Asian Journal of Research in Nephrology

Volume 7, Issue 1, Page 31-38, 2024; Article no.AJRN.111197

Relation of Immunosuppressive Drugs with BK Virus Infection in Renal Allograft Recipient Cases

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/111197

Original Research Article

Received: 15/11/2023
Accepted: 20/01/2024
Published: 25/01/2024

ABSTRACT

Background: Human polyoma viruses are the members of the papova virus family. The most known species of this kind are BK-virus (BKV), JC-virus (JCV) and Simian-virus (SV-40). BK (polyma) virus causes allograft dysfunction in renal transplant recipients. The incidence of BK virus infection among renal transplant recipients in Bangladesh is unknown.
Objectives: To find out the frequency of BK virus infection in renal allograft recipients at sixth month after transplantation.

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Materials and Methods: This cross-sectional study was carried out in the Department of Nephrology at BSMMU, Dhaka. A total of 29 adult patients who fulfilled the inclusion and exclusion criteria were enrolled from the period of July 2015 to June 2016 by convenient sampling. All relevant information from the renal allograft recipients were collected. Blood and urine of these patients were tested for BK viral DNA by PCR.
Results: The frequency of BK virus infection among the enrolled 29 renal transplanted patients was found to be 20.7%. The mean age of BK virus infected patients was 28.67±11.55 years. Among the 6 patients found infected by BK virus, 5(83.3%) were male. Among the 16 tacrolimus (TAC) treated patients, BK virus was detected in 3(18.7%) patients whereas among the 13 cyclosporin (CIC) treated patients, BK virus was detected in 3(23.1%) patients. 2(33.33%) of the BK virus infected patients developed asymptomatic BK virus infection with impaired graft function.
Conclusion: Our data highlights that BK virus infection is prevalent in our center.

Keywords: Renal transplant; BK virus; JC-virus (JCV); Simian-virus (SV-40).

1. INTRODUCTION

"Kidney transplantation (KT) has been established as the most efficient treatment of ESRD with the advantage for the patient to live a nearly healthy life. Opportunistic infections are the leading cause of morbidity and mortality after transplantation. Viral infections are common causes of allograft dysfunction and mortality in these patients" [1]. "Different viral infections have been observed in these patients such as CMV, EBV, Herpes Simplex Virus, and polyoma virus of the BK strain. Human polyomaviruses are members of the approval virus family" [2]. "The most known species of this kind are BK-virus (BKV), JC-virus (JCV) and Simian-virus (SV-40)" [3]. "Among the several types of polyomavirus infections in humans, types BK and JC are the major pathogenic viruses" [4]. "The major pathogen of polyoma virus-associated nephropathy is the BK virus" [5]. "Primary infections seem to occur in early childhood via oral and/or respiratory exposure" [6]. "The virus remains latent in the reno-urinary tract and possible in the lymphoid organs and that it might be reactivated in immuno-compromised state" [7]. "It is estimated that 60-90% of adults have anti-BK virus antibody in their blood and impairment of immune system for any reason like pregnancy or organ transplantation might reactivate this virus" [8]. "Reactivation of latent BK virus might occur in 10-60% of the renal allograft patients and this reactivation is responsible for 1-5% of nephropathy of such cases" [9]. "The graft loss associated with BK nephropathy is reported by different reviews as averaging 50%" [10]. "BK virus infection is a challenging complication in renal allograft recipients and has been associated with haematuria, ureteral stenosis, nephropathy. Reactivation of the virus in renal transplant recipients is particularly worrisome because of its propensity to cause local damage and incite an inflammatory response leading to acute kidney injury and possible graft loss. OPTN (Organ Procurement and Transplant Network) registry analysis suggests that the incidence of BK virus related complications is rising and between June 2004 and December 2008, 823 grafts were lost secondary to BK virus related complications" [11]. "At this time, data suggest that prevention of BKVN through prospective monitoring and pre-emptive reduction in immunosuppression is a reasonable approach. Patients with BKV replication or nephropathy should be monitored very closely. The risk of graft loss remains high in individuals with BKVN and concurrent inflammation. Immunosuppression is the most significant risk factor that promote BKVN. Immunosuppressives especially tacrolimus & mycophenolate mofetil (MMF) have been implicated in BKV infection" [12]. "Other risk factors are pregnancy, chemotherapy, seropositive donor, uncontrolled diabetes, HIV, cytotoxic drugs, male gender & older age of the recipient" [13]. "Patients with BKVN usually do not have any clinical sign or specific symptom, except a decline in renal function. But there may be associated with ureteric stenosis, hemorrhagic cystitis (less common). BKVN is frequently confused with acute rejection but doesn't respond to typical therapy. Typically, native kidneys are not involved" [7]. "Diagnosis of BKV replication and BKVN can be done by assay. Non-invasive method is by identification of decoy cells in the urine under the microscope. The most common method is urine or plasma BKV DNA copy numbers using real-time quantitative PCR assay" [9]. "Invasive tissue diagnosis i.e. the renal allograft biopsy is the gold standard. The diagnosis of BKVN is made based on the presence of typical viral cytopathic

