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TOXOPLASMA GONDII SEROPOSITIVITY IN RENAL PATIENTS: RATE, PATTERN, PREDICTORS AND RELATED MORBIDITY

By

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Abstract:

Infection is a significant cause of morbidity and mortality in patients with chronic kidney disease (CKD) due to their depressed immunity. *T.gondii* is a ubiquitous parasite that causes severe manifestations in immunocomprmised patients. The present study investigated rate, pattern, predictors and related morbidity of *T. gondii* seropositivity in CKD patients. The study included four groups: i-patients on maintenance hemodialysis (HD; n = 60); ii-patients with systemic lupus erythematosus on immunosuppressive therapy for lupus nephritis (SLE; n=30) iii- Renal transplant recipients (RTR; n=30) and iv- healthy controls (HC; n = 30). Anti-*Toxoplasma* IgG, IgM & IgG avidity were determined using enzyme immunoassays. Patients' medical data and information on plausible risk factors for toxoplasmosis were recorded. Results revealed that *T.gondii* seropositivity rates in HD, SLE and RTR groups (61.7, 60 & 70% respectively) were significantly high compared to HC (30 %). Among seropositive patients, 79% of those with negative IgM displayed high IgG avidity confirming past infection. None of IgM positive patients had low IgG avidity. The latter was detected in some IgM negative patients. Multivariate analysis showed that seropositivity was significantly associated with undercooked meat consumption (adjusted OR= 6.256, CI= 2.167-18.056) and blood transfusion (adjusted OR = 5.953, CI= 2.987-11.864). No significant association could be found between *T. gondii* seropositivity and the clinical manifestations of CKD patients.

Keywords: *T. gondii*, chronic kidney disease, IgG avidity, undercooked meat, blood transfusion.

Introduction

Chronic kidney disease (CKD) is an increasingly common medical condition characterized by progressive loss of renal function over a period of months or years (Jha *et al,* 2012). Major causes include diabetes mellitus, hypertension, recurring pyelonephritis and autoimmune disorders such as systemic lupus erythematosus (SLE) (Mahdavi-Mazdeh 2010; El Minshawy 2011). Management of early stage of CKD depends on treatment of underlying causes and associated conditions. In SLE nephritis, cytotoxic drugs combined with steroids are used to preserve renal function. Advanced stages of renal failure require renal replacement therapy, in the form of dialysis or kidney transplantation followed by long term immunosuppressive therapy (Appel *et al,* 2009; Burkhalter *et al,* 2012). The retained uremic toxins as well as hyperparathyroidism, iron accumulation and malnutrition which complicate renal function deterioration induce immune deficiency. Dialysis, transplantation and immunosuppressive therapy cause further impairment of immune functions and increase exposure to and severity of infections (Ison and Nalesnik 2011; Karkar *et al,* 2014).

Toxoplasma gondii is one of the commonest protozoans worldwide with 10-80 % of humans showing seropositivity (Pappas *et al,* 2009). Apart from congenital toxoplasmosis, acquired infection occurs through consumption of undercooked meat (Saleh *et*

al, 2014) and ingestion of infective oocysts dropped from cats (Robert-Gangneux and Dardé, 2012). The host immune status plays a pivotal role in determining the clinical outcome. In primary infection, the parasites display a short stage of rapid asexual multiplication in the form of tachyzoites (Montoya and Liesenfeld, 2004). An interferon gamma cell mediated immune response is critical for signaling parasite differentiation to bradyzoites, the slowly dividing stages. This host immune response is also responsible for elimination of tachyzoites allowing bradyzoites to predominate in diverse locations including the central nervous system and muscle tissue (Skariah *et al,* 2010). The acute stage is followed by formation of tissue cysts where bradyzoites persist long-term in a relatively dormant state (Dubey, 2009). During this latent stage, parasites capable of reinitiating an active infection are periodically released but an efficient immune response ensures their destruction (Denkers and Gazzinelli 1998).Accordingly, toxoplasmosis is generally asymptomatic or is associated with mild, non-specific self-limiting clinical manifestations in immunocompetent individuals. In contrast, a clinically significant disease, either due to primary infection or reactivation, may occur in the immunodeficient patients (Weiss and Dubey, 2009; Scerra *et al,* 2013).

