trimethoprim as adjuvant treatment in schizophrenia: a double blind, randomized, placebo-controlled clinical trial. *Schizophr Bull.* 2010;36 (4):846–51.
- Leweke FM, Gerth CW, Koethe D, Klosterkötter J, Ruslanova I, Krivogorsky B, *et al.* Antibodies to infectious agents in individuals with recent onset schizophrenia. *Eur Arch Psychiatry Clin Neurosci.* 2004;254:4–8.