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BK virus replication in renal transplant recipients: Analysis of potential risk factors may contribute in reactivation

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ABSTRACT

Background: Considering the increasing problem of BK virus infection during post renal transplant surveillance, it is necessary to distinguish the main risk factors leading to reactivation of latent BK virus. Up to now, some probable risk factors have been investigated in some studies, but the results have been confusing and contradictory.

Objectives: The goal of the present study was to determine the frequency and potential risk factors that may play a role in BK polyomavirus reactivation and nephropathy.

Study design: In this cross-sectional study, 110 patients, who underwent consecutive transplantation between 2010 and 2013, were enrolled without preliminary screening. Urine and blood samples were taken, and quantitative Real-time PCR assay was used to detect and measure the viral load. Demographic and clinical characteristics of the patients who had BK viremia and/or viruria were documented.

Results: Among 110 cases of renal transplant recipients, BK viruria and viremia were found in 54 (49%) and 22 people (20%) respectively. The pre-transplant durations of dialysis among patients with BK viruia were found longer in comparison to BK negative patients. Treatment with Tacrolimus ($p = 0.03$) was found to be a risk factor for development of BK viruria. In patients with viruria and viremia the median creatinine levels were 1.45 mg/dl and 1.35 mg/dl respectively, which were higher than those in the patients with negative results for BK viruria ($p = 0.002$) and viremia ($p = 0.02$). Also, treatment with Cyclosporine could significantly increase the incidence of BK virus shedding in both urine and blood among patients who received it ($p = 0.01$). Significant relation between reactivation of BK virus and other factors such as age, sex, acute rejection and diabetes was not found.

Conclusion: Based on our findings, the main potential risk factors for shedding of BK virus into urine in renal transplant recipients were prolonged pre-transplant dialysis and Tacrolimus regimen. Cyclosporine regimens could be considered as risk factor for both BK viruria and viremia. A significant correlation between BK virus replication and elevated creatinine level was seen among our patients.

1. Background

Although the name of BK virus has rarely been mentioned as a pathogenic agent in some extra-renal human diseases, it has been strongly known as a significant viral infection related to nephropathy and renal graft-failure in kidney transplant recipients [1]. The first isolation of BK virus was carried out by Gardner et al. in 1971 [2], and thereafter its clinical importance was demonstrated by Mackenzie et al. in 1978 [3]. It has been reported that 60–90% of healthy populations become seropositive by the age of 10 [4–7]. Following both non-deliberate and deliberately induced immunosuppression, BK viruses begin to replicate in the epithelial cells of the kidney, ureter and bladder and can cause nephropathy in some cases [8]. The most BK virus related nephropathy occurs after kidney transplantation, but it has also been reported infrequently in non-renal solid organ transplant (NRSOT) patients and bone marrow transplant recipients [9]. The relatively recent increase in

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the prevalence of BK nephropathy can be probably as a consequence of administration of more potent Calcineurin Inhibitor (CNI)-based immunosuppressive drugs such as Tacrolimus or Mycophenolate Mofetil (MMF) [10]. A likely hypothesis explaining the increased prevalence of BK virus among kidney transplant recipients is that effective viral control depends on the complementary immunologic interaction between donor and recipient, with decreased affinity of binding and recognition in infected donor uroepithelial cells presenting antigen to recipient $CD8^+$ cells. This model would explain the increased risk of BK viremia and BKN in human leukocyte antigen-mismatching [11–14]. Considering the importance of BK virus in renal transplantation, it is necessary to distinguish the main risk factors leading to BK virus reactivation and nephropathy. Determination of risk factors may allow us to propound algorithms for early prediction of reactivation and ensuing nephropathy.

2. Objectives

The goal of present study was to determine the frequency and potential risk factors that may play an important role in BK polyomavirus reactivation and nephropathy.