The present study investigated seropositivity for *T. gondii* in terms of rate, pattern, predictors and possible association with the clinical manifestations in CKD patients including those with end stage renal disease on maintenance haemodialysis, SLE patients receiving immunosuppressive therapy for lupus associated nephritis and renal transplant recipients (RTR).

Subjects, Material and Methods

The study was carried out on CKD patients attending the Nephrology Unit of the Medical Research Institute Hospital and the Clinical Pathology Lab., Faculty of Medicine, Alexandria University. Three groups of patients were recruited: GI included 60 patients with end stage renal disease on maintenance hemodialysis; GII comprised 30 SLE patients with lupus nephritis who received steroids and cytotoxic drugs; and GIII enrolled 30 RTR who received immunosuppressive therapy to prevent graft rejection. Also, 30 healthy persons served as controls. The study was approved by the Ethical Committee of the Medical Research Institute, and an informed consent was obtained from each participant after explaining the purpose.

A questionnaire sheet was used to collect basic demographic data (age, sex and place of residence) and information on possible risk factors for toxoplasmosis (contact with cats and consumption of undercooked meat). Thorough clinical examination was performed and patients' medical history was recorded stressing on current symptoms, duration of kidney disease and history of blood transfusion.

Blood samples were collected from all participants, and then sera were separated and kept at -20^{o}C until used for serological testing. The commercially available enzyme immunoassays, BIOCHECK Inc. (California) and VIRO-IMMUN Labor-Diagnostika GmbH (Germany) were used for detection of *T. gondii* specific IgM antibodies and quantitative determination of specific IgG respectively. Analyses were performed as instructed by the manufacturers. With each batch of samples tested for IgG, 4 calibrators of known IgG concentrations (10, 50,100, 200 IU/ml) were included. The Cut-off value was defined as the optical density (OD) value of calibrator 1(10IU/ml). Sample with OD values >Cut-off value+10% were considered positive. Serum IgG level of positive samples were determined by comparison with a standard curve using calibrators 1-4. In IgM assay, a cut-off calibrator was included in each run. *Toxoplasma* IgM Index of tested samples was determined by dividing the sample OD value by the cut-off calibrator OD value. Results were defined as follow: index values ≥1, positive; index val-

ues 0 to < 1, equivocal; index values <0.9, negative.

All IgG-positive sera were tested by using IgG avidity assay (VIR-ELISA *Toxo*-IgG avidity, Labor-Diagnostika GmbH, Germany) according to the manufacturer' instructions. Samples with IgG level higher than 100 IU were diluted 1:10 prior to the test. Each sample was tested in two wells. After the initial incubation, the avidity reagent (urea) was added to one of the wells to disrupt low avidity complexes. The avidity index (AI) was finally determined by the percent ratio calculated between the OD of the well treated with urea and the OD of the other well. Interpretation was as follows: <35, low avidity; 35 – 40, equivocal avidity; >40, high avidity.

For validation of the results, positive and negative controls were included in all assays performed.

Statistical analysis: Data analysis was performed using Statistical Package for Social Sciences (SPSS) (SPSS Version 17.0: 2006, SPSS Inc., Chicago, IL, USA). Comparison of frequencies among groups was performed using Chi-square or Fisher's exact test. Normality of quantitative variables was tested by the Kolmogrov-Smirnov test. Levels of IgG were presented as medians and range. Kruskal-Wallis test was used for comparison of IgG levels in more than 2 groups and Mann-Whitney U test for comparison of 2 independent groups. A *P* value less than 0.05 was considered statistically significant. Univariate analysis was used to determine risk factors for *Toxoplasma* seopositivity among CKD patients. Odds ratio (OR) and 95% confidence interval (CI) were used to calculate the ratio of the odds of an event occurring in one risk group to the odds of it occurring in the non- risk group. Multivariate logistic regression analysis was performed to calculate adjusted OR and to identify independent risk factors. All variables that were significant in the univariate analysis were included in this model.

Results

In the present study, anti-*Toxoplasma* antibodies (IgG and/or IgM) were detected in 76 out of 120 renal patients. *T.gondii* seropositivity was significantly greater in CKD patients compared to controls (63.3% vs. 30%) with RTR displaying highest positivity (70%, $p<0.05$) followed by haemodialysis (61.7%, $p<0.01$) and then SLE (60%, $p<0.05$).

