SEROEPIDEMIOLOGY OF TOXOPLASMOSIS IN RENAL PATIENTS

Veeranoot Nissapatorn[1], Teoh Hoe Leong[1], Rogan Lee[2], Init-Ithoi[1], Jamaiah Ibrahim[1] and Tan Si Yen[3]

[1]Department of Parasitology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia; [2]Institute of Clinical Pathology and Medical Research (ICPMR), Westmead Hospital, New South Wales, Australia; [3]Department of Medicine (Nephrology Unit), University of Malaya Medical Center, Kuala Lumpur, Malaysia

Abstract. Toxoplasmosis is an important parasitic disease in immunosuppressed patients. This prospective study was conducted to determine the seroprevalence, associated risk factors and the incidence of clinically confirmed toxoplasmosis among renal patients at the University of Malaya Medical Center, Kuala Lumpur, Malaysia. We interviewed 247 renal patients, each of whom answered an epidemiological questionnaire, and collected blood samples for measurement of anti-*Toxoplasma* IgG and IgM antibodies by ELISA. Overall seroprevalence of latent toxoplasmosis was observed in 126 (51%) renal patients. Race (Malays), marital status (married) and primary level of education, were all factors associated with a greater chance of *Toxoplasma* infection. A case of clinically confirned toxoplasmosis was diagnosed in a renal transplant recipient as a result of immunosuppression. Based on the findings obtained, this preliminary study shows a high prevalence of latent toxoplasmosis in renal patients. Risk factors may have significantly contributed to *Toxoplasma* acquisition in these patients. We recommend further studies be carried out to monitor for trends in toxoplasmosis among immunosuppressed patients.

Keywords: toxoplasmosis, seroepidemiology, renal patients, Malaysia

INTRODUCTION

Toxoplasmosis is a zoonotic disease caused by *Toxoplasma gondii*, an ubiquitous intracellular protozoan parasite. This cosmopolitan parasite is transmitted to humans by ingestion of oocysts shed by cats in the environment, ingestion of undercooked or raw infected meat, transplacentally, and through organ transplantation. Toxoplasmosis is an important parasitic disease in humans which is generally asymptomatic in immunocompetent persons. Toxoplasmosis is the most frequent protozoal opportunistic infection in immunocompromised individuals. Its association with immunosuppression has been known for several decades. Disseminated disease has been observed in solid organ transplant patients (Ferreira and Borges, 2002). Although new infections may be contracted in immunosuppressed

Correspondence: Dr Veeranoot Nissapatorn, Department of Parasitology, Faculty of Medicine, 50603 Kuala Lumpur, Malaysia.
Tel: +603 7967 6618; Fax: +603 7967 4754
E-mail: nissapat@gmail.com, veeranoot@um.edu.my

patients, the most common manifestation is reactivation of a previously latent infection (Wreghitt and Joynson, 2001). *T. gondii* antibody prevalence rates vary greatly by geographic distribution and population among healthy persons (Pordeus *et al*, 2008), pregnant women (Nissapatorn *et al*, 2003), immunocompromised patients, including those with HIV/AIDS (Lindström *et al*, 2006), cancer (Rai *et al*, 2003), end stage renal disease (ESRD) undergoing hemodialysis (Yazar *et al*, 2003) and those having had organ transplantation (Sukthana *et al*, 2001). This impact of *T. gondii* on public health has raised an interest in better understanding of its pathology and consequences. No studies of the clinico-epidemiological aspects of toxoplasmosis in renal patients have been carried out in Malaysia.

This study, therefore, aims to determine the seroprevalence of toxoplasmosis in renal patients, the association between possible and confounding risk factors and *Toxoplasma* seropositivity, and to determine the incidence of clinically confirmed toxoplasmosis in renal patients. This study highlights the significance of this parasitic infection and the need to improve awareness of this parasite and its management in this vulnerable group in this region.

