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POLYOMAVIRUS BK INFECTION IN PEDIATRIC KIDNEY-ALLOGRAFT RECIPIENTS: A SINGLE-CENTER ANALYSIS OF INCIDENCE, RISK FACTORS, AND NOVEL THERAPEUTIC APPROACHES

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Background. **Although a growing body of literature regarding polyoma BK virus (BKV) infection and associated interstitial nephritis in kidney-allograft recipients is becoming available, the impact of BKV infection in the pediatric population has not been fully evaluated.**

Methods. **In a retrospective analysis, we performed polymerase chain reaction (PCR) assays for BKV DNA in serum and urine samples from 100 pediatric kidney-allograft recipients referred to our institution in the last 5 years.**

Results. **BKV viruria was observed in 26 of 100 patients, whereas BKV viremia was demonstrated in 5 patients. Serum creatinine was significantly higher in recipients with positive BK viremia compared with BKV DNA-negative patients (mean 2.66 vs. 1.14 mg/100 mL). Renal biopsy performed in 3 of 5 patients showed graft damage consistent with interstitial nephropathy. In the univariate analysis, negative antibody status of the recipient and the presence of mycophenolate mofetil in baseline immunosuppression were the two factors predictive of active BKV infection.**

Conclusions. **Our study shows that BKV-associated nephropathy is a relevant complication in the pediatric kidney transplantation setting also. Identification of patients at risk of developing virus-associated ne-**

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phropathy, through prospective quantification of viral load, could improve clinical outcome by allowing the use of timely preemptive therapy guided by BKV DNA levels.

Persistent active replication of polyomavirus BK (BKV) in kidney-allograft recipients has been identified as an important cause of interstitial nephritis, which may lead to graft failure in as many as 45% to 67% of the affected patients (*1–5*). Currently, no established antiviral treatment is available, and control of viral infection is tentatively obtained by means of reduction of immunosuppression (*1–4*). Early recognition of active BKV infection is crucial for prompt therapeutic intervention to avoid onset of established nephritis. However, the risk of graft rejection because of lowered doses of immunosuppressive drugs (*4*) suggests application of preemptive treatment only to selected groups of patients at high risk of developing BKV-related complications. Therefore, the means to identify such high-risk patients have to be investigated.

Although a growing body of literature regarding BKV-related complications in kidney allografts has been reported, the clinical impact and the factors associated to BKV infection in the pediatric population has not yet been fully evaluated. Analysis of risk factors, conducted mainly on adult graft recipients, have underscored the central role played by serologic status of the donor, immunosuppressive regimens, and acute rejection (*6*). Furthermore, it has been recently demonstrated that polymerase chain reaction (PCR) testing for BKV DNA in plasma is a sensitive and specific method for identifying viral nephropathy (*2*, *5*). Thus, serial analysis of viral DNA could also help identify cohorts of patients with active BKV infection at risk of progression to BKV-related disease and could be a useful tool to monitor treatment efficacy.

In a retrospective analysis, we performed PCR assays for BKV DNA in serum and urine samples from 100 pediatric kidney-allograft recipients, with the aim of evaluating the incidence and clinical relevance of BKV infection and analyzing risk factors relevant to BKV infection in the pediatric population so as to help identify patients at risk of progressive nephropathy.

PATIENTS AND METHODS

Patients

One hundred consecutive unselected pediatric kidney-allograft recipients, referred to the Pediatric Nephrology Unit of the G. Gaslini Institute-Genova in the last 5 years, were studied retrospectively. The clinical characteristics of the patients are summarized in Table 1. Ninety-five patients received a cadaveric kidney transplant, whereas in 5, a living-donor allograft was performed. Our baseline immunosuppression protocols included induction with anti-CD25 monoclonal antibody (mAb) in 18 patients, and double or triple therapy with either cyclosporine A (CsA) or tacrolimus associated with prednisone alone or prednisone and mycophenolate mofetil (MMF). Treatment of acute rejection consisted of pulse steroids and, in the case of steroid resistance (n=7), antithymocyte globulin or a switch to tacrolimus were employed as rescue therapy.

BKV nephropathy was diagnosed by the presence of intranuclear viral inclusion bodies in tubular epithelial cells and was confirmed by PCR positivity for BKV performed on paraffin-fixed tissue sections or identification of viral antigens on renal biopsy. Treatment of BKV nephropathy consisted of reduction of immunosuppression in all cases; in one patient, cidofovir was also used.

Table 1. Characteristics of patients enrolled in the study

Age (years), median (range)	14 (2–21)
Sex (M/F)	59/41
No. of transplants	
First transplant	94
Retransplant	6
Donor age (years), median (range)	12 (1–51)
Cold ischemia (hours), mean (range)	15 (0–34)
Baseline immunosuppression	
Any regimen + anti-CD25 mAb	18
CsA -based regimen	79
FK -based regimen	21
Any regimen + MMF	22
ATN	18
Acute rejection	36

CsA, cyclosporine-A; FK, tacrolimus; MMF, mycophenolate mofetil; ATN: acute tubular necrosis; mAb, monoclonal antibody.

