

## High Prevalence of John Cunningham Viruria in Renal Transplant Recipients

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### Abstract

**Background** John Cunningham virus (JCV) is one of the important viruses in immunocompromised patients. High JC viruria is seen in kidney allograft recipients; some of them with a polyomavirus associated nephropathy (PVAN) just like BK polyomavirus but to a lesser extent.

**Objective** To detect JCV viruria in a sample of Iraqi renal transplant recipients, and its association with renal function.

**Methods** A prospective study enrolled 71 renal transplant recipients (RTR) and 20 normal donors (ND) as controls. Urine samples were collected from all RTR and ND. Viral DNA was extracted from 1 ml urine samples, and then, JC virus DNA was detected and measured by Taqman quantitative real-time PCR.

**Results** Out of 71 RTRs, 31 (43.66%), and 2 out of the 20 (10%) controls had positive JC viruria. The mean JCV viruria was 6.8 x10<sup>4</sup>, and 1.04x10<sup>3</sup> copies/ml for RTRs and controls respectively.

**Conclusion** There is a relatively high prevalence of JCV viruria in Iraqi RTR patients.

**Keywords** JC virus, renal transplantation, urine, real-time PCR.

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**List of abbreviation:** BKV = BK polyomavirus, CMV = Cytomegalovirus, CSA = Cyclosporine A, D/R = Donor/recipient serostate, IS = immunosuppressive drugs, JCV = JC polyomavirus, MMF = Mycophenolate, PML = Progressive multifocal leukoencephalopathy, PVAN = Polyomavirus associated nephropathy, QRT-PCR = Quantitative real time polymerase chain reaction, RTR = Renal transplant recipients, TAC = Tacrolimus

### Introduction

Human polyomaviruses have become important clinical entities, coincident with the development and use of more potent immunosuppressive agents. Polyomavirus-associated nephropathy (PVAN) is one of the important causes of graft dysfunction with a high rate of graft loss <sup>(1)</sup>.

Two viruses among this group are well known for their association with nephropathy; those are BK and JC viruses <sup>(2)</sup>.

The JC polyomavirus (JCV) is a small non-enveloped, with double-stranded circular DNA nucleic acid <sup>(3)</sup>. The virus has a high prevalence rate worldwide. Approximately 60-80% of adults in the United States have detectable antibodies against JC virus <sup>(4)</sup>. JC virus establishes lifelong latency in the kidneys, central nervous system, and hematopoietic progenitor cells <sup>(5,6)</sup>. It is considered the causative agent of progressive multifocal leukoencephalopathy (PML), which is a rare

disease characterized by the lytic infection of glial cells<sup>(7)</sup>.

Infection by JCV has been observed in renal transplant recipient (RTR) as both nephropathy and/or PML. Renal transplant recipients have the highest risk of developing JCV associated nephropathy in comparison to other organ recipients<sup>(8,9)</sup>.

Risk factors for PVAN are controversial and likely involve multiple determinants, but profound immunosuppression has been generally accepted as a key factor<sup>(9,10)</sup>. Low-level JCV replication and shedding are common in immunocompetent individuals, but in RTRs it is more common to observe high-level polyomavirus replication, as identified by decoy cell shedding. Moreover, progression from viruria to viremia precedes the development of histologically proven polyomavirus nephropathy by several weeks<sup>(11,12)</sup>.

In Iraq, to the best of our Knowledge, there is no such study on JCV in RTRs, and few studies investigated viral infections in Iraqi renal transplants, including BK virus<sup>(13,14)</sup>, human cytomegalovirus<sup>(15)</sup>, Epstein Barr virus<sup>(16)</sup> and Human herpes virus-6<sup>(17)</sup>.

This study aimed to investigate the rate of occurrence of JCV in RTRs, by quantitative real time PCR in urine samples, and to correlate the level of JC viruria in RTRs with renal function test and the types of immunosuppressive regimens.

## Methods

### Study Population

A prospective study conducted from October 2015 to March 2016, seventy-one (71) renal transplant recipients RTRs were enrolled from the (Center of Kidney Diseases and Transplantation) in the Medical City of Baghdad, during their first post-transplantation period. A consent letter obtained from all patients and controls enrolled in the study. This study approved by the ethical Committee of the College of Medicine-Al-Nahrain University. Twenty (20) apparently healthy age and sex-

matched normal donors enrolled in this study as controls.

