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Prevalence of Anti JC Polyomavirus IgG in A Sample of Iraqi Kidney Transplant Recipients and Healthy Blood Donors

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Abstract

Background John Cunningham virus (JCV) is among important Polyomaviridae family, which is involved in PML and nephropathy among renal transplant recipients (RTR), and they become reactivate in immunodeficient situations.

Objective To find out the seroprevalence rate of JC polyomavirus among (RTR) and healthy persons.

Methods A case-control study to detect the presence of JCV IgG antibody in serum samples collected from a total of 400 samples were taken from (200) healthy blood donors as control individuals and (200) RTR age and sex-matched, at the period between February 2021 to March 2022. New experimental indirect enzyme linked immunosorbent assay kit had been designed and manufactured manually for detection Anti-JCV IgG in both RTR group and control group.

Results The results revealed 36 out of 200 (18%) cases of RTR have IgG, while in the control group only 24 out of 200 (12%) were positive for this antibody, no statistically significant difference was noticed between the study groups. However, there was significantly higher mean serum IgG titer in RTR patients as compared to control group (p= 0.016).

Conclusion Seroprevalence of JCV is relatively lower among Iraqi subjects as compared to other countries both RTR and healthy controls, but the IgG titer is increasing during immunosuppression suggesting possible reactivation of the virus among RTR.

Keywords Seroproprevalance, JCV, Kidney transplant recipients, IgG

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List of abbreviations: ELISA = Enzyme linked immunosorbent assay, JC-PyVAN = JC polyomavirus associated nephropathy, JCV = John Cunningham virus, KT = Kidney transplant, PML = Progressive multifocal leukoencephalopathy, RTR = Renal transplant recipient, SPSS = Statistical package for the social sciences

Introduction

Kidney transplantation (KT) is the best type of renal replacement therapy for most patients with stage 5 chronic kidney disease since it improves patients' quality of life and survival rate is cost-effective [(1)]. According to the World Health Organization in 2012, a total of 77,818 KTs were carried out worldwide [(2)]. The success achieved in KT has grown throughout the previous century [(3)]. The usage of immunosuppressive medications in a transplant recipient leads to an increased occurrence of John Cunningham virus (JCV) diseases. Reactivation Polyomavirus in bone marrow and KT recipients is owing to the use of immunosuppressive drugs and also because of immune deficiency. Thus, examination of the incidence of these viruses in the transplant recipients is essential to avoid reactivation of

the virus and to prevent transplantation termination. The genomic prevalence of BKV and JCV in urine specimens of kidney recipients is 46.7 and 23.3%, respectively, and 13.3 and 24.5%, respectively, in healthy subjects [(4)]. JCV is an opportunistic pathogen in the human population that virus in general infects children and can persist in the renal tissue and bone marrow [(5)]. A primary infection with JCV frequently results in an asymptomatic, persistent infection that establishes latency in the urinary tract. Reactivation from latency via iatrogenic immununo-suppression for allograft transplantation may consequence in organ pathology and a possible life-threatening neuropathological disease in the form of progressive multifocal leukoencephalopathy (PML) [(6)]. JCV can be detected in nervous and brain tissue, tonsils, lymph nodes, colon, bone marrow, liver, spleen and in other tissues and fluids, including blood, plasma and lymphocytes [(7,8)].

This study aimed to investigate seroprevalence rate of JCV in kidney transplant patients and healthy control by ELISA technique in serum sample

Methods

Case control study conducted from February 2021 till June 2022. The patients group consisted of two hundred (200) patients with with KT, were admitted to (Nephrology and Renal Transplantation Center in Baghdad Medical City), patients' clinical and lab. data were taken from the consultant nephrologist, age ranged from 18-60 years old, (69.5% men and 30.5 % women). These patients were evaluated for relevant clinical data including age, sex, date of transplantation and type of immune-suppressive drugs. The control group included two hundred (200) apparently healthy age- and sex-matched blood donors' volunteers from the (Iraqi Blood Donation Center) in Baghdad Medical City. This study approved by the Institutional Review Board (IRB) of the College of Medicine-Al-Nahrain University. Three ml serum samples were collected from all the subjects enrolled in this study. Serum samples collected in 1.5 ml sterile tubes and stored at -20 °C until serological tests were done.

New experimental indirect enzyme linked immunosorbent assay (ELISA) kit synthesized manually in research unit and manufacturing of alternatives in College of Health and Medical Technology/Baghdad for detection anti-JCV IgG, by fixation VP1 surface antigen, which is JCV polyomavirus major capsid VP1 full length protein (abcom \USA), and using standard antibody (IgG Ab directed against JCV used as positive control)

Statistical analysis

Statistical analysis was done using the statistical package for the social sciences (SPSS) version 17. The approach to data consisted of two steps (descriptive and analytic statistic). Chi-square test for contingency tables is used to find the statistical association or differences between the two groups for the presence or absence of significance association. P value of <0.05 considered as level of significance. Numerical data were described as mean and standard deviation.