MATERIALS AND METHODS

Patients

A prospective cross-sectional study was conducted at the Department of Medicine (Nephrology Unit), which includes an outpatient clinic, inpatient ward, hemodialysis, and transplantation units of the University of Malaya Medical Center (UMMC), Kuala Lumpur, from May 2007 to March 2008. This study was approved (Ref. No. 552.18) by the ethics committee from this center. The study included 247 eligible subjects who gave informed consent prior to enrollment in the study. Inclusion criteria were: 1) age >15 years, 2) negative anti-HIV antibody serostatus by ELISA technique, and 3) two hundred forty-seven renal patients include 79 patients with renal failure (1 with acute renal failure and 78 with chronic renal failure), 143 patients with end stage renal disease undergoing hemodialysis, 25 renal transplant patients, including 3 new and 22 known cases. Of the 247 renal patients, 184 had secondary causes for their renal failure, including hypertension, diabetes mellitus and heart diseases, 46 had both primary and secondary causes for renal disease, 16 had a primary cause for renal disease, such as systemic lupus erythrematosus (SLE), small kidneys or glomerulonephritis and 1 patient had an unknown cause of renal disease. The duration of the underlying cause in these patients ranged from < 1 year to 30 years, with a median of 10 years.

A questionaire was designed to detect sociodemographic and biologically plausible risk factors for toxoplasmosis, as well as clinical history, presenting signs and symptoms, investigations and treatment outcomes relating to toxoplasmosis. An operational definition was used for the risk factors. Contact with cats was defined as being an owner of at least one cat or coming into close contact with cats through playing with, feeding or sleeping with cats in the house. Consumption of undercooked or raw meat was defined as one who had the habit of eating undercooked meat, such as sausage, sashimi, satay, barbecue or any kind of meat where the method of preparation could not be guaranteed. Blood transfusion was defined as one who had received blood (or blood products) at least 3 months prior to the study period.

Table 1
Seroprevalence of toxoplasmosis in renal patients as assessed by the ELISA test.

ELISA test	Total number of *Toxoplasma* seropositive renal patients = 140 (56.7%)		
	IgG positive	IgM positive	Both IgG and IgM positive
Positive	115 (46.6, 95%CI 40-52)	14 (5.7, 95%CI 3.4-9.3)	11 (4.5, 95%CI 2.5-7.8)
Negative	132 (53.4%)	233 (94.3%)	236 (95.5%)
Total	247	247	247

Serum samples

Approximately 5 ml of venous blood was drawn from a subject then the sera were kept at -20ºC until used.

Detection of IgG and IgM antibodies to *Toxoplasma gondii*

Toxoplasmosis was screened by using a standard ELISA commercial kit (IgG-Trinity Biotech, New York, NY and IgM-Trinity Biotech, New York, NY) in accordance with the manufacturer's instructions and performed at the Department of Parasitology, University of Malaya Medical Center, Kuala Lumpur. A result of >51 IU/ml of anti-*Toxoplasma* IgG antibody was regarded as positive, indicating latent or pre-existing *Toxoplasma* infection; a result >51 IU/ml of anti-*Toxoplasma* IgM antibody was regarded as positive, indicating a recently acquired *Toxoplasma* infection. Anti-*Toxoplasma* IgG and IgM antibodies were used to screen patients with renal disease. In new renal transplant patients, donors were screened for anti-*Toxoplasma* (IgG/IgM) antibodies prior to donation and recipients were screened 1-3 months after transplant.

Statistical analysis

Data obtained from both the questionnaire and laboratory tests were entered, edited and analyzed using the statistical software SPSS version 10 (SPSS, Chicago, IL). The data with quantitative variables were expressed as means (± SD) and ranges, whereas, qualitative variables were estimated and presented as frequencies and percentages. The χ^2 test was chosen to test differences by gender, seroprevalence of toxoplasmosis and determine the association between possible risk factors and disease transmission. Multivariate analysis adjusted by multiple logistic regression was used to determine significant differenes in demographics and confounding risk factors used to determine seropositivity rates among study subjects. A $p < 0.05$ was regarded as statistically significant.

