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Original paper

The effect of toxoplasmosis on renal function in hemodialysis patients

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ABSTRACT. *Toxoplasma gondii* is an obligate intracellular protozoan parasite; it spreads via the circulatory system during infection and causes chronic infection in various organs. Toxoplasmosis affects nearly one third of people worldwide, especially immunocompromised people. This study aimed to determine the effect of toxoplasmosis on renal function in hemodialysis patients. Overall 300 patients referred to the Medical City, Al-Karama General Hospital, Baghdad, Iraq were enrolled from 2021 to 2022. All serum samples were tested for *T. gondii* immunoglobulins (IgG and IgM) antibodies, urea and creatinine levels. In patients undergoing hemodialysis, the results revealed a high positivity percentage for anti-*Toxoplasma* IgG. In hemodialysis patients infected with *T. gondii*, the urea and creatinine levels were higher than the controls. The mean urea level was high in hemodialysis patients infected with toxoplasmosis compare with hemodialysis patient without toxoplasmosis in different gender and age while the level of creatinine had no significant differences in hemodialysis patient with or without toxoplasmosis. These finding suggest that the incidental rate of toxoplasmosis could be considered as an indication to the high risk of hemodialysis patients.

Keywords: toxoplasmosis, hemodialysis, urea, creatinine

Introduction

Toxoplasma gondii is an obligate intracellular protozoan parasite; it is a unicellular eukaryote that survives by living in host cells [1]. *T. gondii* has long been thought to be the only taxonomic species in the genus *Toxoplasma* [2]. This parasite has complex life cycle. It has both sexual and asexual phases in its life cycle where sexual reproduction occurs in intermediate host [3] and cats are the only animals that go through the sexual life cycle, making them the ”definitive” hosts that eventually shed millions of oocysts containing four sporozoites [1]. The severity of *T. gondii* infection depends on the patient’s immunological status. In immuno-competent people, it is typically asymptomatic. The age and immune condition of the patient determine the clinical manifestations of toxoplasmosis [4]. Pregnant women and people with impaired immune systems are much more likely to contract *T. gondii* infection than healthy people. In people with impaired immune systems, a previously acquired latent infection can reactivate toxoplasmosis with encephalitis. Toxoplasmic encephalopathy and extensive toxoplasmosis have been observed in patients with immunodeficiency due to a variety of conditions, including Hodgkin’s disease or immunosuppressive therapy for various cancers [5]. Urea as the main nitrogenous waste product of metabolism, urea is produced when proteins are broken down. It is almost entirely removed from the body by the kidneys through urine, and measurement of its concentration, initially in urine and afterwards in blood, has been used clinically for more than 150 years to evaluate kidney (renal) function [6]. The most prevalent screening test for renal failure is serum creatinine. Creatinine was more sensitive in detecting severe renal failure, but only 45.5 percent of the time [7]. Due to immune system dysfunctions such phagocytosis, chemotaxis, and the complement system in hemodialysis patients, these patients are categorized as immunocompromised. These persons are consequently more vulnerable to opportunistic infections like *T. gondii* [8].

Table 1. The serological examination of anti-*T. gondii* antibodies IgG and IgM in studied subjects

Antibodies	Control	No %	HD	No %	Chi-square
IgG (+)	39	39%	114	38%	36.76 **
IgG (-)	61	61%	186	62%	63.25 **
IgM (+)	0	0%	6	2%	2.09 NS
IgM (-)	100	100%	294	98%	95.52 **
Chi-square	–	41.83 **	–	37.05**	–

** ($P \leq 0.01$)

Materials and Methods

Subjects and blood collection

This study was permitted by the Ethical Committee of Iraqi Ministry of Health, in which 300 blood samples were enrolled in this study and their age was between (20–70 years old). One hundred samples were taken from outpatient clinics as control groups and two hundred samples hemodialysis patients (HD) from Al-Karama Hospital and Medical City in Baghdad, Iraq. Samples of 5 ml blood were taken from patients' vein. The samples were collected in sterilized Gel Clot activator vacuum tubes and left for 10 min at room temperature for clotting. Then, the samples were centrifuged at 3000 round per minute for 5 min then dispensed into Eppendorf tubes and stored at –20ºC until the test day (Reference No. CSEC/1021/0101).

