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BK Virus Prevalence in the Plasma of Chronic Kidney Disease Patients Awaiting Renal Transplantation

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Authors' contributions

This work was carried out in collaboration between all authors. Author Mediha Boran designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author EB participated in the writing of the paper, revised the article. Author EGO collected the data, managed the literature searches. Author Mertay Boran participated in analysis of the data, participated in the writing of the paper, revised the article. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Aims: BK virus (BKV) infection in renal transplant recipients is an important problem. Although pre-transplant hemodialysis (HD) patients undergo routine screening for cytomegalovirus, herpes virus and other viruses, and post-transplantation receive antifungal, antibacterial and CMV prophylaxis, BKV infection, including viruria and viremia, has been ignored. In this study, we investigated the

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prevalence of plasma BKV positivity in 100 HD patients.
Study Design: Prospective observational study.
Place and Duration of Study: Department of Nephrology, Hemodialysis and Transplantation, Turkiye Higher Education Hospital, and Department of Nephrology, Ankara Diskapi Yildirim Beyazit Training and Research Hospital, Nephrology Department, Turkey; between March 2014-June 2014.
Methods: The study population consisted of 41 female and 59 male (mean age: 46.1±12.3 years) HD patients from different units (median dialysis history: 60 months; range 24–132), who were awaiting renal transplantation and 25 age- and sex-matched healthy controls (10 females and 15 males; mean age: 44.6±7.8 years). The exclusion criteria for patient selection were HD patients with residual diuresis and age > 65 years. Because the absence of diuresis was among the study's inclusion criteria, only the prevalence of BKV in plasma was determined using quantitative real-time polymerase chain reaction.
Results: BKV replication was not detected in the plasma samples of either the controls or the HD patients.
Conclusions: Whether there is virological variance and changing virulence in BKV over time in pre- or post-transplant patients remains to be determined in future studies.

Keywords: Hemodialysis; BK virus; preoperative period; kidney transplantation; real-time polymerase chain reaction.

1. INTRODUCTION

Patients with chronic kidney disease (CKD) of different etiologies who are being treated with renal replacement therapy (RRT) are immunocompromised [1], as both factors (CKD and RRT) are involved in the pathogenesis of immunodeficiency [2,3]. During hemodialysis (HD), contact between the blood and HD membrane can lead to leukocyte degranulation and complement activation [4], in turn causing alterations to the cellular or humoral components of the immune system. In kidney transplant recipient, aggressive immunosuppression results in an immunocompromised status. Infection with BK virus (BKV) is most commonly seen in immunocompromised individuals [5]. A primary BKV infection during childhood, which manifests as upper respiratory tract symptoms, may result in sustained elevated titers of the virus throughout life [6]. Although reactivation of latent BKV is typically not seen in the immunocompetent host, an altered immune status can lead to transient, asymptomatic BKV activation [7]. Pre-transplant HD patients do not undergo routine screening aimed at the detection of BKV, whether as viruria or as viremia. Therefore, in this study, we used real-time polymerase chain reaction (PCR) to measure the plasma BKV levels in 100 HD patients without preserved diuresis who were on a waiting list for kidney transplantation and in 25 age- and sex-matched healthy controls.

2. METHODOLOGY

The study population consisted of 100 patients diagnosed with CKD who were undergoing HD at different units and 25 age- and sex-matched healthy controls. The exclusion criteria for patient selection were HD patients with residual diuresis and age > 65 years. All HD patients had been placed on a waiting list for kidney transplantation 60–90 days after their first HD session. The clinical data obtained from the patients included age, sex, HD history (months of renal replacement treatment), and the etiology of CKD. Because the absence of diuresis was among the study's inclusion criteria, BKV load was measured only in plasma samples using quantitative real-time PCR (Q-PCR). BKV infection was defined according to Kidney Disease Improving Global Outcomes 2009 guidelines on the basis of viremia evaluated using Q-PCR, with a cutoff of > 1,000 copies of viral DNA per mL of sample [8]. Blood samples obtained from the patients and the controls were centrifuged at 3,000 rpm for 15 min and incubated in Eppendorf tubes. DNA was extracted within 43 min using the Ez 1 Advanced Virus card V2.0 (Qiagen) and carrier RNA according to the manufacturer's instructions. BKV was PCR-amplified using an artus BKV rotor gene PCR V1 kit (24). Plasma samples were quantitatively assayed for BKV-DNA using the Qiagen Corbett Rotor Gene 6000 (Q) system (series 060833). Amplification data were analyzed after 108 min with software provided by