RESULTS

Seroprevalence of toxoplasmosis in renal patients

The seroprevalence of toxoplasmosis in renal patients was found to be 56.7% (140/247) in whom 46.6% (115, 95% CI 40-52) were positive for anti-*Toxoplasma* IgG antibody (latent infection), 5.7% (14, 95% CI 3.4-9.3) were positive for anti-*Toxoplasma* IgM antibody, and the remaining 4.5% (11, 95% CI 2.5-7.8) were positive for both anti-*Toxoplasma* IgG and IgM antibodies, as shown in Table 1.

Seroprevalence of toxoplasmosis in relation to demographic characteristics and risk factors

During this study period, a total number of 247 subjects were recruited

Table 2
The seroprevalence of toxoplasmosis in renal patients by the demographic characteristics.

Characteristic	Renal patients		*p*-value
	Total (*n*, %) *N*=247	*Toxoplasma* positivity[a] (*n*, %) *N*=126	
Age			
Range 21-89 years			
Mean 56.7±13.96 years			
Age group			0.042
21-40	30 (12.2)	9 (30)	
41-60	117 (47.4)	61 (52.1)	
≥61	100 (40.5)	56 (56)	
Sex			0.881
Male	140 (56.7)	72 (51.4)	
Female	107 (43.3)	54 (50.5)	
Race			0.004
Malay	82 (33.2)	54 (65.9)	
Chinese	123 (49.8)	52 (42.3)	
Indian	42 (17.0)	20 (47.6)	
Marital status			0.000
Single	25 (10.1)	4 (16.0)	
Married	222 (89.9)	122 (55.0)	
Address			0.074
Kuala Lumpur	46 (18.6)	18 (39.1)	
Outsider	210 (81.4)	108 (51.4)	
Occupation			0.129
Laborer	8 (3.2)	5 (62.5)	
Non-laborer	45 (18.2)	17 (37.8)	
Unemployed	194 (78.5)	104 (53.6)	
Education			0.04
Primary	107 (43.3)	64 (59.8)	
Secondary	112 (45.3)	51 (45.5)	
Tertiary	28 (11.3)	11 (39.3)	
Past history of drug use			0.333
No drug use	234 (94.7)	117 (50.0)	
Drug related to ATT	5 (2.0)	4 (80.0)	
Drug unrelated to ATT	8 (3.2)	5 (62.5)	
Type of renal diseases			0.04
Renal failure (acute and chronic)	79 (32.0)	41 (51.9)	
End-stage renal disease with hemodialysis	143 (57.9)	78 (54.6)	
End-stage renal disease with renal transplant	25 (10.1)	7 (28)	

[a]Overall seroprevalence of anti-*Toxoplasma* IgG antibody (126, 51%) in the study subjects.

Table 3
The seroprevalence of toxoplasmosis in renal patients by plausible risk factors.

Characteristic	Renal patients		*p*-value
	Total (*n*, %) *N*=247	Toxoplasma positivity[a] (*n*, %) *N*=126	
Contact with cats			0.364
Yes	27 (10.9)	16 (59.3)	
No	220 (89.1)	110 (50.0)	
Consumption of uncooked meat			0.012
Yes	23 (9.3)	6 (26.1)	
No	224 (90.7)	120 (53.6)	
Receiving blood transfusion			0.991
Yes	53 (21.5)	27 (50.9)	
No	194 (78.5)	99 (51.0)	
Drinking water			0.665
Boiled/filtered	16 (6.5)	9 (56.3)	
Pipe/tap/rain	231 (93.5)	117 (50.7)	

[a]Overall seroprevalence of anti-*Toxoplasma* IgG antibody (126, 51%) in the study subjects.