changes in the renal tubular epithelial cells" [14]. There is no established treatment other than prompt reduction of immunosuppression to aid viral clearance. Early detection, prompt diagnosis and therapies including preventive measures have resulted in better outcomes [15]. This investigation is not included routinely in pre and post-transplant management protocol. This study was conducted to find out the frequency and proportion of patients of BK virus infection in renal allograft recipients of BSMMU at sixth month after transplantation.

2. MATERIALS AND METHODS

This was a cross-sectional study, conducted from July 2015 to June 2016 for a period of 1 year in the Department of Nephrology at Bangabandhu Sheikh Mujib Medical University, Dhaka, among adult renal allograft recipients who fulfilled the exclusion and inclusion criteria. A total of 29 patients were recruited as study population.

2.1 Study Procedure

Renal allograft recipients who underwent renal transplantation in BSMMU and presented for follow up to our department at sixth postoperative month were enrolled as study subjects. For BK virus detection approximately 5 ml of venous blood and 10 ml of midstream urine were collected simultaneously in an EDTA tube and in a conical sterile tube respectively from each patient. Collected blood was centrifuged at 1400 rpm for 5 minutes and collected urine was centrifuged at 1400 rpm for 30 minutes. The supernatant plasma & urine were collected and stored at −20ºC with proper labeling. BK viral DNA was extracted from both serum and urine samples by using a commercially available DNA extraction kit- QIAamp DNA Mini Kit (QIAGEN, GERMANY) and PCR was done by the StepOne™ PCR machine (StepOne™ Applied Bio system, USA) using real time PCR kit (Geno-Sen's BK real time PCR kit, Genome Diagnostics, Netherlands) according to manufacturer's instructions. DNA concentration was measured in ng/µl by spectrophotometer (Nanodrop 2000/2000C) measured at the ratio of absorbance at 260 and 280 nm. PCR assay were performed by the StepOne™ PCR machine (StepOne™ Applied Bio system, USA) using real time PCR kit (Geno–Sen's BK real time PCR kit, Genome Diagnostics, Netherlands). The four quantitative standards and negative control (NC) provided in the kit are treated in the same way as extracted samples and the same volume is used i.e. 10µl instead of the sample. Standards and NC curves were generated in PCR machine (Step One™, Applied Biosystem, USA) as per manufacturer`s instruction. The results were visualized in FAM channel. Data analysis was performed with the Step One™ software according to the manufacturer's instructions (StepOne™ Operator's Manual). Each DNA amplification was associated with generation of a fluorescence signal measurable in FAM channel and in JOE channel (for IC) resulting in a sigmoid growth curve (log scale). Before interpretation of results, the obtained data was checked to ensure that the run was valid. BKV DNA was determined based upon the CT values for the sample BKV DNA and four standard curves resulting from analysis of quantitation standard and the assay specific calibration coefficient. BKV DNA concentration was expressed in (copies/µl). The linear regression coefficient (R2) of the reference curve was maintained between 0.98 and 1.00. Total laboratory procedure was carried out at the Department of Virology, BSMMU.

2.2 Inclusion Criteria

Adult patients aged between 18 to 60 year's old who have undergone successful renal transplantation six months ago.

2.3 Exclusion Criteria

- Patients with findings of any known bacterial infection.
- Patients with drug related impairment of graft function.