Clinical and laboratory data were obtained from each patient. From all RTRs and controls, 5 ml urine samples collected and preserved in deep freeze for viral DNA extraction.

Two main Standard immunosuppressive regimens were mainly followed in RTRs; either the cyclosporine A (CSA), mycophenolate (MMF), and prednisolone, or the regimen that included tacrolimus (TAC) instead of CSA, in addition to MMF and prednisolone.

### Viral DNA Extraction

For viral DNA extraction from the urine samples; Geneius™ Micro g DNA Extraction kit (Geneaid, England) was used. One ml urine sample was used in viral DNA extraction, according to the manufacturer protocol.

### Real Time PCR for Measuring JC Viruria

For the quantitative detection of JCV; GeneProof PCR kit ISIN Version kit (England) is a Real-Time test, which is based on the principle of the so-called - "TaqMan" probe. Thirty µl of Master Mix were added into PCR tubes, and 10 µl of the (sample DNA, positive or negative controls, or standards) were added to the master mix. The final reaction volume was 40 µl. All components were kept at +2 °C to +8 °C during the PCR preparation. Real time PCR instrument used in this work was STRATAGENE MxPro QPCR (Agilent Technologies, USA). The thermal protocol for Geneproof PCR kit is composed of a two hold steps, and one amplification cycle. The real-time data is collected at the third step of the amplification cycle as demonstrated in table (1).

At the end of the thermal protocol, the Real-Time PCR (MxPro QPCR) instrument software automatically calculates the baseline cycles and the threshold. The standard curve is plotted using the data obtained from the defined standards, with the (Y) axis is the Ct-Threshold Cycle, and the (X) axis is the viral DNA copy number. According to the manufacturer

$$\text{copy/ml} = \frac{\text{SC} \times \text{EV}}{\text{IV}}$$

instructions, JCV DNA copies was calculated according to the following formula:

SC = Sample Concentration (copy/μL)  
 EV = Elution Volume (μl)  
 IV = Isolation Volume (ml)

**Table 1. JCV real time PCR amplification profile**

Steps	Temperature	Time	Data collection	Cycle
1-hold	37 °C	2 min		1
2-hold	95 °C	10 min		1
	95 °C	5 s		
3PCR	60 °C	40 s	FAM+HEX	45
	72 °C	20 s		

**Statistical analysis**

The Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA), Version 20 was used for statistical analysis. Categorical data formulated as count and percentage. Chi-square test used to describe the association of these data. Alternatively, Fisher exact test was used if there is 25% of cells less than expected count. Numerical data were described as mean and standard deviation. Independent sample t-test was used for comparison between two groups. The lower level of accepted statistical significant difference is equal or below to 0.05.

**Results**

Among the 71 RTR; 61 (85.90%) were males, and 10 (14.10%) were females, their mean age was 38.54±8.01 years, ranging between 18 and 77 years. Statistically, there was no significant difference (P=0.117) between the mean of the RTRs and control group indicating that they were of a comparable age.

Quantitative real time PCR (QRT-PCR) run gave positive viruria in 31 out of 71 (43.7%) RTRs and 2 (10%) out of the 20 controls, which was significantly higher in RTRs, (P=0.007).

The mean of JCV viruria was 6.8 x10<sup>4</sup>, and 1.04x10<sup>3</sup> copies/ml for RTRs and controls respectively, which is significantly higher in RTRs (P<0.001).

On the other hand, table (2) demonstrated that 15/25 (60%) of RTR with elevated serum creatinine values, were positive for JC viruria, which was statistically significant (P=0.048). In addition, on comparing JC viruria with the type of immunosuppression regimen, 21 out of the 31 viruria patients (67.7%), were on CSA regimen, and the remaining 10/31 (32.3%) were on TAC regimen, however, these results were statistically not significant (p= 0.146), table (2) demonstrate the clinical data demographic data of RTR patients in relation with JC viruria.

**Discussion**

There's a growing evidence on the high seroprevalance of JCV and its association with significant deadly diseases <sup>(18-20)</sup>. In this study, JCV was investigated in urine of RTRs using QRT-PCR, and 31 out 71 (43.66%) of RTRs had positive JCV viruria (JCV DNA in urine); the frequency was higher in comparison to other studies, ranging from 13.7 to 36.8% <sup>(21-24)</sup>.