The majority of positive patients (88.2%) were IgG seropositive and IgM seronegative, while 7.9% were seropositive for both antibodies. IgM antibodies were detected only in SLE patients and RTR. There was no statistically significant relation between IgG avidity and IgM antibodies; 10.5% of patients with no detectable IgM displayed IgG antibodies of low avidity compared to none of IgM seropositive patients. All seropositive controls (n=9) were IgM negative and IgG was of low avidity in 2 individuals.

Anti-*Toxoplasma* IgG concentration (IU/ml) was higher among CKD patients (median= 198.89 & range=32.33-607.82) compared to controls (median=102.63 & range=17.69-418.14), but without significant difference ($p= 0.091$). The median value of IgG concentration was lower in RTR (172.9) compared to haemodialysis (244.43) and SLE patients (259.72). The difference between the three groups of CKD patients was not statistically significant ($p=0.087$).

In the present study, the older age group (>50 years) displayed significantly higher risk *T.gondii* seropositivity compared to those under 30 years (OR=5.077, P= 0.033). Patients consuming undercooked meat had 5.83 higher risk compared to those eating well cooked meat ($P < 0.001$). The long duration of kidney disease (≥ 2 years) increased significantly the risk of *T. gondii* positivity (OR=11.842, CI= 1.376-101.935). Besides, blood transfusion one or two times resulted in significantly high risk of positivity (OR =8.782, CI=3.231-23.869), the risk was higher with more number of blood transfusion (OR=24.626, CI =9.378-64.666).

Multivariate logistic regression was performed to show variables which still had statistically significant association with *Toxoplasma* positivity after adjusting for other variables. Independent predictors of *Toxoplasma* positivity in CKD patients were eating undercooked meat (adjusted OR= 6.256, CI= 2.167- 18.056, p<0.001) and blood transfusion (adjusted OR= 5.953, CI= 2.987-11.864, p<0.001).None had lymphadenopathy or signs suggestive of CNS involvement and there was no significant association between *Toxoplasma* positivity and presence of fever, headache, dyspnea, fatigue or blurring of vision in CKD patients. Details are in tables (1 to 5) and Fig. (1).

Table 1: *Toxoplasma* seropositivity in patients with CKD and controls

Participants group	No. (%)
Haemodialysis (n=60)	37 (61.7)**
SLE (n=30)	18(60.0)*
RTR (n=30)	21(70.0)**
Total CKD (n=120)	76(63.3)**
Control (n= 30)	9 (30.0)

SLE: Systemic lupus erythematosus; RTR: renal transplant recipients; CKD: chronic kidney disease.
* (p<0.05) and ** (p<0.01) in comparison to control group using Chi-square test.

Table 2: Pattern of *Toxoplasma* seropositivity in CKD patients based on IgG, IgM and IgG avidity

Anti-*Toxoplasma* IgG&IgM	IgG avidity	CKD patients			
		Haemodialysis	SLE	RTR	Total
Positive IgG and negative IgM	Low	3 (8.1)	3 (21.4)	1 (6.3)	7(10.45)
	Equivocal	4 (10.8)	2 (14.3)	1 (6.3)	7(10.45.)
	High	30 (81.1)	9 (64.3)	14 (87.4)	53(79.1)
	Subtotal*	37(100)	14 (77.8)	16 (76.2)	67 (88.2)
Positive IgG and positive IgM	Equivocal	0	0	1 (25)	1(16.7)
	High	0	2 (100)	3 (75)	5(83.3)
	Subtotal*	0	2 (11.1)	4 (19.0)	6 (7.9)
Negative IgG and Positive IgM	-	0	2(11.1)	1(4.8)	3(3.9)
Total positive	-	37 (100.0)	18 (100.0)	21 (100.0)	76(100)

SLE: Systemic lupus erythematosus; RTR: renal transplant recipients; CKD: chronic kidney disease.
*Percentage calculated from the total number of seropositive patients in each CKD group