2.4 Data Analysis

All data were recorded systematically in preformed data collection forms (questionnaire). Quantitative data were expressed as mean and standard deviation and qualitative data were expressed as frequency, distribution and percentage. Statistical analysis was performed by using a Windows based computer software, Statistical Packages for Social Sciences (SPSS-22). Association between categorical variables was analyzed by chi-squared test and continuous variable by student t-test. For all statistical tests, we considered p value <0.05 as statistically significant.

3. RESULTS

In this study, by convenient sampling 29 adult patients who fulfilled the exclusion and inclusion criteria were enrolled from the period of July 2015 to June 2016. Males and females were 25 and 4 respectively. The mean ages of BK virus detected patients were 28.67±11.55 years and that of in undetected patients was 28.43±6.49 years with the age range of 16 to 48 years.

Table 1 showed BK virus status in patients who underwent kidney transplantation. BK virus was found to be present in 6 (20.7%) cases.

Table 2 showed viral load in blood and urine of BK virus positive patients.

Table 3 showed the mean age of patients in BK virus positive and negative groups were similar (p>0.05). The age (Mean ± SD) of BK virus detected patients was 28.67 ± 11.55 years and that of in undetected patients was 28.43 ± 6.49 years with the age range of 16 to 48 years.

Table 4 showed distribution of patients according to gender in BK virus detected and undetected groups. Among six BK virus infected patients, 5 (83.3%) were male and 1 (16.7%) were female. There was no significant difference in gender between BK virus infected and BK virus non infected patients.

Table 5 showed that the mean serum creatinine in patients with and without BK virus infection. In BK virus non infected group, mean serum creatinine at two weeks after transplantation was 1.25 mg/dl and at 6th month it was 1.43 mg/dl, showing no statistical significant difference (P=0.068). In BK virus infected group, mean serum creatinine at two weeks after transplantation was 1.27 mg/dl and at 6th month it was 1.81 mg/dl, showing statistically significant difference (P = 0.035).

Table 1. Frequency of BK virus infection in renal allograft recipients. (N=29)

BK virus	Frequency (n)	Percentage (%)
Not detected	23	79.3
Detected	6	20.7
BK virus PCR positive in both urine and blood	1	3.4
BK virus PCR positive in urine only	5	17.3
BK virus PCR positive in blood only	0	0.0

Table 2. Viral load in blood and urine of BK virus positive patients (n=6)

Patient Sl. No.	Viral load in blood (copies/ml)	Viral load in urine (copies/ml)
1	Nil	9.3×10^2
2	1.9×10^4	7.9×10^3
3	Nil	2.5×10^3
4	Nil	9.94×10^7
5	Nil	1.5×10^3
6	Nil	5.38×10^5

Table 3. Distribution of patients according to age in BK virus detected and undetected groups (N=29)

Age (years)	BK virus status		P value
	Detected (n=6)	Undetected (n=23)	
≤20 yrs.	1(16.7%)	2(8.7%)	0.948
21- 30 yrs.	2(33.3%)	12(52.2%)	
31- 40 yrs.	2(33.3%)	8(34.8%)	
>40 yrs.	1(16.7%)	1(4.3%)	
Total	6(100.0%)	23(100.0%)	
Mean ± SD	28.67 ± 11.55	28.43 ± 6.49	
Min - Max	16 - 48	20 - 48	

Table 4. Distribution of patients according to gender in BK virus detected and undetected groups. (N=29)

Gender	BK virus status		P value
	Detected (n=6)	Undetected (n=23)	
Male	5(83.3%)	20(87.0%)	0.819
Female	1(16.7%)	3(13.0%)	
Total	6(100.0%)	23(100.0%)	

Table 5. Serum creatinine in patients with and without BK virus infection. (N=29)

S. Creatinine (mg/dl)	Group		P value
	Detected (Mean ±SD)	Undetected (Mean ±SD)	
At two weeks after KT	1.27 ± 0.21	1.25 ± 0.18	0.413
At 6th month after KT	1.81 ± 0.92	1.43 ± 0.51	0.189
P value (between serum creatinine at two weeks vs. at 6th month after KT)	0.035	0.068	

