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Polyomavirus BK and JC infections in well matched Finnish kidney transplant recipients

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Summary

Since 2003, only one case of polyomavirus-associated nephropathy (PVAN) has occurred in our clinic despite screening protocols. In contrast to BK virus, the role of JC virus in PVAN is unclear. We studied the incidence and impact of polyomavirus BK and JC viruria and PVAN in well-matched Finnish kidney transplant recipients. All Helsinki University Hospital kidney transplant recipients between 2004 and 2006 were prospectively followed ($n = 163$). Patients with a 12-month protocol-biopsy taken and polyomavirus urinary secretion screened by PCR were studied ($n = 68$). Cyclosporine-based triple-drug immunosuppression was usually used. BK or JC viruria was detected in 18 (27%) and 14 (21%) patients after transplantation respectively. Persistent BK or JC viruria was found in 5 (7%) and 9 (13%) patients. No cases of PVAN were diagnosed from protocol biopsies or from biopsies taken for clinical indications. A positive BK or JC viruria or persistent viruria was not associated with reduced renal function at follow-up, histopathologic changes in 12-month protocol biopsies, or acute rejections. The incidence of BK and JC viruria was similar to what has been previously reported, but no cases of polyomavirus-associated nephropathy were seen in our well-matched kidney transplant population.

Introduction

After BK polyomavirus was recognized as a pathogen causing severe nephropathy in transplant recipients, infections in renal transplant patients have raised increasing concern [1–3]. After primary infection occurring in healthy individuals during childhood, polyomaviruses BK and JC remain latent in the kidney and genitourinary tract epithelium [4,5]. Low-level replication and secretion of polyomaviruses in the urine is found in approximately 30–60% of healthy immunocompetent individuals, with a predominance of JC virus [6–8]. In immunosuppressed kidney transplant recipients, the frequency of the secretion of the BK-type polyomavirus in urine is increased, and is found in 23–57% of recipients [9–11].

Polyomavirus BK can cause polyomavirus-associated nephropathy (PVAN), diagnosed by typical histopathologic changes and immunohistochemical evidence of polyomavirus in a kidney biopsy sample [12]. The reported incidence of PVAN is 1–9% in different kidney transplant populations [9,13–16], and PVAN may result in premature graft loss in as much as 50% of cases [17]. Risk of PVAN is thought to increase with more potent immunosuppression [14], with a majority of reported PVAN cases using tacrolimus-based immunosuppressive regimens [18]. International guidelines recommend screening of polyomavirus in urine after kidney transplantation either by PCR or by detecting decoy cells by microscopy. In patients with BK viruria, a blood PCR is recommended, as viremia is associated with increased risk of PVAN

[18,19]. The role of JC virus in the development of pathologic changes to the allograft is unclear. It is thought to be of minor significance [20], although a recent study reported PVAN in 21% of recipients with positive decoy cells and exclusive JC viruria or viremia and an overall 0.9% incidence of JC virus associated nephropathy after kidney transplantation [13].

The kidney transplant population in Finland differs somewhat from the study populations of all previous studies. Almost all grafts in Finland are from cadaveric donors and well-matched with modest waiting-times. Despite relatively conservative immunosuppressive treatment, acute rejection rates are low (10%) (Kline L, personal communication). We have detected only one case of polyomavirus-associated nephropathy in 2003, although staining for the polyomavirus large T antigen has been routinely performed in all kidney transplant biopsies since 2003 and urine screening by PCR has been applied since 2004 in our clinic. The aim of this study was to examine the impact of BK and JC polyomaviruses and the incidence of BK and JC viruria and polyomavirus-associated nephropathy in a well-matched Finnish kidney transplant population.