the manufacturer. All samples are expressed as copies of viral DNA per mL of sample. Standard precautions were taken to prevent contamination. All studies were performed using four standard positive controls and one negative control. A BKV copy number of ≤ 30 copies/mL was considered negative. All subjects provided informed consents prior to entering the study.

2.1 Statistical Analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov/Shapiro-Wilk tests were used to determine whether the data were normally distributed. The results of descriptive statistics are expressed as the mean ± SD or median (minimum-maximum) depending on the distribution characteristics. A paired-sample *t*-test was used to determine differences between continuous variables; a χ^2 test was used to determine differences between categorical variables. $P < 0.05$ was considered to indicate statistical significance.

3. RESULTS

The 41 female (41%) and 59 male (59%) HD patients had a mean age of 46.1±12.3 years and a median dialysis time of 60 (24–132) months. The etiologies of CKD were: Chronic glomerulonephritis (14%), hypertensive nephrosclerosis (23%), diabetic nephropathy (15%), tubulo-interstitial nephritis (18%), shrunken kidney of unknown etiology (25%), and polycystic kidney disease (5%). The 10 females (40%) and 15 males (60%) comprising the healthy controls had a mean age of 44.6±7.8 years. There were no significant differences between the two groups with respect to their age (p=0.438) and sex (p=0.927) distributions. Q-PCR failed to detect BKV replication in the plasma of any of the HD patients or the controls. There were no deaths in this cohort.

4. DISCUSSION

The exact pathogenesis of BKV infection is unclear. In the urinary tract, BKV remains dormant, with urothelium cells as the primary site of viral latency. Consequently, BKV replication in urine precedes BK viremia [9,10]. Latent BKV infection reactivation in the renal epithelium after immunosuppressive treatment has been proposed as the cause of BKV infection [11]. The development of a BKV infection in kidney transplant recipients has been attributed to pre-transplant bilateral native nephrectomy and to the activation of a previously latent BKV infection in the ureteral and bladder mucosa after aggressive immunosuppression [11]. Bohl et al. [12] provided strong evidence of the donor kidney being the source of BKV infection in renal transplant recipients, and they showed that a high level of anti-BKV antibodies in the donor confers an increased risk of BKV infection in the recipient. Recent studies also support the donor origin of the virus [13–15].

Following a BKV infection, BKV-specific antibody titers decrease progressively with increasing age, such that the seroprevalence decreases from 87% in individuals 20–29 years of age to 71% in those 50–59 years of age [16]. In this study, the mean age of the HD patients and the age- and sex-matched controls was 46.1±12.3 years and 44.6±7.8 years, respectively. Plasma BKV replication was not detected in either group. It has been reported that viruria is detected in 30–40% of renal transplant recipients and the amount is 100-fold over that of blood [11]. Also 10,000,000 copies/mL for urine suggested clinical significance and led to therapeutic interventions after renal transplantation [17]. Urinalysis in HD patients with a long dialysis history would be difficult because a low urine volume and a low or completely absent frequency of urination is typical. In this study, diuresis was not preserved in any of the HD patients, such that BKV replication was assayed only in plasma. Our choice of (Q) real-time PCR was based on its high sensitivity in detecting viral DNA, even when viral titers are low [18]. In a study of 100 HD patients with residual diuresis, BKV was not identified in any of the urine samples [19]. Because of the findings of previous studies [11,19], patients with residual renal function were excluded from our study.

5. CONCLUSION

Despite the negative findings of this study, BK viremia and viruria screening of all prospective kidney transplant candidates and their donors as well as routine post-transplant screening should not be ignored. In patients with viruria, immunosuppressive therapy should be reduced, as this will contribute to a better outcome. Whether BKV status changes over time and its effect on HD and post-transplant patients remain to be determined in future studies.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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