in our study. The age range in renal patients was 21-89 with a mean of 56.7 ± 13.96 years. Majority of the main age group was between 41 and 60 years (117, 47.4%). Majority of these patients were males (140, 56.7%), Chinese (123, 49.8%), married (222, 89.9%), and stayed outside Kuala Lumpur (210, 81.4%). Most were unemployed (194, 78.5%), had received secondary level of education (112, 45.3%). It was found that a large number of renal patients who participated in this study had no history of antibiotic use (234, 94.7%) and were diagnosed having end-stage renal disease with hemodialysis (143, 57.9%). As a single risk factor, this study found that age group, race, marital status, level of education, and type of renal diseases were significantly associated with *Toxoplasma* seroprevalence ($p<0.05$), as shown in Tables 2 and 3. After multi-logistic analysis was applied, it was interesting to find that race (Malay), marital status (married) and primary level of education were identified as significant risks for *Toxoplasma* infection, as shown in Table 4.

A case report of active and disseminated toxoplasmosis in a post-renal transplant recipient

A female patient, born in 1972, had bilateral small kidneys and underwent a first renal transplant from a cadaveric donor, in June 1997; the transplant was a success although part of the operative recovery was complicated by the re-implantation of her ureter from the peritoneum to the bladder. Her graft function was not perfect and she was left with a moderate degree of renal failure and anemia. Immunosuppressive therapy consisted of Prednisolone, FK 506 (tacrolimus), and Myfortic. From 1997-2006, she was regularly followed up (every 2-3 months) and had health problems from time to time, including recurrent urinary tract infec-

Table 4
Multivariate logistic regression analysis for various risk factors associated with *Toxoplasma* seropositive[a] renal patients.

Variable	Adjusted odds ratio (OR)	95% CI		*p*-value
Age ≥ 41 years	0.91	0.31	2.66	0.87
Malays	2.65	1.48	4.74	0.001
Married	5.84	1.62	21.09	0.007
Primary level of education	2.13	1.22	3.72	0.008
End-stage renal disease	0.92	0.52	1.64	0.78

[a]Overall seroprevalence of anti-*Toxoplasma* IgG antibody (126, 51%) in the study subjects. Adjusted variables included age group, race, marital status, level of education, and types of renal disease in this statistical analysis.

tion, nephritis, a vaginal polyp, dengue fever, *E. coli* bacteremia, hypertension and varicella infection. She had multiple blood transfusions and drug allergies. In January 2007, she had 2 weeks of blurred vision of the right eye and 1 week of diarrhea for which she was admitted to this hospital. On funduscopic examination, her right eye had a swollen disc, was hyperemic, had an infiltrate with Roth's spots, and deep retinal necrosis. Physical examination showed no further abnormalities. At this point, foscarnet and ganciclovir were given intravenously due to suspicion of cytomegalovirus (CMV) retinitis. Laboratory examination revealed an elevated creatinine of 265 (nomal value, 62-115 µmol/l), a urea of 20 (normal value, 2.5-6.5 mmol/l), a leukocyte differential of 85% of neutrophils, an erythrocyte sedimentation rate of 42 mm/hr (normal range:, 3-9 mm/hr); PCR assays for CMV and Herpes Simplex were negative. Toxoplasmosis was considered a diagnostic possibility. Serologic testing for *Toxoplasma* antibodies was positive for both IgG and IgM antibodies. A PCR assay for *T. gondii* was positive on a CSF sample. It is not known what the *Toxoplasma* serostatus of the renal transplant donor or the recipient were at the time of transplantation. A positive anti-*Toxoplasma* (IgG) antibody was found on a subsequent serum sample 1 month after treatment. After admission, her clinical condition deteriorated, with one generalized tonic clonic seizure for which phenytoin was given. A computed tomography scan showed no abnormalities. The cerebrospinal fluid (CSF) showed both elevated protein and leukocyte levels (1.27 g/l and 60/ml, respectively). A presumptive diagnosis of toxoplasmosis was made based on clinical features and laboratory evidence. The patient was successfully treated with a combination of clindamycin (600 mg, qid) and Fansidar (1 tab once a week) for 6 weeks. She made a full ophthalmoscopic recovery, including visual improvement, and had only an old scarred lesion but no acute retinitis. Clindamycin, a continuing life-long secondary chemoprophylaxis, was started because of chronic immunosuppression by steroid in this post-renal transplant patient.