Patients and methods

All Helsinki University Hospital district adult kidney transplant recipients who received a graft between 2004 and 2006 (n = 163) were prospectively followed. Polyomavirus PCR detecting both BK and JC virus was prospectively screened from the urine altogether from 102 patients. Protocol biopsy at 12 months was taken from 94 patients. Patients with a functioning graft and both a protocol biopsy taken at 12 months according to the policy of our clinic and polyomavirus PCR screened from urine after transplantation were investigated (n = 68). Patient selection is described in detail in Fig. 1. Baseline immunosuppression was usually a triple-drug regimen with Cyclosporine A, mycophenolate mofetil (MMF) and steroid. In immunologically high-risk-bearing patients (long waiting time, poor match, re-transplantation) cyclosporine was replaced by tacrolimus, and/or induction therapy with basiliximab was administered. In patients with stable graft function and especially in patients with problems in glycemic control or osteoporosis, steroids were withdrawn slowly during the second post-transplant year. Biopsy-proven acute rejections of grade I-II [21] were treated with high-dose intravenous corticosteroids, and/or conversion of cyclosporine to tacrolimus.

Qualitative PCR from urine was routinely performed at 3 and 12 months after transplantation. Briefly, nucleic acids were extracted from urine using MagNA Pure (Roche Applied Science, Mannheim, Germany) and amplified for 40 cycles using the inner primer set of the originally nested polyomavirus PCR assay [22]. Amplified products were typed by *Bam*HI or *Hin*fI restriction fragment analysis in agarose gels, where distinct patterns were visualized for BKV and JCV [22]. Quantitative blood PCR for BK virus was performed only in selected cases using a method modified from Hirsch *et al.* [23]; no routine screening for viremia was applied. Urinary decoy cells were not routinely screened. Polyomavirus was detected from paraffin-embedded biopsy samples by indirect immunoperoxidase staining using a monoclonal antibody against Simian virus 40 (SV40) T-antigen (Calbiochem, Darmstadt, Germany) which cross-reacts with the human polyomaviruses BK and JC [2,12] using the *ultra*View™ Universal DAB Detection Kit (Ventana Medical Systems, Illkirch Cedex, France).

Protocol biopsies at 3 and 12 months were performed under ultrasound guidance with either Bard Magnum® or Bard Biopty® devices or 18 gauge Biopty-cut® needles. Two biopsy cores were obtained. For light microscopy, serial tissue sections were stained with hematoxylin and eosin, PAS, methenamines silver, and Masson's trichrome. All biopsies were scored according to the chronic allograft damage index (CADI) [24], with the individual parameters scored from 0 to 3 according to Banff '97 classification [21], except for the percentage of globally sclerosed glomeruli, which is not included in the Banff classification (0, no globally sclerosed glomeruli; 1, <15%; 2, 16 to

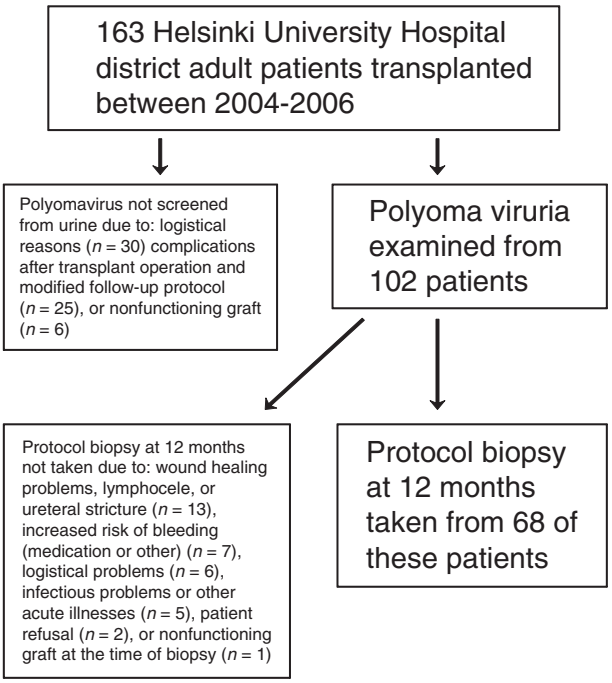

Figure 1 A flow chart of the patients selected in the study.