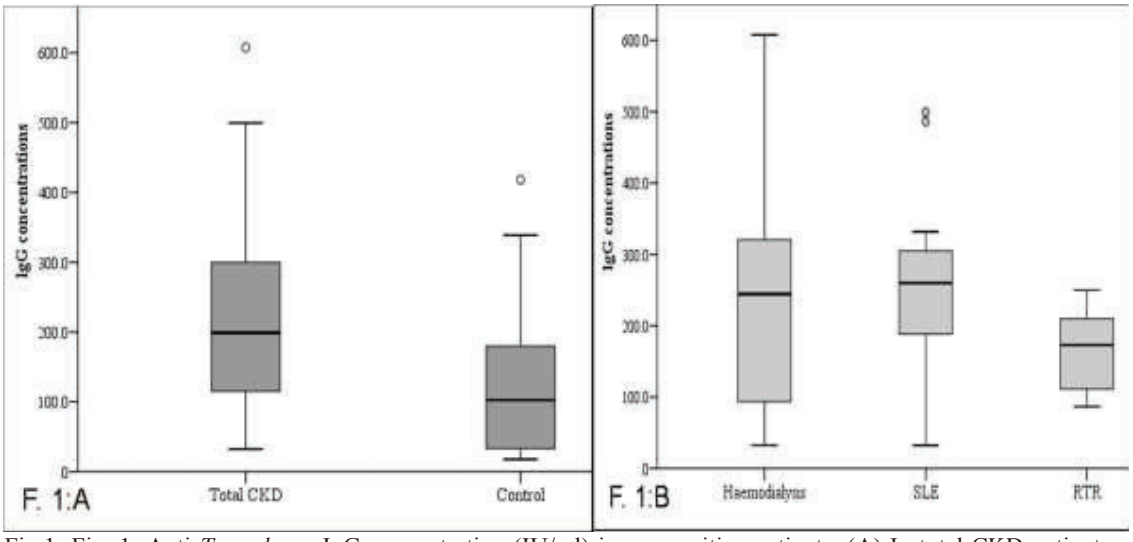

Fig.1: Fig. 1: Anti-*Toxoplasma*IgG concentration (IU/ml) in seropositive patients: (A) In total CKD patients an controls, Mann Whitney test, p=0.091; CKD: chronic kidney disease. (B) In different groups of CKD patients, Kruskal Wallis test, p= 0.087. SLE: Systemic lupus erythematosus; RTR: renal transplant recipients.

Table 3: Univariate analysis of predictors of *Toxoplasma* seropositivity among 120 CKD patients.

Characters		CKD patients examined	Seropositive patients		OR	95% CI	p
			No.	%			
Age	<30	48	26	54.2	1	-	
	30 – 50	58	38	65.5	1.608	0.734-3.523	0.234
	>50	14	12	85.7	5.077	1.024-25.171	0.033*
Gender	Male	59	38	64.4	1	-	
	Female	61	38	62.3	0.913	0.434- 1.920	0.810
Residence	Urban	88	58	65.9	1.504	0.658-3.434	0.332
	Rural	32	18	56.3	1	-	
Contact with cats	Yes	21	16	76.2	2.080	0.705 – 6.138	0.178
	No	99	60	60.6	1	-	
Uncooked meatconsumption	Yes	58	48	82.8	5.83*	2.503- 13.571	
	No	62	28	45.2	1	-	<0.001*
Duration of CKD	<2 years	7	1	14.2	1	-	
	≥2 years	113	75	66.4	11.842*	1.376-101.935	0.006*
Number of Blood transfusion	0	28	3	10.7	1	-	
	1-2	30	20	66.7	8.782*	3.231-23.869	<0.001*
	>2	62	53	85.5	24.626*	9.378-64.666	<0.001*

OR: odds ratio, CI: confidence interval, CKD: chronic kidney disease.

Table 4: Multivariate analysis of predictors of *Toxoplasma* seropositivity among 120 CKD patients.

Variables	Adjusted OR	95% CI	P
Age (>50)	1.488	0.658-3.368	0.340
Consumption of uncooked meat	6.256*	2.167-18.056	0.001*
Blood transfusion	5.953*	2.987-11.864	<0.001*
Duration of CKD	1.396	0.421-4.626	0.585

OR: odds ratio, CI: confidence interval; CKD: chronic kidney disease.

