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BK Viremia among Iranian Renal Transplant Candidates

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KEY WORDS

BK virus (BKV)
Prevalence
Renal transplant candidates

ABSTRACT

Background: Primary infection with BK virus (BKV) is occurred during childhood and usually asymptomatic, but after initial infection, BKV may persist lifelong in the kidney and genitourinary tract. Reactivation may occur in individuals with compromised immunity such as renal transplant recipients. Due to the role of BKV in BK virus-associated nephropathy (BKVAN) and potentially renal allograft rejection, the detection of BKV in renal transplant candidates is very important. The aim of this study was to evaluate the frequency of BK viremia in end stage renal disease cases who were candidates for renal transplantation.

Methods: In this cross-sectional study, 50 cases with end stage renal disease who were candidates for renal transplantation were recruited from the main dialysis unit in Tehran, Iran. Presence of BK viremia was determined in plasma samples of cases using real time PCR.

Results: A total of 50 renal transplant candidates with mean age 37.8 ± 13 yr were enrolled in the study. Fifty two percent of subjects were male. Forty six (92%) of them were under HD and 4 (8%) were on PD. BK virus was not detected in any plasma samples of renal transplant candidates.

Conclusion: This study showed absence of BK viremia in our renal transplant candidates. However, due to the important role of BKV in BKVAN and renal graft failure and rejection, further studies involving larger number of cases are required to elucidate the rate of the BKV in renal transplant candidates.

ARTICLE INFO

Received 18 Oct 2015;

Accepted 01 Mar 2016;

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Introduction

BK virus (BKV) belongs to genus Polyomavirus within the Polyomaviridae, a family of small, nonenveloped, double-stranded

DNA viruses (1). Its genome is divided into 3 regions: the early, late and transcriptional control region (TCR). Early genes code the regulatory small and large T proteins and late genes code the viral capsid proteins (VP1, VP2, and VP3)

and agnoprotein (1, 2). TCR included elements for transcriptional control of both early and late gene expression (1, 3).

The primary infection with BKV usually occurs in early childhood. It is estimated that 35-90% of the general population will acquire the primary infection during infancy and its seroprevalence reaches 46%-94% in adults depending on the studied regions (1, 4, 5). Primary infection is usually asymptomatic, but after initial infection, BKV may persist lifelong in the kidney and genitourinary tract epithelium and possibly peripheral blood mononuclear cells, tonsils and other hematopoietic tissues (6, 7).

BKV may be reactivated in subjects with altered immune responses such as patients infected with human immunodeficiency virus (HIV), old age, diabetes mellitus, pregnant women, cases who receiving chemotherapy and in bone marrow and solid organ transplant recipients (7-10).

BKV infection in renal allograft recipients can cause tubulo-interstitial nephritis, ureteric stenosis, haemorrhagic cystitis, transient renal dysfunction and progressive renal impairment due to BK virus-associated nephropathy (BKVAN) (1). BKVAN is one of the most important causes of graft failure and loss in renal allograft recipients (7). BKVAN can be detected in about 1-10% of renal transplant recipients and is an important cause of loss of renal allograft ranging from 0% to 80% in patients, depending on detection time, different immunosuppressive protocols and diagnostic approaches (1, 7, 11).

Renal transplantation (RT) is the best therapeutic option for patients with end stage renal disease (ESRD) who undergoing hemodialysis (HD) or peritoneal dialysis (PD). BKV replication usually starts early after transplantation and after initiation of therapy for rejection when immunosuppression is high and immune control is low (8).

Due to the role of BKV in BKVAN and potentially renal allograft rejection, the detection

of BKV in renal transplant candidates (ESRD patients) is very important. The aim of this study was to evaluate the frequency of BK viremia in end stage renal disease cases who were candidates for renal transplantation.

Materials and Methods

In this cross-sectional study, 50 cases with end stage renal disease who were candidates for renal transplantation were recruited from the main dialysis unit in Tehran, Iran, from March to June 2015. A questionnaire was used to collect data such as age, sex, length of time on dialysis and history of receiving blood transfusion or erythropoietin.

This project was approved by the Iranian Society for Support of Patients with Infectious Diseases Ethics Committee and informed consent was obtained from patients prior to their enrollment.

Red blood cells (RBCs), hemoglobin (Hb) and hematocrit (HCT) were tested in all cases. Anemia in cases with chronic kidney disease (CKD) was defined as Hb levels below 13 g/dl in males and below 12 g/dl in females.

A peripheral blood sample was collected in an EDTA-containing sterile tube. Plasma was separated by centrifugation and stored at -80 °C for further tests. BK viremia was determined by real time PCR in all cases.

DNA Extraction and Real time PCR

Viral DNA was extracted from 200 µl of plasma using RTP DNA/RNA Virus Mini Kit (Invitek, Berlin, Germany) following the manufacturer's instructions.