50%; and 3, >50% globally sclerosed glomeruli). All the biopsies analysed in this study were taken according to our clinical follow-up protocol, and as no extra biopsy or blood samples were taken for the purpose of this study, approval of the ethics committee was not required. A research license from the Helsinki University Hospital research committee was granted before the initiation of this study.

Baseline clinical data at the time of transplantation and clinical follow-up data at 1, 3, 6, 12, 18 and 24 months after transplantation and at the latest follow-up were collected from patient charts and laboratory data-base. Baseline data included: recipient and donor age and gender, cold ischemia time, delayed graft function as defined by the need of dialysis during first post-transplant week, and HLA A-, B-, and DR-mismatch. Follow-up data included: kidney function as measured by plasma creatinine and estimated glomerular filtration rate (GFR) using the Cockcroft–Gault equation [25], trough levels of cyclosporine and tacrolimus, and polyomavirus PCR findings.

All data are expressed as mean ± 1 standard deviation, unless otherwise indicated. Difference in the distribution of continuous and ordinal variables was assessed using the nonparametric Mann–Whitney's *U*-test. Comparisons between more than two groups were calculated with the nonparametric Kruskal–Wallis one-way analysis, and significances between groups were assessed with the Dunn test. Relation between binary variables was calculated with the Fisher's exact test. The calculations were performed with SPSS statistical software (version 15.0; SPSS Inc., Chicago, IL, USA). *P*-values of<0.05 were considered significant.

Results

Of the 68 patients included in the study, four lost the graft and returned to dialysis during follow-up. Reasons for graft loss were: tubulointerstitial nephritis associated with antibiotic treatment at 38 months, chronic allograft nephropathy at 37 months, acute renal failure caused by pyelonephritis at 30 months, and withdrawal of immunosuppression because of post-transplant lymphoproliferative disease (PTLD) at 19 months after transplantation respectively. Mean time of follow-up was 28 months (range 18-46). Mean estimated GFR at the end of follow-up was 68.90 ± 23.17 ml/min. Acute rejection developed in 15 patients (22%) included in the study. Of the acute rejections, four were grade II rejections, others were of grade I. All rejections were fully reversible with intravenous corticosteroids and/or conversion of cyclosporine to tacrolimus.

During the whole study period, urinary polyomavirus secretion was screened from 102 patients. Polyomavirus PCR was positive in 46 patients (45%). JC virus was found in 23/102 (23%) patients and BK virus in 22/102 (22%) patients. In one patient included in the study, virus typing failed because of inadequate urine sample. No cases of polyomavirus-associated nephropathy were diagnosed in patients transplanted during the study period 2004–2006 among or outside our study population. In the 68 patients who had a protocol biopsy taken at 12 months and were included in the analysis, polyomavirus secretion in the urine was found in 33 patients (49%). BK virus was found in 18 patients (27%) and JC virus in 14 patients (21%). No co-infections with both BK and JC virus were detected. More than two samples for the detection of polyoma viruria were taken from 16 patients included in the study (range 3–4). The rate of BK viruria at 3 months was 13% (9/68 patients) and 19% (13/68) at 12 months. The rate of JC viruria at 3 months was 15% (10/68) and 19% (13/68) at 12 months. Polyomavirus was not screened from urine after 12 months after transplantation. No reduction of immunosuppression was applied because of polyomavirus findings. Comparison of study patients with or without BK or JC viruria is presented in Table 1. The one patient with undefined polyomavirus type is not shown in the table. Renal function at the end of follow-up did not differ between patients with or with viruria. No histopathologic changes were associated with either BK or JC virus. Number of HLA mismatches or occurrence of acute rejection after transplantation did not differ between polyomavirus positive and negative patients. Tacrolimus therapy was less frequent among patients with BK viruria than among patients with JC viruria or no viruria, although the difference did not reach statistical significance ($P = 0.05$) (Table 1). Altogether 14 patients had persistent viruria, as defined by a positive polyomavirus finding in two consecutive samples. Persistent BK viruria was found in five patients and persistent JC viruria in nine patients. Persistent BK or JC viruria was not associated with any histopathologic changes or reduced renal function (data not shown). Quantitative BK virus PCR from the blood was performed in 12 of the study patients with viruria, and no cases of viremia were recorded.