It is well known that all organ transplant recipients are immunocompromised subjects because of the chronic use of IS drugs, therefore these patients are subjected to develop reactivation of any latent viruses <sup>(25)</sup>. JCV is among the viruses that remains latent for the whole life of the infected person <sup>(5,6,8,26,27)</sup>.

Table 2. Clinical and demographic characteristics of RTR patients in relation with JC viruria

		Viruria positivity		Total	P value	RR	CI
		Present No. (%)	Absent No. (%)				
Age groups	< 40 years	15 (42.86)	20 (57.14)	35	0.542		
	≥ 40 years	16 (44.44)	20 (55.56)	36			
Gender type	Female	4 (44.44)	5 (55.56)	9	0.616		
	Male	27 (43.55)	35 (56.45)	62			
Donor relation	Un related	19 (38.78)	30 (61.22)	49	0.163		
	Related	12 (54.55)	10 (45.45)	22			
PTP	< 6 months	16 (55.17)	13 (44.83)	29	0.084		
	≥ 6 months	15 (35.71)	27 (64.29)	42			
Serum Creatinine	Abnormal	15 (60)	10 (40)	25	<b>0.048</b>	1.72	1.02 -2.87
	Normal	16 (34.78)	30 (65.22)	46			
Creatinine clearance	Abnormal	19 (57.58)	14 (42.42)	33	0.495		
	Normal	12 (31.58)	26 (68.42)	38			
CMV IgG D/R	-/-	8 (34.78)	15 (65.22)	23	0.495		
	-/+	5 (45.45)	6 (54.55)	11			
	+/-	3 (75)	1 (25)	4			
	+/+	15 (45.45)	18 (54.55)	33			
CMV IgM D/R	-/-	30 (44.12)	38 (55.88)	68	0.416		
	-/+	0 (0)	1 (100)	1			
	+/-	0 (0)	1 (100)	1			
	+/+	1 (100)	0 (0)	1			
IS regimen	CSA	21 (50)	21 (50)	42	0.146		
	TAC	10 (34.48)	19 (65.52)	29			
UTI	None	25 (42.37)	34 (57.63)	59	0.431		
	UTI	6 (50)	6 (50)	12			

PTP: post-transplantation period, CMV: cytomegalovirus, D/R: donor/recipient serostate, IS: immunosuppression, CYC: cyclosporine, TAC: tacrolimus, UTI: urinary tract infection.

Studies on polyomavirus viruria have shown different patterns of shedding for each of these viruses in normal and immunosuppressed hosts (28,8,29,30). BKV viruria is rare in healthy individuals (0-6%) and significant BKV urinary replication and shedding are clearly dependent on disruptions of cellular immunity (8,28,29,31-33). Thus, BKV viruria increases in HIV patients in whom viruria correlates with lower CD4 counts (8,29,30,34). In contrast, asymptomatic JCV viruria commonly found in immunocompetent hosts (could reach up to 40%) (8,28,29,30,34) and the

relationship of JCV viruria to immune dysregulation is less clear than that of BKV.

The fact that the JCV has the potential to cause renal disease albeit less commonly than BKV, is confirmed in sporadic cases (31,35). Specifically, JCV-mediated nephropathy has been reported by Kazory et al., 2003 (36), and Wen et al., 2004 (2) in RTRs. Recently, a study showed that infection of primary human renal tubule epithelial cells with JCV and BKV results in divergent innate immune responses that control JCV but fail to control BKV (37).

In another study, Drachenberg et al., 2007<sup>(21)</sup>, they have found that one fifth of renal transplant recipients were shedding JCV developed biopsy-proven JCV nephropathy. Results of the current study showed that 15 out of 25 (60%) RTRs who had high serum creatinine, were positive for JC viruria. These results are in agreement with that of other studies, which suggested a role of JCV in allograft nephropathy in RTRs just like BKV<sup>(3,21,38-40)</sup>.