DISCUSSION

Overall, the seroprevalence of latent *Toxoplasma* infection was found in more

than half of renal patients, which is not surprising. Malaysia is endemics for toxoplasmosis and has been documented in other high risk patients (Ravichandran *et al*, 1998; Nissapatorn *et al*, 2007). Toxoplasmosis has a high prevalence in other groups of immunosuppressed patients, such as cancer and AIDS patients (Ekweozor *et al*, 1994; Nissapatorn *et al*, 2004). The risk for infection in individual patients depends on two factors: the prevalence of toxoplasmosis in the community and the degree and nature of immunosuppression (Wreghitt and Joynson, 2001). The seroprevalence of *Toxoplasma* infection among ESRD patients on hemodialysis was 31.6%. This prevalence is lower than other studies from different countries: 38.3% in Egypt (Abbas *et al*, 1996) and 56.1-76.5% in Turkey (Yazar *et al*, 2003; Ocak *et al*, 2005). Survelliance should be periodically performed in highly endemic areas to monitor for latent stages of toxoplasmosis and seroconversion among immunosuppressed patients. The prevalence of latent toxoplasmosis was 5.6% in post-renal transplant recipients. There are a few studies reporting the seroprevalence of toxoplasmosis (11% to 67.1%) in renal transplant recipients (Figueiredo *et al*, 1983; Derouin *et al*, 1987; Sukthana *et al*, 2001; Iqba *et al*, 2003; Gourishankar *et al*, 2008). Despite the low prevalence of latent toxoplasmosis among renal transplant recipients, we support routine screening for toxoplasmosis in donors and recipients prior to transplantation to obtain baseline serodiagnosis and evaluate the potential risk for toxoplasmosis after transplantation (Iqba *et al*, 2003).

The seroprevalence of recently acquired toxoplasmosis was low in renal patients. No infections were found in 3 new renal transplant recipients (before or after the transplant) or their donors (prior to the transplant). The risk of donor-acquired toxoplasmosis in renal transplant recipients is much lower than other organ tranplant recipients, such as heart or liver (Wreghitt and Joynson, 2001). The presence of IgM antibodies in a donor is not necessarily a reason to reject the kidneys, but it should lead to close clinical and laboratory monitoring of the recipients to ensure the earliest start of specific treatment if toxoplasmosis is suspected (Renoult *et al*, 1997). Six week prophylactic treatment (Sukthana *et al*, 2001) should be considered as the other option to be given to renal transplant recipients receiving kidneys from a *Toxoplasma* seropositive donor.

An important question is whether risk assessment should play a more important role in screening. A higher rate of toxoplasmosis was found among older patients, which is not surprising due to the fact these patients usually have a well established socioeconomic status leading to greater risk of exposure to *Toxoplasma* than younger patients. *Toxoplasma* infection was more common among Malays than other ethnic groups, especially in those with a lower education level. Close contact with cats as domestic pets is common among these people. Based on the results obtained, there are demographic risk factors for acquiring *Toxoplasma* infection. Health education regarding toxoplasmosis and its consequences need to be given to prevent primary infection among the general population irrespective of their race or socioeconomic status.