Altogether 160 biopsies were taken from the 68 patients included in the study; 38 biopsies for clinical indications from 26 patients, 54 protocol biopsies at 3 months, and 68 protocol biopsies at 12 months. No T-antigen or viral inclusions suggestive of PVAN was found in any of the biopsies taken during the study period. In the patient with graft loss because of steroid-resistant tubulointerstitial nephritis, no viral inclusions were seen, and T-antigen staining was negative in all three biopsies taken for the diagnosis of tubulointerstitial nephritis.

Table 1. Description of patients with or without BK or JC viruria detected at any time point after transplantation. The differences do not reach statistical significance.

	BK viruria (*n* = 18)	JC viruria (*n* = 14)	No viruria (*n* = 35)
Recipient age	47 ± 12	45 ± 14	46 ± 13
Donor age	47 ± 15	46 ± 14	52 ± 10
HLA A, B, and DR mismatch	2.2 ± 0.8	2.1 ± 0.8	2.6 ± 0.8
No. of patients on tacrolimus (%)	1 (5%)	6 (43%)	9 (26%)
No. of patients with acute rejection (%)	3 (17%)	3 (21%)	9 (26%)
Time of follow-up (months)	28 ± 7	28 ± 7	28 ± 6
eGFR at the end of follow-up (ml/min)*	70.8 ± 24.9	71.8 ± 20.4	66.9 ± 23.7
CADI at 12 months†	1.7 ± 2.2	2.4 ± 2.0	2.3 ± 2.0
Interstitial inflammation at 12 months biopsy (0–3)‡	0.3 ± 0.5	0.4 ± 0.7	0.4 ± 0.6

All data expressed as mean ± 1 SD unless otherwise indicated.
*Estimated glomerular filtration rate using the Cockcroft and Gault equation [25].
†Chronic allograft damage index [24].
‡Scored according to Banff '97 classification [21].

Discussion

In the Finnish kidney transplant population, polyomavirus-associated nephropathy is very rare; only one case has been identified so far in our clinic and no cases of PVAN were detected in patients transplanted during this study period. The occurrence of BK or JC viruria was 23% and 22% respectively. Neither BK nor JC virus was associated with any histopathologic changes in 12-month protocol biopsies or reduced renal function at any time point after transplantation.

The incidence of BK virus secretion in the urine among renal transplant recipients varies between 23% and 57% [9–11]. JC virus secretion in urine after renal transplantation is not well documented, but one study reported JC virus DNA in the urine of 22% of renal transplant recipients [26]. In our study, the incidence of polyomavirus viruria was in accordance with other reports. During the whole study period, BK viruria was detected in 22% and JC viruria in 23% of kidney transplant recipients. However, we have diagnosed only one case of polyomavirus-associated nephropathy in 2003, and no patients after that have suffered from PVAN, including patients analysed in this study. The prevalence of serum antibodies against BK virus has been studied in Finland in the 1970s with the seroprevalence being approximately 60% [27]. However, in a recent study of Finnish pregnant women, the seroprevalence of BK virus was 96% and the seroprevalence of JC virus 72% in mothers age >25 years [28]. Differences in these studies may be because of different methods for detecting antibodies and different cut-off values for positive findings. These figures are similar to previously reported figures in other populations [29,30], suggesting that differences in polyomavirus seroprevalence do not explain the low incidence of PVAN in our population. Our study is limited by the lack of seroepidemiologic data of this study population. As JC and BK viruria is detected also in healthy immunocompetent individuals [6–8], it would have been interesting to analyse also donor urine samples, but no donor urine samples were unfortunately available for this study.