Table 6. BK virus infection in renal allograft recipients receiving different CNIs. (N=29)

Immunosuppressive	BK virus status		Total
	Detected (n=6)	Undetected (n=23)	
CIC (Cyclosporin)	3(23.1%)	10(76.9%)	13
TAC (Tacrolimus)	3(18.7%)	13(81.3%)	16
Total	6(20.7%)	23(79.3%)	29

Table 7. CNI levels in BK virus detected and undetected patients. (n=13)

	BK virus status		P value
	Detected (n=3) [Mean ±SD]	Undetected (n=10) [Mean ±SD]	
Cyclosporin C2 level (ng/ml) At 6th month after KT	626.7 ± 20.8	610.4 ± 17.2	0.669
Trough (tacrolimus) level (µg/l)	Detected (n=3) [Mean ±SD]	Undetected (n=13) [Mean ±SD]	
At 6th month after KT	7.16 ± 0.42	7.38 ± 0.96	0.615

Table 8. Status of renal function in BK virus infected patients. (n=6)

Status of renal function	Frequency (n)	Percentage (%)
Impaired renal function	2	33.33
Normal renal function	4	66.67

Table 6 showed that BK virus infection in renal allograft recipients receiving different CNIs. Among 13 cyclosporin treated patients, BK virus was detected in 3(23.1%) patients and BK virus was not detected in 10(76.9%) patients. Among 16 Tacrolimus treated patients, BK virus was detected in 3(18.7%) patients and BK virus was not detected in 13(81.3%) patients.

Table 7 showed that Cyclosporin C2 levels in BK virus detected and undetected patients. Mean cyclosporin C2 level was similar in BK virus detected and undetected patients at 6th month after KT (626.7 ± 20.8 ng/ml vs. 610.4 ± 17.2 ng/ml; p=0.669). Mean tacrolimus trough level was similar in BK virus detected and undetected patients at 6th month after KT (7.16 ± 0.42µg/lvs. 7.38 ± 0.96µg/l; p=0.615**).**

Table 8 showed that status of renal function in BK virus infected kidney transplantation patients.