Table 5: Association of *Toxoplasma* seropositivity with symptoms among renal patients.

Symptoms	*Toxoplasma* serology						p
	Negative (n = 44)		Positive (n = 76)		Total (n = 120)		
	No.	%	No.	%	No.	%	
Fever	17	38.6	22	28.9	39	32.5	0.275
Headache	19	43.2	42	55.3	61	50.8	0.202
Dyspnea	6	13.6	10	13.2	16	13.3	0.941
Fatigue	20	45.5	43	56.6	63	52.5	0.240
Blurring of vision	20	45.5	36	47.4	56	46.7	0.840
Asymptomatic	10	22.7	18	23.7	28	23.3	0.905

P values calculated using Chi square test

Discussion

Physicians' awareness of infections in CKD patients, identification of patients at risk and close monitoring can improve the outcome (Dalrymple and Go, 2008; Malhotra *et al,* 2012). Being responsible for significant morbidity and mortality in immunocompromised patients, the protozoan parasite, *T. gondii* has been recognized as an opportunistic organism of serious concern for the medical community (Scerra *et al,* 2013).

In the present study, significantly higher rates of *Toxoplasma* seropositivity were observed in different groups of CKD patients compared to healthy controls. The detected rates are also relatively high compared to those reported recently among groups of healthy persons in Egypt (El-Nahas *et al,* 2014; El-Tantawy *et al,* 2014). Results of the present study are consistent with earlier reports documenting great susceptibility of CKD patients to toxoplasmosis and other opportunistic infections (Seyrafian *et al,* 2006; Saki *et al,* 2013). This can be related to pervasive immune defects induced by the disease itself and by iatrogenic immunosup-

pressive therapy in RTR and SLE patients (Vaziri *et al,* 2012). In addition, transmission of *T. gondii* through solid organ transplantation (Barsoum, 2006; Campbell *et al*, 2006; Robert-Gangneux and Dardé, 2012) may have partially contributed to the relatively high percentage of seropositivity observed in RTR. Although hemodialysis itself exposes the patients to bacterial infection through vascular access and extra-corporeal circuit (Karkar *et al,* 2014), the implication of these procedures to transmission of *T. gondii* has not been documented. In Egypt, Abbas *et al*. (1996) studied the prevalence of *T. gondii* and cytomegalovirus (CMV) antibodies in patients with CKD with and without haemodialysis. They found high percentages of positivity for *Toxoplasma* and CMV antibodies in CKD patients undergoing haemodialysis and this correlated to the number of the dialysis sessions. They recommended that CKD patients undergoing haemodialysis must be screened for *Toxoplasma* and cytomegalovirus before dialysis to prevent the dissemination of these infections via dialysis procedure.

Quantitive ELISA testing showed that the median level of anti-*Toxoplasma* IgG concentration in CKD patients was high compared to that of healthy controls. Moreover, RTR had the lowest IgG level but this did not reach statistical significance. In immunocompromised patients infected with *T. gondii*, reactivation may induce antibody rebound, even without clinical manifestations (Correa *et al,* 2007). So, CKD patients especially those receiving immunosuppressive drugs had impaired ability to mount an efficient antibody response (Beaudreui *et al,* 2011).

The IgM and IgG avidity have important implication in timing *Toxoplasma* infection (Robert-Gangneux and Dardé, 2012). In the present study, IgG antibodies of high avidity were detected in 79% of IgM seronegative infected patients confirming past infection. IgM was detected in some patients with high avidity index while low avidity antibodies were found in IgM negative ones. This agreed with Montoya *et al.* (2002) who reported high avidity antibodies in 75% of IgM positive sera. Wulf *et al.*(2005) descried a RTR with primary toxoplasmosis in whom IgG avidity was still low at a time when IgM was no longer detected. Such discrepancy between IgM serology and avidity tests as markers of recent infection might be due to the fact that IgM antibodies persist for long periods after acute phase of infection in some individuals (Gras *et al,* 2004). Besides, low to high avidity switching varied considerably between persons and low avidity persisted for months to more than one year especially in immunocompromised patients (Lutz *et al,* 1994; Montoya *et al,* 2002; Wulf *et al,* 2005). This supports the concept that determination of the infection status of toxoplasmosis whether acute or latent should ideally depend on the combination of more than one serological assay. In this regard, seropositivity to IgM alone is not usually considered an acceptable criterion for acute infections and simultaneous detection of IgM and low avidity IgG antibodies has the highest predictive value (Siddiqui *et al,* 2014). Accordingly, recent infection with *T. gondii* could not be confirmed in any of the studied CKD patients.