Serological tests

Specific IgG antibodies were measured using commercial *Toxoplasma* IgG and IgM EIA Test Kit (ACON Laboratories, Inc. USA) (I231-1101) (I231-1101) based on the principle of ELISA. The blood urea and serum creatinine were measured by using spectrophotometer according to the manufacturing guidelines. The measurement ranges of the assay for urea was 15–45 mg/dl and serum creatinine for male 0.6–1.1 mg/dl while female 0.5–0.9 mg/dl.

Statistical analysis

The Statistical Analysis System-SAS (2012) program was used to show the effect of difference factors in study parameters. Chi-square test was used to significant compare between percentage and least significant difference – LSD test was used to significant compare between means in this study with values of $P<0.05$ and 0.01 considered statistically differences.

Results

Anti-T. gondii antibodies IgG and IgM in hemodialysis patients (*HD*) *and control group*

According to this study result, the percentage of seropositive of anti-*Toxoplasma* IgG in HD patient was 38% compare to the control group which was 39%; there were no positivity rates for anti-*Toxoplasma* IgM in control group while the

Table 2. Age distribution of positive cases of toxoplasmosis in HD patients

Age	Control		HD patients		*P*-value
	Toxo (–ve)	Toxo (+ve)	Toxo (–ve)	Toxo (+ve)	
21–30	23(38%)	9(23%)	14(8%)	8(7%)	0.0036 **
31–40	15(25%)	11(28%)	19(10%)	9(8%)	0027 *
41–50	8(13%)	8(21%)	2614(%)	17(15%)	00063 **
51–60	6(10%)	7(18%)	54(29%)	27(24%)	0.0051 **
61–70	9(15%)	4(10%)	73(39%)	53(46%)	0.0001 **
Total	61	39	186	114	0.0001 **
P-value	0.0001**	0.038 *	0.0001**	0.0001**	–

* ($P \leq 0.05$), ** ($P \leq 0.01$)

Table 3. The mean levels of anti-*Toxoplasma* IgG in different gender of studied subjects

Gender	Control		HD patients		*P*-value
	Toxo (–ve)	Toxo (+ve)	Toxo (–ve)	Toxo (+ve)	
Male	16(26%)	9(23%)	106(57%)	54(47%)	0.0001 **
Female	45(74%)	30(77%)	80(43%)	60(53%)	0.0001 **
Total	61	39	186	114	0.0001 **

** ($P \leq 0.01$)

Table 4. The mean levels of blood urea in control groups and HD patient according to toxoplasmosis

Studying groups	Blood urea mg/dl		
	Toxo (–ve)	Toxo (+ve)	*P*-value
Control	27.032±1.25	32.589±1.04	0.407 NS
HD	151.967±13.98	161.149±14.23	0.216 NS
P-value	0.0001 **	0.0001 **	–

** ($P \leq 0.01$)

Table 5. The blood urea means levels in males of HD patients according to toxoplasmosis

Studying groups	Blood urea mg/dl		
	Toxo (–ve)	Toxo (+ve)	*P*-value
Control	27.625±1.05	37.21±1.45	0.084 NS
HD	162.1509±14.8	169.75±9.7	0.174 NS
P-value	0.0001 **	0.0001 **	–

** ($P \leq 0.01$)

Table 6. The blood urea means levels in females of HD patients according to toxoplasmosis

Studying groups	Blood urea mg/dl		
	Toxo (–ve)	Toxo (+ve)	*P*-value
Control	26.822±0.85	31.677±1.13	0.348 NS
HD	143.375±11.93	153.40±8.45	0.336NS
P-value	0.0001 **	0.0001 **	–

** ($P \leq 0.01$)

positivity rates for anti-*Toxoplasma* IgM among the HD patient was (2%) (Tab. 1).

The incidence rate of toxoplasmosis in HD patient in different ages

In this study, the age range of HD patients was 20–70 years old. Table 2 summarized the distribution of toxoplasmosis infection in HD patients with different ages. The high rate of toxoplasmosis infections in HD patients which are seropositive to anti-*T. gondii* IgG was in the age group 60–71 years old which was 46.00%, followed by age 51–60 which was 24.00%, 41–50 years old which was 15.00%, 31–40 years old which was 8.0% and age 21–30 which was 7.0%.

The mean levels of anti-Toxoplasma IgG in different gender of the studied subjects

According to the test, 114 of the HD patients' samples were seropositive to anti-*T. gondii* (the female was 60 samples and male was 54). The seropositive of toxoplasmosis in female with HD was (52.00%) with statically significant differences ($P \leq 0.01$) and in male was (48.00%) with statistically significant differences ($P \leq 0.01$) (Tab. 3).