4. DISCUSSION

The primary BK virus infection occurs in early childhood and leads to lifetime persistence in the kidney. Reactivation occurs in immunocompromised patients. In the setting of renal transplantation, viral reactivation further leads to BK virus nephropathy (BKVN), which compromises renal function and can lead to graft failure [12]. Many renal allograft recipients present to us with asymptomatic rise in serum creatinine. BK virus infection is one of the cause in this regard worldwide and more so in South Asian countries like India. So far no study was conducted on the incidence of BK virus infection among renal allograft recipients in Bangladesh due to lack of technical feasibility like BK virus DNA extraction and detection of BK virus by polymerase chain reaction (PCR). So for the first time, an attempt to see the frequency of BK virus infection among renal allograft recipients in this center has been undertaken. This cross-sectional study was carried out in the Department of Nephrology at Bangabandhu Sheikh Mujib Medical University, Dhaka. In this study, by convenient sampling 29 adult patients who underwent renal transplantation were enrolled from the period of July 2015 to June 2016.We had collected detailed information from renal transplant patients and recorded them using data collection sheets. We evaluated the frequency of BK virus infection in renal allograft recipients. All BK virus infected renal allograft recipients were asymptomatic. The mean age of patients in BK virus positive and negative groups were similar ($p>0.05$). The age (Mean ± SD) of BK virus detected patients was 28.67 ± 11.55 years and that of undetected patients was 28.43 ± 6.49 years with the age range of 16 to 48 years. Soleymanian et al., [16] worked on a total of 50 renal transplant candidates where the mean age was 37.8±13 years. Sachdeva et al., [17] reported in a study done in India the age of the renal transplant patients ranged from 13 to 65 years, with a mean age of 39 years. There was no significant difference in gender between BK virus infected and BK virus non infected patients. Among BK virus infected patients, 83.3% were male and 16.7% were female. 52% of subjects were male, as stated by Soleymanian et al., [16]. Sachdeva et al., [17] had done a study on 321 renal transplant patients where 84% were male. This finding is agreeable with our findings. Among patients who received cyclosporin (n=13), BK virus was detected in 23.1% patients. Among those who received tacrolimus (n=16), BK virus was detected in 18.7% patients. Mean cyclosporin C2 level was similar in BK virus detected and undetected patients at 6th month after renal transplantation (626.7 ± 20.8 ng/ml vs. 610.4 ± 17.2 ng/ml; $p=0.669$). Mean tacrolimus trough level was also similar in BK virus detected and undetected patients at 6th month after renal transplantation (7.16 ± 0.42 µg/l vs. 7.38 ± 0.96 µg/l; $p=0.615$). Therefore, the CNI levels in the BK virus infected patients were within the normal limit defined for renal allograft recipients at the 6th post- operative month. Sachdeva et al., [17] concluded that there was a high incidence of BK (polyoma) virus infection in Indian renal allograft recipients possibly due to administration of cyclosporine and azathioprine based immunosuppression. Brennan et al., [18] found that viruria was the highest with patients on tacrolimus plus mycophenolate (46%) and the lowest in those on cyclosporine and mycophenolate (13%). Serum creatinine level in patients without BK virus infection showed no statistical significant difference between the levels at two weeks and that at 6th month after kidney transplantation but in the BK virus detected group serum creatinine rose from 1.27 to 1.81 mg/dl which was statistically significant. White et al., [19] assessed BKVN in renal transplant patients in London and reported that serum creatinine rose from a baseline of 1.7 to 2.2 mg/dl due to the infection. The frequency of BK virus infection among patients of kidney transplantation was found to be 20.7%. Among them, 17.3% patients were found PCR positive in urine and the rest (i.e. 3.4%) were found PCR positive in both urine and blood. No patient was detected positive for BK virus in only blood samples without BK virus in urine. Comparable with our findings, Jozpanahi et al., [20] also reported that BK virus was not detected in any plasma samples alone of renal transplant candidates whose urine were negative for BK virus PCR. In another study by Soleymanian et al., [16], BK viremia was reported in 2.5% of renal transplant recipients during the first year of renal transplantation. In this study, we found that BK (polyoma) virus infection is prevalent in renal transplant patients. High environmental load, genetic factors or poor nutritional status of patients might account for the incidence. Nasiri et al., [21] showed that 3.3% of renal transplant recipients had BK viremia. Pezeshgi et al., [22] conducted a study to see the incidence of BK virus nephropathy in renal allograft recipients. They evaluated 31 consecutive kidney transplant recipients (21 men and 10 women) and found BK virus in 45% of the urine samples. However, Samarbasf-Zadeh et al., [10] performed a study

on 78 renal recipient cases and found that 6.4% were positive for BK virus. In that study 10 urine samples (12.8%) turned out as positive for this virus one month after transplant operation and 30 of urine specimens (38.5%) became positive for BK virus six month's post-transplantation. Of the 78 plasma samples of these cases, none of them was found positive for BK virus before transplantation. One plasma specimen (1.3%) turned out as positive for BK virus one month after transplantation and 16 plasma samples (20.5%) were positive for this virus six months after transplantation. On the other hand, Bressollette-Bodinet al., [23] reported a higher number of BK virus infected patients by DNA uria and DNA emia which occurred in 57% and 29% of patients respectively by real-time PCR. Comparable to this study, Sachdeva et al., [17] found a high incidence of BK (polyoma) virus infection in Indian transplant recipients which was found to be 9.3%. Status of graft function in BK virus detected patients were as follows: 33.3% developed asymptomatic BK virus infection with impaired renal function, 66.7% developed asymptomatic BK virus infection with normal renal function. Gardner et al., [24] in their study reported that 26% BK virus infected patients had impaired graft function. In another study by Soleymanian et al., [16], BK viremia was reported in 2.5% of renal transplant recipients during the first year of renal transplantation.

5. CONCLUSION

This study was carried out to find out the frequency and proportion of patients of BK virus infection in renal allograft recipients of BSMMU at sixth month after transplantation. According to this study it could be concluded data highlights that BK virus infection is prevalent in our center.

CONSENT AND ETHICAL APPROVAL

Ethical clearance was taken from the ethical committee of BSMMU, Dhaka. Written informed consent was obtained from each respondent.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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