More than half the seropositive patients in our study had close contact with cats. These findings are similar to other studies conducted among renal transplant recipients (Sukthana *et al*, 2001) and in HIV-infected patients (Wallace *et al*, 1993; Nissapatorn *et al*, 2001, 2002). This suggests

cats play an important role in transmitting *Toxoplasma* infection. Prevention involves common sense measures, such as adequate hand washing, proper disposal of animal waste, and ensuring that infected cats are diagnosed and treated (Rabinowitz *et al*, 2007) to reduce transmission. Special precautions should be taken in immunosuppressed patients. Only 26% of seropositive patients had eaten uncooked meat. Meat contaminated with *T. gondii* has the potential to spread infection to a large number of people (Magaldi *et al*, 1969; Teutsch *et al*, 1979; Choi *et al*, 1997; Carme *et al*, 2002). Our findings indicate these people generally are well cooked food, include meat. Immunosuppressed patients should follow good personal hygienic in food handling and preparation. Our results show half of seropositive patients received blood transfusions. Blood transfusion is generally not a major cause of *Toxoplasma* transmission, but in endemic areas *Toxoplasma* screening should be considered. When considering blood transfusion for immunocompromised or immunosuppressed patients, it would be wise to exclude those with chronic toxoplasmosis (Al-Amari, 1994). Drinking contaminated water has been implicated as a source of *Toxoplasma* infection in humans worldwide (Martínez Sáchez *et al*, 1991; Ertug *et al*, 2005; Lin *et al*, 2008), and was found in half our seropositive patients. However, there were no statistically significant association between these risk factors and *Toxoplasma* seropostivity in our study. Future studies with a larger sample size are recommened to verify these associations in immunosuppressed patients.

To our knowledge, this is the first study of toxoplasmosis among renal transplant recipients in Malaysia. Toxoplasmosis in patients with renal transplantation has received little attention and remains a rare but serious pathogen in renal transplant recipients (Renoult *et al*, 1997; Barsoum, 2004). The incidence was low in these kidney recipients, coinciding with a low incidence worldwide. Most cases of toxoplasmosis in immunosuppressed patients result from secondary reactivation of latent infection. This patient developed reactivation of toxoplasmosis 10 years after renal transplant, similar to other studies describing infection up to 7 years after transplantation (Da Cunha *et al*, 1994; Aubert *et al*, 1996; Renoult *et al*, 1997; Giordano *et al*, 2002). Only 35 cases of visceral or cerebral toxoplasmosis complicating renal transplantation have been described (Wulf *et al*, 2005). The diagnosis of either focal or disseminated toxoplasmosis is based on the clinical presentations, with routine and specific investigations. It is imperative that clinicians have a high index of suspicion for toxoplasmosis in immunosuppressed patients who present with neurological or ocular symptoms. Serological diagnosis is useful for early screening of *Toxoplasma* serostatus, as seen in this patient before and after treatment. In a patient who was *Toxoplasma* seronegative or has an unknown serostatus (Wulf *et al*, 2005), it does not exclude the diagnosis. Other antibodies, such as IgA and IgE, have emerged as interesting markers for toxoplasmosis in immunosuppressed patients and may provide valuable assistance in the diagnosis, since tests for specific IgM are disappointing (Pinon *et al*, 1995). This patient's diagnosis was confirmed by polymerase chain reaction (PCR) to detect *Toxoplasma* DNA; this method is useful for detecting disseminated disease (Johnson *et al*, 1993; Khalifa *et al*, 1994; Aubert *et al*, 1996; Lewis *et al*, 2002; Wulf *et al*, 2005). This suggests routine serologic testing after organ transplantation should be

backed up by PCR when clinical manifestations are consistent with toxoplasmosis (Aubert *et al*, 1996). The diagnosis of *Toxoplasma* infection is complex because the immune response in these patients is low; clinical awareness of the possiblity of infection is therefore important (Wreghitt and Joynson, 2001). Toxoplasmosis can result in significant morbidity and mortality in immunosuppressed patients. Early diagnosis and treatment, are important in this life-threatening condition. Life-long secondary chemoprophylaxis should be given to prevent recurrence of toxoplasmosis in immunosuppressed patients.

In conclusion, this preliminary study shows a high prevalence of latent toxoplasmosis in renal patients. A case of clinically confirned toxoplasmosis occurred as a result of immunosuppression. We recommend further studies to determine the changing epidemiology of toxoplasmosis in immunosuppressed patients.

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