3. Study design

3.1. Renal transplant recipients

In present cross-sectional study, 110 patients who underwent consecutive transplantation between 2010 and 2013 were enrolled without preliminary screening. No pretransplant BK status data was available. There was no prophylaxis, intervention and treatment for BK virus infection among our patients before. The median age of the renal allograft recipients was 43.9 years (range: 18–77). There were 44 women (40%) and 66 men (60%). The median sampling time after transplantation was 42 months. Twenty-two (20%) of the 110 recipients were diabetic. Mean duration of dialysis before transplantation was 14.2 months. Five (4.5%) patients have had episode of acute rejection (Table 1).

3.2. Sampling and real-time PCR

From each patient, one urine and one peripheral EDTA-blood samples (5 mL) were collected. Pelleted urine samples were prepared by centrifugation in 3500 rpm for 10 min based on recommendation of Pinto et al. [15]. The supernatants of centrifuged blood were discarded and pellets were harvested for DNA extraction process. Cell-free plasma, obtained after blood centrifugation, and pelleted urine samples were kept at −20 °C until DNA extraction. Extraction of BK virus DNA from 200 µL of plasma and urine were carried out using spin column-based QIAamp DNA mini kit (Qiagen, Hilden, Germany) and eluted into a final volume of 50 µL. Extracted DNA samples were stored at −80 °C for later quantitative polymerase chain reaction (qPCR) testing. BK virus DNA detection and quantitation was performed by qPCR using RealStar® BK VIRUS PCR Kit (Altona Diagnostics GmbH, Hamburg, Germany) in the Molecular Diagnostics Center, Guilan University of Medical Sciences. The quantification standards, QS1–QS4 (10–10,000 copies/mL), used for the BK virus quantification were included within the kit. The following cycling steps were used: initial denaturation at 95 °C for 10 min, followed by 45 cycles of 95 °C for 15 s and 58 °C for 1 min. Demographic and clinical characteristics of patients who had BK viremia and/or viruria were documented. BK viruria was defined as detecting BK virus DNA above a diagnostic threshold of 2500 copies/mL, high-level BK viruria as urine DNA loads of > 7 log 10 copies/mL. BK viremia was defined as plasma BK virus loads above the lower diagnostic limit of detection of 1000 copies/mL, high-level BK viremia as plasma BK virus loads of > 4 log10 copies/mL [16].

Table 1
Baseline characteristics of study population.

Age, mean(sd)	43.98	12.7
Sex, n (%)		
female	44	40
male	66	60
DM, n (%)	23	20.9
Cr, mean(sd)	1.32	0.47
Duration of Dialysis, month, mean(sd)	14.2	1.8
Acute Rejection episode (history), n (%)	5	4.5
Duration of transplant, month, mean (sd)	42.01	9.4

Abbreviations;: SD, Standard Deviation; DM, Diabetes Mellitus; Cr, Creatinine level

3.3. Immunosuppressive regimens

Three main immunosuppression drugs were used among patients before sampling as follows: 105 (95.5%) patients received Mycophenolate Mofetil (Cellcept, Roche, Basal, Switzerland), 98 (89.1%) recipients were treated by Prednisolone pulse therapy, and 86 (78%) patients were prescribed Cyclosporine (CsA; Iminoral, Zahravi, Iran). Whereas a lower percent of patients received other drugs as follows: Azathioprine in 14 (12.7%), Tacrolimus (Prograf, Fujisawa Pharmaceutical Co. Ltd.) in 13 (18%) and Sirolimus in 11 (10%) participants.

3.4. Statistical analysis

Risk factors for BK virus replication and the associated inflammatory signature were analyzed using the statistical software packages, SPSS version 21 for Windows. Result was reported as mean (standard deviation) or frequency (percentage) for numerical or qualitative data, respectively. We used the chi-square test to compare the frequency of qualitative variables according to presence of BK in blood or urine. Also, independent *t*-test was used to assess the numerical variables in groups with and without BK. P value less than 0.05 was considered statistically significant.