BKV-DNA was determined by real-time PCR using RealStar BKV PCR kit (Altona Diagnostics GmbH, Germany) on the Rotor-Gene 6000 real-time thermal cycler (Corbett Research, Sydney, Australia). The detection limit of the kit is 50 IU/ml according to the user manual.

Statistical Analysis

The Chi-square and Fisher exact test were used with the SPSS 16 Package program for statistical analysis (Chicago, IL, USA). Data are presented as mean±standard deviation or, when indicated, as an absolute number and percentage.

Results

A total of 50 renal transplant candidates with mean age 37.8±13 yr were enrolled in the study. Fifty two percent of subjects were male. Forty six (92%) of them were under HD and 4(8%) of them were on PD. The mean duration of dialysis was 59.4±52.6 months and dialysis interval was 3 times a week.

Anemia was observed in 80% of cases (23 male and 17 female). Mean hemoglobin levels was 10.8±1.6 g/dl (range: 7.9-14.4 g/dl) and mean HCT was 34.3±5.3% (range: 23%-45.6%). 32% of patients had previously received blood transfusion (mean 1.9±1.3 times). All of the cases received erythropoietin (EPO) with mean duration of 32.8±26.3 months.

BK virus was not detected in any plasma samples of renal transplant candidates.

Discussion

In this study, the frequency of BK viremia in renal transplant candidates was investigated. BK virus was not detected in any cases. This result is in accordance with other Iranian studies which also reported low frequency of BK infection in dialysis patients, renal transplant recipients and BKVAN cases (12-15).

Renal transplant recipients are at high risk of infections that may endanger the allograft and patient outcome. Complications due to infectious agents are associated with serious morbidities in these cases. Several investigations have reported the incidence of post transplantation infections from 49% to 81% (16-18). BKV

infection is currently one of the most common infections in renal transplant recipients (19) and BKVAN is an important post renal transplant complication, which, if untreated, can progress to allograft failure and rejection (11). BKVAN therapy is difficult and no antiviral drug is currently approved for its treatment (20). Since anti-BK specific immunity monitoring is not widely available, molecular screening of BKV replication and reduction of immunosuppression in addition to regular monitoring can prevent or resolve BKVAN and improve renal function by stabilizing serum creatinine in renal transplant recipients (21-24).

Other investigations from Iran also reported low BKV frequency in dialysis patients, renal transplant recipients and BKVAN cases. Sharif et al. (12) studied BK viremia in hemodialysis and peritoneal dialysis patients. They reported BK viremia in 3.03% of PD and none of HD subjects. Soleymanian et al. (13) reported BKVAN in 0.93% of kidney allograft biopsies and in 1.04% of kidney transplant recipients. In another study (14) "BK viremia reported in 2.5% of renal transplant recipients during the first year of renal transplantation but BKVAN did not develop in any of them". Nasiri et al. (15) showed that 3.3% of renal transplant recipients had BK viremia.

Kaydani et al. (25) investigated urine samples of kidney transplant recipients in Ahvaz, southwest of Iran and found BKV-DNA in 41.8% of urine samples. Pakfetrat et al. (20) reported BKV replication in 15.7% of plasma and 11% of tissue samples of kidney transplanted patients in Shiraz, southwest of Iran. These differences may be due to variation in BKV infection rates between different parts of the country, because the rate of BKV infection is related to the environmental conditions and population density which are important factors for BKV transmission (26, 27).

Other investigations were conducted in dialysis and renal transplant recipients showed different rates of BK viremia. Mitterhofer et al. (28) reported BK viremia in 33% of HD patients

and none of the PD cases. Miller et al. (29) found BK viremia in 43.3% of kidney recipients. Naumnik et al. (30) showed BK viremia in 10.3% of renal transplant recipients. A study in United Arab Emirates kidney transplant recipients found 2.7% BK viremia in studied cases (31). In Tunisia, BK viremia was detected in 5.5% of renal transplant recipients (32).

In this study we found no BK viremia in our renal transplant candidates. The absence of BKV replication in this study is in accordance with low frequency of BKV infection in the Iranian dialysis patients and renal transplant recipients (12-15). In the similar study to our survey in candidates for kidney transplantation living in the Brazilian Amazon Region, also none of the cases was infected with the BKV as our subjects (33). We acknowledge that the potential limitation of our study was small number of enrolled patients and absence of control group for comparing BKV frequency.

Conclusion

This study showed absence of BK viremia in our end stage renal disease cases who were candidates for renal transplantation. However, due to the important role of BKV in BKVAN and potentially renal allograft rejection, further studies involving larger number of cases are required to elucidate the rate of the BKV in renal transplant candidates.

Acknowledgements

The authors are grateful to Iranian Society for Support of Patients with Infectious Diseases for financial support of this study. The authors declare that there is no conflict of interests.

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How to cite this article:

Jozpanahi M, Ramezani A, Ossareh S, Banifazl M, Bavand A, Mamishi S, et al. BK Viremia among Iranian Renal Transplant Candidates. Iran J Pathol. 2016; 11(3):210-5.