The mean levels of blood urea in control groups and HD patient according to toxoplasmosis

According to the mean levels of urea in control group (27.032±1.25 mg/dl) that consider non-significant normal range for urea 15–45 mg/dl. Blood urea levels were different between the group's case and the control; the highest mean level of urea appear in HD patients that infected by toxoplasmosis (161.149±14.23 mg/dl) with statistically significant differences while in patients not infected with *T. gondii* was (151.967±13.98 mg/dl) (Tab. 4).

The mean levels of blood urea in patients with different gender of HD patients according to toxoplasmosis

According to the mean levels of urea in males and females with HD patients infected with *T. gondii*, the lowest mean levels of urea was in females (153.40±8.45 mg/dl), and in males was (169.75±9.7 mg/dl) (Tab. 5 and 6).

The mean levels of blood urea in different age of HD according to toxoplasmosis

The different age of HD patients that may have effect on the level of IgG antibody to *T. gondii* in HD patients was investigated. The result showed

Table 7. The mean levels of blood urea in different age of HD according to toxoplasmosis

Age	Control		HD patients		*P*-value
	Toxo (–ve)	Toxo (+ve)	Toxo (–ve)	Toxo (+ve)	
21–30	22.65±1.35	28.55±1.24	142.0±7.45	160.7±13.4	0.0001 **
31–40	28.733±1.83	30.27±1.72	149.12±12.4	143.3±11.8	0.0001 **
41–50	27.43±1.07	32.37±1.66	169.61±13.6	137.8±9.42	0.0001 **
51–60	30.83±1.52	37.11±2.07	152.48±11.08	184.5±16.4	0.0001 **
61–70	37.77±1.87	41.50±2.05	170.2±14.6	190.7±13.8	0.0001 **
P-value	0.0094 **	0.0089 **	0.0367 *	0.0084 NS	–

* ($P \leq 0.05$), ** ($P \leq 0.01$)

Table 8. The mean levels of serum creatinine in control groups and HD patient according to toxoplasmosis

Studying groups	Serum creatinine mg/dl		
	Toxo (–ve)	Toxo (+)	*P*-value
Control	0.514±0.06	0.625±0.02	0.804 NS
HD	7.940±0.53	10.03±0.64	0.319 NS
P-value	0.0001 **	0.0001 **	–

** ($P \leq 0.01$)

Table 9. The serum creatinine mean levels in males of HD patients according to toxoplasmosis

Studying groups	Serum creatinine mg/dl		
	Toxo (–ve)	Toxo (+ve)	*P*-value
Control	0.553±0.08	0.71±0.03	0.791 NS
HD	8.76103±0.57	10.1944±0.62	0.503 NS
P-value	0.0001 **	0.0001 **	–

** ($P \leq 0.01$)

Table 10. The serum creatinine mean levels in females of HD patients according to toxoplasmosis

Studying groups	Serum creatinine mg/dl		
	Toxo (–ve)	Toxo (+ve)	*P*-value
Control	0.502±0.03	0.609±0.08	0.803 NS
HD	7.781±0.25	9.136±0.73	0.419 NS
P-value	0.0001 **	0.0001 **	–

** ($P \leq 0.01$)

that the higher mean titer was in (61–70) year that are seropositive to anti-*Toxoplasma* IgG which was 190.7±13.8 mg/dl followed by (51–60) year that is seropositive to anti-*T. gondii* IgG mean titer 184.5±16.4 mg/dl and then followed (21–30) year by that is seropositive to anti-*T. gondii* IgG which was 160.7±13.4 mg/dl and then followed (31–40) year by that is seropositive to anti-*T. gondii* IgG which was 143.3±11.8 mg/dl and finally the (41–50) year that is seropositive to anti-*T. gondii* IgG and the mean titer was 137.8±9.42 mg/dl (Tab. 7).

The mean levels serum creatinine in control groups and HD patient according to toxoplasmosis

According to the mean levels of serum creatinine in control group was (0.625±0.02 mg/dl) that consider non-significant normal range for urea 0.4–1.1 mg/dl. Serum creatinine levels were different between the group's case and the control; the highest mean level of creatinine appear in HD patients that infected by toxoplasmosis (10.03±0.64 mg/dl) with statistically significant differences while in patients not infected with *T. gondii* was (7.940±0.53 mg/dl) (Tab. 8).