4. Results

4.1. Prevalence of BK virus replication

The present cross-sectional study included 110 kidney transplant recipients, from the North of Iran, who underwent transplantation between 2010 and 2013, and Real-time PCR was used for the detection of BK viruria and viremia. Of these, 54 (49%) patients were found to have BK DNAuria with an average age of 43.29 years; 30 were male and 24 were female. 20% (n = 22) of them had BK DNAemia as well, with an average age of 41.4 years; 17 were male and 5 were female. There was no documented case with positive plasma BK DNA without viruria among our participants. The median time to detect viruria and viremia was 35 and 39 months after transplantation.

4.2. Immunosuppressive drugs and BK virus replication

Among the 110 recipients, the immunosuppressive drugs were scheduled before sampling as follows: Mycophenolate Mofetil for 105, Prednisolone for 98, Cyclosporine for 86, Azathioprine for 14, Tacrolimus for 13 and Sirolimus for 11 renal transplant recipients. We examined whether immunosuppressive regimen was different between BK virus replication positive or negative groups. Based on our findings, treatment with Mycophenolate did not affect the virus replication, since the difference between patients with BK virus replication (n = 52 (96.39%)) and those without (n = 53 (94.6%)) was not significant (p = 0.6). Like Mycophenolate, Prednisolone regimen, in BK positive group (n = 48 (88.9%)) and BK negative group (n = 50(89.3%)) did not show any significant difference as well (p = 0.9). Tacrolimus receiving patients showed higher prevalence of BK viruria (n = 10

Table 2
Demographic and clinical characteristics of renal transplant recipients and incidence of BK virus reactivation.

	BK viruria		P value	BK viremia		P value
	+ [54]	− [56]		+ [22]	− [88]	
Age, mean (sd)	43.3 (12.4)	44.5 (13.2)	0.6	41.4 (11.1)	44.6 (13.1)	0.3
Sex, n (%)			0.3			0.05
female	24 (44.4)	20 (35.7)		5 (22.7)	39 (44.3)	
male	30 (55.6)	36 (64.3)		17 (77.3)	49 (55.7)	
DM, n (%)	8 (14.8)	15 (26.8)	0.1	2 (9.1)	21 (23.9)	0.1
Cr, mean(sd)	1.45 (0.5)	1.18 (0.3)	**0.002**	1.35 (0.4)	1.21 (0.3)	**0.02**
Duration of Dialysis, month, mean(sd)	17.07 (1.8)	11.2 (3.7)	**0.04**	14.36 (8.1)	14.10 (6.1)	0.9
Time Post-Transplantation, month, mean(sd)	35.8 (8.7)	48.5 (9.4)	0.09	39.4 (4.7)	42.6 (3.5)	0.7
Acute Rejection episode(history)	2 (3.7)	3 (5.4)	0.6	2 (9.1)	3 (3.4)	0.2
Immunosuppressive drugs						
Mycophenolate mofetil	52 (96.3)	53 (94.6)	0.6	20 (90.9)	85 (96.6)	0.2
Prednisolone	48 (88.9)	50 (89.3)	0.9	20 (90.9)	77 (88.6)	0.7
Cyclosporin	37 (68.5)	49 (87.5)	**0.01**	13 (59.1)	73 (80.1)	**0.01**
Azathioprine	7 (13)	7 (12.5)	0.9	5 (22.7)	9 (10.7)	0.1
Sirolimus	6 (11.1)	5 (8.9)	0.7	3 (13.6)	8 (9.1)	0.5
Tacrolimus	10 (18.5)	3 (5.4)	**0.03**	3 (13.6)	10 (11.4)	0.7

Statistically significant values are formatted in bold.

(18.5%)) in comparison with the patients who did not received it (n = 3 (5.4%)) (p = 0.03). Also, treatment with Cyclosporine could significantly increase the incidence of BK viruria and viremia among patients (p = 0.01). In patients who received Azathioprine and Sirolimus, the frequency of antirejection treatments did not show any difference between the BK virus replication positive and negative groups (Table 2).