Results

The result showed that 36 (18.0%) out of 200 (100%) cases of renal transplant recipient (RTR) have a positive result for IgG, while in control group only 24 (12.0%) were positive for this antibody. However, there is no significant difference between seropositivity of JCV IgG antibody among the studied groups (P value = 0.093), table 1 represents this result.

The mean age of patients for JCV (IgG) seropositivity was 38.83±12.13 years and for seronegative samples was 36.71±12.61 years, while the mean of age in positive control cases was 35.95±10.03 years and 35.21±10.31 years in control negative cases, there was no significant difference (P value = 0.36, 0.73 respectively) (Table 2).

The results in table 3 shows that the mean of level of IgG antibody for RTR was 6.23± 4.14 IU/ml, while in control group was 4.14± 1.46 IU/ml and there was a significant difference at P value = 0.016.

Table 1. Seroprevalence of JCV in RTR and control groups

Group		Seropositivity JC IgG		Total
		Negative	Positive	
Patients	Count	164	36	200
	% within patients	82.0%	18.0%	100%
Control	Count	176	24	200
	% within control	88.0%	12.0%	100%
P value		0.093		

Table 2. Distribution of seropositivity of JCV according to the age in studied groups

Group	Seropositivity of JCV (IgG)	N	Age (yr)		P value
			Mean	Std. Deviation	
Patients	Negative	164	36.71	12.61	0.36
	Positive	36	38.83	12.13	
Control	Negative	176	35.21	10.31	0.73
	Positive	24	35.96	10.03	

Table 3. Mean of JCV IgG level among the study groups

Serum JCV IgG (IU/ml)	RTR	Control
Mean	6.23	4.14
Standard deviation	3.47	1.46
Median	4.72	3.62
Minimum	2.90	2.20
Maximum	15.44	7.64
P value	0.016	

Regarding RTR donors' relation, 14 (13.5%) of RTR who were received transplant from their relative were positive for JCV IgG, and 22 (22.9%) that RTR patients that received transplant from unrelated person were positive, while 90 (86.5%) of RTR received transplant from related person and 74 (77.1%) of RTR that received transplant from unrelated donors were negative for JCV IgG, P value = 0.082. All these statistical differences were showed in table (4)

Table 4. Relation of JCV IgG with other variables in the studied groups

Parameter		JCV IgG +ve No. (%)	JCV IgG -ve No. (%)	% with JCV +ve	P value
Age (RTR)	≤30 yr	10 (13.2%)	66 (86.8%)	27.8%	0.163
	>30 yr	26 (21%)	98 (79.0%)	72.2%	
Sex (RTR)	Male	24 (17.3%)	115 (82.7%)	66.7%	0.683
	Female	12 (19.7)	49 (80.3%)	33.3%	
Sex (control)	Male	13 (9.4%)	125 (90.6%)	54.2%	0.094
	Female	11 (17.7%)	51 (82.3%)	45.8%	
Region	Baghdad	17 (18.3%)	76 (81.7%)	46.3%	0.924
	Another region	19 (17.8%)	88 (82.2%)	53.7%	
PTP	≤12 month	23 (16.3%)	118 (83.7%)	63.9%	0.337
	>12 month	13 (22.0%)	46 (78%)	36.1.%	
HT (RTR)	Yes	17 (23.6%)	55 (76.4)	47.2%	0.121
	No	19 (14.8%)	109 (85.2%)	52.8%	
DM (RTR)	Yes	5 (11.1%)	40 (88.9%)	86.1%	0.172
	No	31 (20%)	124 (80%)	13.9%	
IS (RTR)	TAC	23 (16.9%)	113 (83.1)	63.9%	0.559
	CYC	13 (20.3%)	51 (79.7%)	36.1%	
Donors' relatedness	Related	14 (13.5%)	90 (86.5%)	38.9%	0.082
	Unrelated	22 (22.9%)	74 (77.1%)	61.1%	

PTP = Post-transplantation period, DM = Diabetes mellitus, IS = Immunosuppression, HT = Hypertension, TAC = Tacrolimus, CYC = Cyclosporine

Results in table 5 shows a significantly higher mean serum IgG in RTR patients as compared to healthy controls (P value = 0.016), also it was significantly higher among females as compared to males (P value = 0.03). Though not significant, but the mean serum concentration of IgG among RTR transplanted within less than 12 months 5.85±3.62 IU/ml, versus 5.27±2.66 IU/ml among those with more than 12 months PTP.

Discussion

In this study JCV was investigated in serum of both RTRs and control group using ELISA and showed that 36 out of 200 (18.0%) cases of RTR have a positive IgG, while in the control group only 24 out of 200 (12.0%) were positive for this antibody with no statistically significant difference between them.

In Iraq, a previous study has been done on samples gained from Al-Kheial Hospital, (which is a private renal transplantation center in Baghdad), for detection of JC polyomavirus IgG and the result showed higher seroprevalence 29.2% (21 out of 72) cases of RTR had IgG, and this antibody was not detected in the control [(9)]. In Switzerland, a study has been done on samples gained from 400 blood-donors aged between 20-59 years, and JC polyomavirus IgG IgG seroprevalence was 58% (231 of 400) [(10)]. In another study on pregnant women, JC polyomavirus seroprevalence was 72% in mothers aged more than twenty-five years [(11)]. These differences among studies may be due to the difference in the test has been used in the diagnosis, size of samples, types of the patients, and time of sampling.