The mean levels of serum creatinine in patients with different gender of HD patients according to toxoplasmosis

According to the mean levels of serum creatinine in males and females with HD patients infected by *T. gondii*, the lowest mean levels of serum creatinine was in females (9.136±0.73 mg/dl), and in males was (10.1944±0.62 mg/dl) (Tab. 9 and 10).

The mean levels of serum creatinine in different age of HD according to toxoplasmosis

The result showed that the higher mean titer was in (61–70) year that are seropositive to anti-*Toxoplasma* IgG which was 190.7±13.8 mg/dl followed by (51–60) year that is seropositive to anti-*T. gondii* IgG mean titer 184.5±16.4 mg/dl and then followed (21–30) year by that is seropositive to anti-*T. gondii* IgG which was 160.7±13.4 mg/dl and then followed (31–40) year by that is seropositive to anti-*T. gondii* IgG which was 143.3±11.8 mg/dl and finally the (41–50) year that is seropositive to anti-*T. gondii* IgG and the mean titer 137.8±9.42 mg/dl (Tab. 11).

Table 11. The mean levels of serum creatinine in different age of HD according to toxoplasmosis

Age	Control		HD patients		*P*-value
	Toxo (–ve)	Toxo (+ve)	Toxo (–ve)	Toxo (+ve)	
21–30	0.43±0.08	0.62±0.07	8.9±0.52	9.16±0.63	0.0001 **
31–40	0.52±0.06	0.53±0.02	8.3±0.46	9.41±0.57	0.0001 **
41–50	0.61±0.08	0.68±0.06	9.12±0.61	10.22±71	0.0001 **
51–60	0.60±0.04	0.71±0.06	9.5±0.67	10.73±0.74	0.0001 **
61–70	0.80±0.06	1.2±0.08	10.2±0.72	11.52±0.81	0.0001 **
P-value	0.0061 **	0.0084 **	0.089 NS	0.061 NS	–

* ($P \leq 0.05$), ** ($P \leq 0.01$)

Discussion

In immunocompromised patients, toxoplasmosis can be severe and it is considered as a serious disease in which the reactivation of a dormant infection can be fatal. The prevalence and concentration of IgG antibodies may influence the incidence of reactivated toxoplasmosis [9]. Patients with chronic renal failure gradually become immunocompromised. In uremic renal failure patients, humoral and cellular immunity are suppressed and, in such patients, weakened cell functions have been reported. Absolute number of circulating T-cells will reduce and suppressor cells increase, so that hemodialysis is unable to restore the impairment of the immune system [10]. The parasitic with *T. gondi* infection considers the most frequent protozoan causing opportunistic infections in immunocompromised individuals. As it is evident, the patients undergoing hemodialysis are considered to be immunocompromised, mainly due to immune response dysfunctions regarding phagocytosis, chemotaxis, and the complement system [11]. In this study, the percentage of seropositive of anti-*Toxoplasma* IgG in HD patient was 38% which mean that nearly ¼ samples of HD patients infected with toxoplasmosis. Acute infections result in higher levels of IgM, IgG, and IgA, but reactivations do not result in acute infections and instead produce high levels of IgG and IgA with negative IgM tests [12]. It has been established that infections are more likely to occur and to be more severe in the elderly. An important factor in this elevated risk is believed to be immuno-senescence, the state of dysregulated immune function with aging [13]. These results clearly indicate that age is an important confounding factor that must be accounted for when studying the association between *T. gondii* exposure and chronic kidney failure. Previous studies explain that the seroprevalence rate of toxoplasmosis increased with age [14]. According to the current study, the highest rate of toxoplasmosis in patients undergoing HD was in (61–70) year's old and lowest rate in (20–30) years old; in the present study, some tendency was observed that the lowest positive rate was seen in those aged 21–30 years, and the rates slowly increased with age. The reason for the rise in quantitative titers with age is not clear, although the reason might be the increased possibility of an individual coming into contact with more than one of the transmission routes [15,16]. A study [17] showed that seroposivity of toxoplasmosis increase with age among the 51–70 and then decline in later lifespan. The result of this study agrees with the results recorded by [18] who revealed that the higher rate was 56 (56%) in the age group ≥ 61, and our result disagree with [19] who explained that IgG antibodies were higher in the age group 1–10 and it was 1(25%) and IgM antibodies was higher in the age group 21–30. Toxoplasmosis is more dangerous in women than in men. The majority of women infected with toxoplasmosis are asymptomatic; primary infection during pregnancy can result in disease transmission through the placenta and lead to hazardous consequences such as abortion, stillbirth, mental and blindness [20]. A study by [21] showed that *T. gondii*-antibodies were higher in females 46 (51.1%) than in males 26 (28.9%). This result agrees with the results recorded by [22] who showed that the prevalence of anti-*Toxoplasma* IgG antibodies were higher in females 72 (55.81%) than in males 57 (44.18%), with significant difference between them ($P<0.05$). Blood urea nitrogen levels are inversely correlated with the decline of kidney function and are also affected by extrarenal factors such as protein intake, gastrointestinal bleeding, catabolic states, malnutrition, heart failure,