4.3. Transplant variables and BK virus replication

The demographic and transplant variables of the 54 renal allograft recipients with BK virus replication and the 66 recipients without BK virus replication are summarized in Table 2. Mean creatinine levels in patients with BK virus viruria or viremia (1.45 mg/dl and 1.35 mg/dl, respectively) were higher than patients who had negative results for BK viruria (p = 0.002) and viremia (p = 0.02). Patients with BK viruria were also dialyzed longer in comparison to BK negative patients (p = 0.04). No significant relation was seen between reactivation of BK virus and other factors such as age, gender, acute rejection and diabetes (P > 0.05). Five of the 110 patients were treated for clinical acute rejection. Three of them were negative for BK replication and two people were positive. Our analysis showed that the risk of BK virus replication in those with acute rejection therapy (n = 5) compared with those without acute rejection therapy (n = 105) was not different and that the antirejection therapy did not increase the risk of BK virus replication (p = 0.6). Patients with confirmed diabetes mellitus consist 23 from total 110 renal transplant recipients, and 8 of them were positive for BK viruria, so no significant correlation was seen between diabetes and BK virus replication (p = 0.1). The median duration of dialysis before transplantation among our recipients was 14.2 months. In BK positive groups, the mean duration of pre-transplant dialysis was 17.07 months, whereas in negative group it was 11.22; and significant correlation between prolonged dialysis and probability of BK virus reactivation after renal transplantation was found (p = 0.01).

5. Discussion

Human and animal polyomaviruses with significant clinical disorder has risen in recent years [17]. Polyomavirus-associated nephropathy (PVAN) has become the most common viral complications in renal transplant recipients and is an increasingly recognized cause of renal transplant dysfunction and graft loss.

Since the first description of PVAN in 1995, an increasing prevalence rate from 1% to 10% has been evidenced [18]. Before the mid-1990s, no research was practically confirmed, and risk factors promoting viral nephropathy were poorly understood; the main factor for the development of disease appeared to be new immunosuppressive drug regimens that could provide the right window of opportunity for viral replication [19]. Besides, as reported by Drachenberg et al., and Hirsch et al., neither the mechanisms for allograft fibrosis, nor the basis for BK virus nephropathy resulting in end stage renal disease (ESRD) was known [20,21]. Although 90% of populations worldwide were seropositive for BK virus and 7% of healthy adults shed BK virus in urine asymptomatically, approximately 40% kidney transplant recipients reactivated the virus post-transplantation and approximately 10% of them showed nephropathy [22–24]. A fact that only 20–30% of renal transplant recipients have shown BK viremia and 10% have experienced the related nephropathy arose a question regarding the probable risk factors contributing in reactivation of dormant virus after transplantation. Nevertheless, some prospective and retrospective studies were performed in renal-transplant recipients to investigate the potential risk factor leading to BK virus replication and nephropathy (10, 11, and 14). The answer may conduct us to prepare a defined algorithm for prediction of reactivation during post transplantation. It seems that these investigations about risk factors contributing in BK virus reactivation will guide us to propose a determinative algorithm for the behavior of BK virus after kidney transplantation. In present study, we have focused on exploring the association between some clinical and demographic characteristics and polyoma BK replication among renal transplant recipients. The 49% prevalence rate observed among urine samples was collected from our participants by quantification of viral DNA in urine. This was higher than previously reported numbers about the prevalence of BK virus among Iranian kidney transplant recipients [25–27]. Also the 24% viremia frequency result among our patients confirmed previous epidemiological studies accomplished among the Iranians and other nationalities as well [25,28]. Our cross-sectional retrospective study has identified that Tacrolimus therapy regimen increased the risk for BK virus replication in adult recipients of human renal allografts. Our observations about Tacrolimus confirmed the findings reported in previous studies by others [29–32]. In a randomized study of 200 renal allograft recipients induced with ATG, Brennan et al. noted that the incidence of BK viruria was higher with the Tacrolimus/Mycophenolate regimen compared with Cyclosporine/Mycophenolate, but Tacrolimus, Mycophenolate or Cyclosporine were not independently associated with viruria or viremia [33]. Prince O. et al. also found that Immunosuppression with