Table 5. The mean of JCV IgG antibody level among the studied groups

Parameter		N	Serum JC IgG (IU/ ml)		P value
			Mean	Std. Deviation	
Group	Patients	200	5.44	2.98	0.016
	Control	200	4.70	3.08	
Age group (RTR)	≤ 30y	156	4.87	2.85	0.28
	> 30y	244	5.20	3.17	
Sex (Control)	Female	62	5.55	4.31	0.03
	Male	138	4.32	2.25	
Sex (RTR)	Female	61	5.52	3.31	0.8
	Male	139	5.41	2.83	
Hypertension	No	128	5.17	2.30	0.13
	Yes	72	5.93	3.87	
Region	Another region	93	5.35	2.77	0.68
	Baghdad	107	5.52	3.15	
Diabetes	No	155	5.59	3.11	0.19
	Yes	45	4.94	2.42	
Donor' relativity	Unrelated	96	5.84	3.09	0.07
	Related	104	5.08	2.83	
Chemotherapy	Tacrolimus	136	5.43	3.05	0.93
	Cyclosporin	64	5.47	2.83	
PTP	> 12 months	141	5.27	2.66	0.2
	< 12 months	59	5.85	3.62	

In the current study, there was no association or significant difference in the seropositivity of JC polyomavirus IgG among age groups or sex in both the studied groups, these results are supported by other studies such as the study in which seropositivity was measured in 441 European solid organ transplanted recipients [12]. Most previous investigations have not found any difference in seroprevalence with respect to sex [13,14] with the exception of one that reported a significantly higher JC polyomavirus IgG seroprevalence in English men than in women [15].

In Switzerland, a study found no difference in JC polyomavirus IgG seroprevalence or the level of JC polyomavirus IgG activity was apparent between women and men (113 [57%] of 200 vs. 118 [59%] of 200. However, in concerning of age JC polyomavirus IgG seroprevalence, was increased from 50% (50 of 100) in the youngest group to 68% (68 of 100) in the oldest group [10]. Also, the study by Antonsson et al., [12] showed that the seroprevalence of JC polyomavirus IgG increased with age. Another study made on 7724 patients from 10 countries multiple sclerosis disease. Overall anti-JC polyomavirus IgG antibody prevalence was 57.1%. Seroprevalence was significantly associated with increasing age, (P <0.0001) [16]. Gardner and colleagues [17] performed a prospective serological study for the evidence of JC polyomavirus IgG infection in 48 RTR, finding that 54% of the patients were seropositive

already before the operation, and that in 23% of the seronegative patients JC polyomavirus infection occurred within the first three months after transplantation.

However, it is important to remember that different methods for detection of antibodies have been used in the above-mentioned studies, indicating that the results cannot be compared directly. In addition, the low rates of Polyomavirus infection reported here may represent an epidemiological feature of the virus in a sample of Iraqi patients from Baghdad, which may be related to the population density and environmental conditions, which are of paramount importance for JCV transmission. These differences in rate of virus could be attributed to different study designs and follow-up sampling timings also different methodology and small sample size may be the possible reasons.

On the other hand, the current study showed significantly higher mean serum IgG in RTR patients as compared to normal controls (P value = 0.016) and this result consistent with the study of Kamminga et al., [18] that reported an increase in IgG levels during follow-up were observed for JC polyomavirus IgG among RTR, while blood donor antibody levels remained stable.

The current study also showed that the mean of IgG in healthy groups was significantly higher among females as compared to males (p= 0.03) that may be due to that females mount higher innate and adaptive immune responses than males, which can result in faster clearance of viruses also females mount higher antibody responses and experience more adverse reactions than males [19].

The current study showed though not significant, but the mean serum level of IgG among RTR who had PTP within less than 12 months was 5.85 versus 5.27 among those with more than 12 months PTP also 23 out of 36 (63.9%) of that were positive for JCV IgG were within the group equal or less than 12 months after transplantation, while only 13 out 36 (36.1%) were within the group more than 12 months after transplantation and this result consistent with other Iraqi study that reported cases of study according to PTP were divided into two intervals. The first one (1-12) month under this interval there were elevated in both IgM and IgG level more than levels under the second interval≥13 months [9]. And with other study from Finland that reported that the serological responses occurred during the second half of the first-year post-transplant, when immunosuppression is typically lower. However, as exemplified in the one case diagnosed with biopsy-proven JC-PyVAN, the serological responses, including IgM and IgG titer increases, may be highly variable and even delayed, as it is common for immunosuppressed transplant patients [20].

In conclusion, the seroprevalence of JCV is relatively lower among Iraqi subjects both in RTR and healthy controls.

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Author contribution

Dr. Hussein: Collection of specimens, detection of JCV IgG by ELISA, writing of the references. Dr. Hussein MR: Consultant nephrologist help in providing all patients' data. Dr. Al-Obaidi: Supervision and writing of the manuscript.

Conflict of interest

Authors declare they have no conflict of interest.

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