dehydration, use of glucocorticoids, and hepatic urea synthesis. Higher BUN levels were identified as a risk factor for kidney disease progression in patients with moderate to severe chronic kidney disease [23]. In chronic renal failure the risk of toxoplasmosis is increased with higher exposure to dialysis [24]. Urea is the main metabolite derived from the turnover of food proteins and tissue proteins. The increase in the urea concentration may due to *Toxoplasma* deleterious effects on the kidney which decrease the excretion of urea from the body and subsequently increased its serum level. *Toxoplasma* cysts were found in the kidneys of the infected mice and led to many pathological changes in their tissues. *Toxoplasma* may infect and damage kidney, which increase protein excretion in the urine and lead to hypoalbuminemia [25]. The study showed that male has higher mean of urea compared to female subjects; it became increasingly evident that female subjects tended to give lower values than males. The same observation was made by [26]. In patients with chronic renal disease has reported that men have a more rapid progression of renal insufficiency. Women with nondiabetic renal disease experience a slow progression [27]. Our observations are insufficient in terms of age distribution and number to establish a clear relationship, if any, between blood urea concentration and age. The blood urea does, however, appear to have a propensity to rise with aging. The intake of protein is reduced in older people. This may account for the poorer urea clearance, however in the event of lower protein intake, anticipate lower plasma urea values than in younger control patients who consumed more protein. On a low-protein diet, there is a reduction in urea excretion [28]. According to this, the mean level of serum creatinine in HD patients infected with *T. gondii* was raised. In chronic renal failure there is a steady and continued decrease in renal clearance or glomerular filtration rate (GFR), which leads to the gathering of urea, creatinine and other chemicals in the blood. A study by [29] showed that serum creatinine level was higher than normal range (up to 1.4 mg/dl) in CKD patients undergoing dialysis. Most of the patients have serum creatinine level between 7.6–12 mg/dl (57%) and 12–15 mg/dl (27%) before dialysis. The increase in urea and creatinine concentrations in infected group may be explained as *Toxoplasma* parasite causes glomerular lesions and urinary abnormalities which lead to renal failure. Renal failure is described as a decrease in glomerular filtration rate. Biochemically, renal failure is typically detected by an elevated serum creatinine level in the urine [30]. The most widely used indicator of renal function in clinical situations is serum creatinine. However, the limitations of using serum creatinine as a marker of kidney function are well known. In example, because muscle mass changes with age, height, gender, and race/ethnicity, food consumption has a significant impact on creatinine generation. This study agrees with that showed the mean serum creatinine was 0.71 mg/dl and was higher in male than in female individuals [31]. The mean serum creatinine concentration in females is lower than that for males and supports the reported findings reported by [32]. Serum creatinine concentration increased steadily with age; in females from the age of 40 years and 60 years for males. Reference intervals for males and females aged from 20 to 94 years were established. Advancing age affects serum creatinine levels, especially in the "vascular" age group of 60 to 80 years [33]. There have been previous studies, which have reported an increase in serum creatinine concentration with age and calculated reference intervals after the exclusion of subjects outside three standard deviations [34].

In conclusion, this study shows a higher rate of *T. gondii* infection in HD patients. Thus, the incidental rate of toxoplasmosis could be considered as an indication to the high risk of HD due to the fact that the latent *Toxoplasma* infection leading to the compromised immunity of the patients. This finding shows a high prevalence of *T. gondii* infection in hemodialysis patients with a high level of urea and creatinine with higher means in males, thus hemodialysis patients should be screened for *Toxoplasma* routinely. Clinicians should be more careful with this patient's group to prevent the possibility of severe toxoplasmosis.

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