Mycophenolate and/or Tacrolimus and ATGAM, could be risk factors for PVN development and other drugs such as Cyclosporine, Azathioprine and Sirolimus had no effect on BK virus replication [34]. In our study, the number of neither the Mycophenolate, nor Prednisolone regimen person was significantly different between the BK virus replication positive and the BK virus replication negative group. We also found that the Sirolimus and Azathiprine receiving patients were not different between the two groups. Nonetheless, not all studies demonstrated a lower incidence of BK viremia with Tacrolimus, compared with Cyclosporine-treated patients. Based on our knowledge, our result about Cyclosporine was the first report of clinical significance of Cyclosporine in BK virus reactivation post renal transplantation. However considering the low percentage of Tacrolimus receiving patients among our population, the result about Tacrolimus could be a bias as a result of this limitation.

The correlation between elevated serum creatinine and BK virus reactivation was reported in some previous studies. Ghafari et al. found a significant correlation between BK virus associated nephropathy and elevated creatinine level among 160 participants involved in their study [35]. In present study, since biopsy (for the diagnosis of BK virus nephropathy) was not done in BK positive patients, the answer to the question is whether increased level of creatinine could be a risk factor for the reactivation of BK virus, or an elevated level of creatinine results from BK nephropathy; that is the issue requires further investigation.

It was repeatedly documented in previous studies that the incidence of reactivation of BK virus after kidney transplantation was accompanied by a diminishing pattern during years post-transplant follow-up [36–38]. The risk of BK virus replication was the highest during the first year after the surgery. Our retrospective cross sectional results showed that the prevalence of BK virus among recipients who were grafted in near time to sampling had a higher incidence in comparison to patients with elapsed time post transplantation (no statistically significant difference).

Although neither acute rejection nor antirejection therapy was associated with an increased risk of BK virus replication in our study, the low incidence of acute rejection among patients (5 of 110 subjects were treated with antirejection therapy) may have contributed to the lack of association. We also identified that prolonged dialysis before transplantation surgery was an independent risk factor for BK virus replication. Girmaneva et al. reported that prolonged dialysis before transplantation could be a risk factor for reactivation of BK virus in a cohort study [39]. Hirsch and Hariha et al. also reported that there was a significant linear correlation between longer time of dialysis and increased rate of reactivation after transplant surgery [40]. Our observation confirmed these results.

Age, gender, diabetes mellitus and acute rejection were not associated with BK virus replication in our study. A similar lack of association between BK virus replication and nephropathy and several of the demographic and transplant variables has also been reported [41,42]. However, analyzing rare events through large multicenter helps us to uncover information that is not easily gleaned from single-center series.

In summary, our cross-sectional retrospective study of 110 renal allograft recipients suggests that the main potential risk factors for shedding of BK virus into urine in renal transplant recipients are the prolonged pre-transplant dialysis and Tacrolimus regimen. Cyclosporine regimens could be considered as a risk factor for both BK viruria and viremia. A significant correlation between BK virus replication and elevated creatinine level was seen among our patients. However, elevated level of serum creatinine may either results from BK associated nephropathy, or leads to BK reactivation. Yet, it needs further investigation.

Competing interests

The authors declare that the results presented in this paper have not been published previously in whole or in part. There is no competing interests.

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Ethical approval

All participants provided written informed consent, and the study protocol was reviewed and approved by the Research Ethics Boards at the Guilan University of Medical Sciences and ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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