There was no significant association between JCV viruria and age, a result which is supported by other reports from Brazil (Melo et al., 2013)<sup>(41)</sup>, Spain (Lopez et al., 2008)<sup>(42)</sup>, Iran (Taheri et al., 2011)<sup>(40)</sup>, (Bozorgi et al. 2012)<sup>(43)</sup> and USA (Agostini et al., 1996)<sup>(44)</sup>.

Similarly, no significant difference was observed between different genders regarding JC viruria, which was the same as reports from Italy (Pagani et al., 2003)<sup>(45)</sup>, Poland (Kmieciak et al., 2008)<sup>(46)</sup> and Serbia (Karalic et al. 2014)<sup>(47)</sup>. Although, 27 out of 31 (87.09%) who had positive JC viuria were males, which is in consistence with other studies that found significantly higher frequency of the virus in males, in USA (Agostini et al., 1996)<sup>(43)</sup>, and Japan (Zhong et al., 2007)<sup>(48)</sup>.

The current study found no correlation between JCV viuria and CMV IgM and IgG donor/recipient (D/R) serostate. The frequency of CMV IgG D+/R+ was 15 out of 31 JCV positive viuria, while CMV IgM D+/R+ was 1 out of 31 JCV positive viuria. A study on multiple sclerosis in Denmark showed that out of 123 patients, fifty-three patients (43.1%) were JCV negative and 70 (56.9%) positive. CMV-IgG antibodies were detected only in six patients, otherwise no IgM antibodies were detected<sup>(49)</sup>.

Results of this study showed that the number of patients with early < 6 post-transplantation period was 16 out of 31 JCV positive viuria and number of patients with late post-trnsplantation period  $\geq$  6 were 15 out of 31 JCV positive viuria. Statistically, there' was no significant difference between JCV frequency and the post-transplantation period, which is

consistent with the findings of others studies which showed that JC virus prevalence was consistent regardless of the time after renal transplantation<sup>(40,50)</sup>.

The current study found no significant difference between the prevalence of JCV viruria and donor relation with recipient and this finding agrees with other study which showed no correlation to donor relatedness<sup>(51)</sup>. However, 19 out of 31 (61.2%) positive patients had living unrelated donor, which could be explained by the fact that the most of the nephrologist increase the dose of IS drugs in patients who had allograft from unrelated donor due to increased risk of HLA-mismatch. This may activate stronger cell mediate-immunity response, and thus increase the risk of viral infections or reactivations<sup>(52)</sup>.

Studies on BKV, showed that better HLA matching reduces the risk of kidney allograft rejection and the risk of viral nephropathy<sup>(53)</sup>.

The mean and frequency of JC viruria in RTRs were significantly higher than in healthy controls ( $p < 0.007$ ). These results are consistent with the findings in Taiwan (Lai et al., 2008)<sup>(54)</sup>; (Yin et al. 2010)<sup>(55)</sup> and China (Hu et al., 2011)<sup>(56)</sup>. This could explain the role of immunosuppressive regimens used in RTRs. Immunosuppressive drugs were considered as risk factor for reactivation of JCV in RTRs which is documented by different studies<sup>(21,56)</sup>.

Although in the current study there was no significant correlation between JCV and type of IS regimen, 21 out of 31 (67.7%) positive JC viruria were on CSA regimen, and that agrees with study by (Hu et al., 2011)<sup>(56)</sup> who showed CSA is a risk factor for JCV reactivation.

Some studies have reported that therapy containing MMF, or CSA or azathioprine significantly increase the risk of polyomavirus infection<sup>(25,57,58)</sup>, while other studies have failed to find a correlation between the frequency of JCV viruria and the use of immunosuppressive drugs.<sup>(31,59)</sup> However, in this study, CSA use was an important independent predictor of JCV infection.

One limitation of the present study was lack of confirmation of the detection by kidney biopsy because of unapproved protocol biopsy in our center.

In conclusion, the relatively high prevalence of JC viruria as compared with control group.

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### Author contributions:

Jasim: Collection of specimens, DNA extraction, and real time-PCR, writing of the references. Dr. Al-Saedi: Consultant nephrologist helped in selection of patients. Dr. Hussein: Consultant nephrologist help in providing all patients' data. Dr. Al-Obaidi: Supervision and performance of viral DNA extraction and real time-PCR run, writing of the manuscript. Dr. Kadhim: Final editing of the manuscript.

### Conflict of interest

Authors declare no conflict of interest.

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