Several risk factors for PVAN have been suggested, including higher intensity of immunosuppression using tacrolimus and MMF [1,14], HLA mismatch [31], HLA C7 allele [32], male gender and older donor age [33]. The Finnish population is genetically somewhat isolated, and a good HLA match is possible for cadaveric grafts with relatively short waiting times. Immunosuppression is generally conservative with most patients receiving cyclosporine-based immunosuppression. Also our policy of taking protocol biopsies at 3 months may guide treatment decisions in avoiding overimmunosuppression. We hypothesize that the low number of mismatches and our policy of conservative cyclosporine-based immunosuppression and steroid withdrawal may explain the low incidence of PVAN in Finland. The majority of reported PVAN cases have occurred in patients using tacrolimus-based immunosuppression [18], although a high incidence of PVAN has also been reported in India with all reported patients using cyclosporine [15].

Polyomavirus type JC is associated with the development of progressive multifocal leucoencephalopathy (PML) in acquired immunodeficiency syndrome (AIDS) patients [34], and JC virus has also been associated with tumors of different organs, including the brain, the gastrointestinal tract and the lungs [35]. In healthy immunocompetent individuals, JC virus secretion in the urine can be found with the rate increasing with age [7,8]. Like BK virus, JC virus remains latent in kidney tissues after primary infection [4]. Unlike BK virus, however, some evidence indicates that the activation of JC virus is not dependent on the level of immunosuppression [6,36]. The association of JC virus with PVAN is somewhat controversial. Case reports have associated JC virus with PVAN [37,38]. In one study, JC virus DNA was found in 7/19 kidney allograft biopsies with interstitial nephritis as a co-infection BK virus, while BK virus DNA was found in all 19 biopsies [39]. JC virus alone was not found in any of the biopsies. No co-infections with both BK and JC viruria were detected in our study; although previous studies report the incidence of co-infection being 4% in

all renal transplant recipients studied [26] and 16.5% of decoy cell-positive patients [13]. The low incidence of co-infection with both BK and JC virus may explain the lack of co-infections seen in our study. In a recent study, JC virus associated nephropathy was found in 0.9% of kidney transplant recipients and 21% of decoy cell positive patients had exclusive JC viruria or viremia [13]. Some studies, on the other hand, have failed to show JC virus DNA in kidney biopsies with PVAN [20]. In our study, JC viruria was common but was not associated with any histopathologic changes or reduced renal function and no cases of PVAN were detected. These findings do not support the role of JC virus in PVAN.

Qualitative PCR from urine is thought to be sensitive for the detection of polyomaviruses, but its predictive value for the development of PVAN is low [40]. As we failed to diagnose any cases of PVAN, the usefulness of screening polyomavirus PCR from urine in our transplant population to predict PVAN is very limited. Furthermore, no histopathologic changes were associated with BK or JC viruria. Our study is limited by the lack of quantitative urine PCR, and the lack of systematic blood PCR samples. Furthermore, JC viremia was not assessed from any of the patients in this study. However, qualitative PCR is thought to be sensitive enough to detect all those positive patients who are at risk of PVAN. As no cases of PVAN were detected in the biopsies, we assume not to have missed any cases by qualitative PCR at least in the study population where protocol biopsies were taken. Because of the very low positive predictive value of urinary PCR, quantitative blood PCR may be preferable as a screening test for polyomavirus-associated nephropathy in our low-risk population, especially in patients receiving intensified immunosuppression. Also, the value of SV40 staining in all protocol biopsies with no evidence of polyomavirus infection is very limited.

In conclusion, we report an incidence of BK and JC viruria similar to that in the literature, but no cases of polyomavirus-associated nephropathy were detected. The low incidence of PVAN in our population may be explained by the low number of mismatches and the use of cyclosporine-based immunosuppression in our population. Neither BK nor JC virus secretion in the urine was associated with reduced renal function or any histopathologic changes, not supporting the role of JC virus in the development of pathologic changes after transplantation. Polyomavirus screening strategies in our transplant population need to be reconsidered.

Authorship

IH: primary researcher in this study (study design, manuscript preparation, clinical data collection). FO: Clinical data collection, histopathologic analyses. EA: PCR methods and analyses. ARS: Histopathologic analyses. ML: Clinical Virology, PCR methods. IL: Virology, study design. PK: Clinical nephrology, study design, head of the project.

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