Data of the present study indicated lack of significant relation between *T. gondii* infection rates and patients' sex or place of residence. Several studies confirmed similar exposure to the sources of infection (Studenicová *et al,* 2006; Aboelhadid *et al,* 2013; Bayani *et al,* 2013). On the other hand, detection of *T. gondii* antibodies was positively linked to old age and long duration of kidney disease in the univariate analysis. However, both were identified as independent predictors of *Toxoplasma* positivity in the multifactorial analysis. The increase in *T. gondii* seroprevalence with age was attributed to greater opportunity to contract infection (Abu-Madi *et al,* 2010; Robert-Gangneux and Dardé, 2012). Likewise, longer duration of kidney disease was asso-

ciated with more marked deterioration of immune functions, repeated blood transfusion and prolonged exposure to *Toxoplasma* infection. This agreed with Bayani *et al.* (2013) who reported higher seroconversion rate (80%) in seronegative haemodialysis cases reassessed one year later compared to a healthy volunteers (11.1%). Aufy *et al*. (2009) found that 85.7% of anti-*Toxoplasma* IgM seropositive renal transplant recipients were detected one year post-transplantation and 14.3% of cases after the first year of transplantation.

In the present study, no association was found between contact with cats and *T. gondii* positivity while undercooked meat consumption was a significant independent risk factor for infection. The increased consumption of undercooked meat served in fast-food enhances exposure to infection in people who prefer this type of food (Fu *et al,* 2014). Environmental contamination by oocysts excreted in cat faeces and poor sanitation contribute substantially to acquiring *T. gondii* infection even in those who are not in contact with cats (Boyer *et al,* 2012).

In the present work, a positive history of blood transfusion was a significant risk factor for seropositivity in the univariate analysis. The potential of transmitting toxoplasmosis to susceptible immunosuppressed recipients through whole blood or leukocyte transfusion was previously suggested (Siegel *et al,* 1971; Steele 2012). *Toxoplasma* seroprevalence in the blood donors was studied worldwide (Galvan *et al*, 2005; Sarkari *et al,* 2014). Elsheikha *et al.* (2009) highlighted the prevalence among Egyptian blood donors and focused on possible risk factors.

The patients with defective immunity are at risk of developing severe manifestations of toxoplasmosis; primary infection can be disseminated and latent infection is liable to reactivation. The most frequently involved organs are the brain, the lungs and the eyes. The disease severity is related to the level of immunosuppression (Weiss and Dubey, 2009). In the present study, none of seropositive patients had lymphadenopathy or neurologic signs. In addition, symptoms such as fatigue, headache, blurring of vision, fever and dyspnea were not more frequently recorded in comparison to seronegative patients. Similar results were reported by Mahgoub *et al.* (2009). A potential explanation is that the clinical manifestations of toxoplasmosis in immunosuppressed patients are mostly non-specific and indistinguishable from those of the underlying disease. CKD patients are susceptible to many other infections with overlapping symptoms (Wulf *et al,* 2005; Dalrymple and Go 2008). Frank disease attributable to *Toxoplasma* dissemination or reactivation was rare; a multicenter study showed the identification of active toxoplasmosis in 0.08% of 7709 kidney recipients (Fernàndez-Sabé *et al,* 2012). Noteworthy, clinically evident toxoplasmosis can develop up to ten years following transplantation (Nissapatorn *et al,* 2011). Despite being rare, early diagnosis and treatment are important in this life-threatening condition.

Conclusion

Patients with CKD are at increased risk of *T. gondii* seropositivity. Consumption of undercooked meat and blood transfusion are important predictors of seropositivity. Neither IgM nor low IgG avidity detection can be used singly to confirm recent infection with *T. gondii*.

No association could be found between *Toxoplasma* seropositivity and the clinical manifestations in CKD patients.

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