One hundred eighty-two serum and urinary samples were collected during routine laboratory tests at various times after transplantation and were stored for the 100 patients enrolled. Pretransplant serum samples of both patients and graft donors were also analyzed. This retrospective study was performed in accordance with Institutional guidelines.

Virologic Methods

BKV DNA detection in urine and serum samples was performed by a previously described nested PCR method that amplifies a sequence of the transcription control region of the BKV genome (*7*). This reaction can detect one BKV genome copy in the reaction volume as the result of amplification of the serial dilution of the BKV Gardner's strain genome, cloned in pBR322 in our laboratory. Urine samples found to be BKV DNA positive by nested PCR were also analyzed by a competitive quantitative PCR as previously described (*8*). Patients' and donors' sera were titrated against BKV by a hemagglutination inhibition (HI) test. HI titers greater than or equal to 1:40 were considered indicative of past infection.

Statistical Analysis

Data were expressed as either mean±SD or as median and range, as appropriate. The correlation of clinical parameters with BKV viruria and viremia was evaluated by Student's *t* test. The contribution of various risk factors to BKV infection–reactivation was evaluated by Chi-square test. *P* values less than 0.05 were considered statistically significant; *P* values from 0.05 to 0.1 were not considered significant but were reported in detail, while *P* values greater than 0.1 were reported as not significant (NS). Statistical analysis was performed using the SAS System (SAS, Cary, NC).

RESULTS

BK Viruria and Viremia and Correlation with Clinical Parameters

Cross-sectional analysis of BKV DNA was performed on urine and serum samples collected simultaneously at some time point within the fifth year posttransplant. All patients were evaluated retrospectively at a single point of time after transplantation, and data analysis was performed on that sample. Some patients, and in particular the 5 viremic patients, were also evaluated prospectively. Data regarding follow-up of viremic patients are reported in Table 2.

Of the 100 patients, 26 were found to be positive for BKV in their urine samples. BK viremia was demonstrated in 5 of

TABLE 2. Clinical profile of the five patients with positive BKV viremia

Patient	Time Tx–BKV (mos)	Basal creatinine (mg/100 mL)	Creatinine at dx (mg/100 mL)	Renal biopsy	Treatment	BKV DNA outcome	Follow-up after dx (mo)	Clinical outcome
1	3	1.3	2.0	ND	↓ IS	U: + S: −	15	Uretheric stenosis; creat 1.8
2	32	1.1	6.5	yes	↓ IS cidofovir	U: +[a] S: −	3	Graft loss; second renal Tx after 18 mo
3	29	1.6	1.9	ND	↓ IS	U: + S: −	18	Creatinine 1.8
4	1	1.2	1.5	yes	↓ IS	U: + S: −	16	Creatinine 1.5
5	4	1.1	1.4	yes	↓ IS	U: + S: +	14	Creatinine 1.4

[a] Upon BKV treatment, the patient persisted as positive for BK viruria. Following graft loss, however, with consequent discontinuation of IS, DNA on urine samples cleared.

Tx, kidney transplantation; dx, BKV diagnosis; ND, not done; IS, immunosuppressive drugs; U, urine; S, serum.

26 viruria-positive patients (3 evaluated in the first year and 2 in the third year posttransplant) and in 0 of 74 viruria-negative patients. In the patients with detectable viremia, higher BKV viruria levels, measured by quantitative PCR, were observed as compared with allograft recipients without concomitant BKV positivity in serum (genome copy range 10^5–10^8/100 μL vs. 10^2–10^6/100 μL). Records of renal-function parameters were then reviewed in relation to BKV viral load (Fig. 1). In comparison with BKV DNA-negative patients, serum creatinine was significantly higher in allograft recipients with positive BK viremia (mean serum creatinine 1.14 vs. 2.66 mg/100 mL, $P<0.0001$); patients with positive BK viruria in the absence of viremia also showed increased values of serum creatinine, although this was not statistically significant (1.30 mg/100 mL vs. BKV-negative patients, $P=0.09$). Comparable results were also observed for calculated creatinine clearance (Fig. 1B). After a median follow-up of 8 months, a reevaluation of serum creatinine and calculated creatinine clearance in the previously stratified groups showed that the significant negative correlation between BKV infection and renal function was maintained (data not shown).

Three of the five patients with BK viremia and a significant increase of serum creatinine levels were biopsied and showed histopathologic features consistent with BKV-associated tubulointerstitial nephritis. The clinical profile of the five viremic patients is shown in Table 2.

Risk Factors for BKV Active Infection

Relation of BKV active infection, evaluated as positivity for BKV DNA in urine, to the patients' clinical data was evaluated in a univariate analysis. No differences in age at transplant, sex, primary renal disease, use of living-donor graft, number of previous grafts, and number and class of matched donor-recipient human leukocyte antigen (HLA) alleles existed between infected and uninfected patients (data not shown). In addition, no correlation was found between duration of cold ischemia, presence of acute tubular necrosis, and occurrence of graft rejection (Table 3).

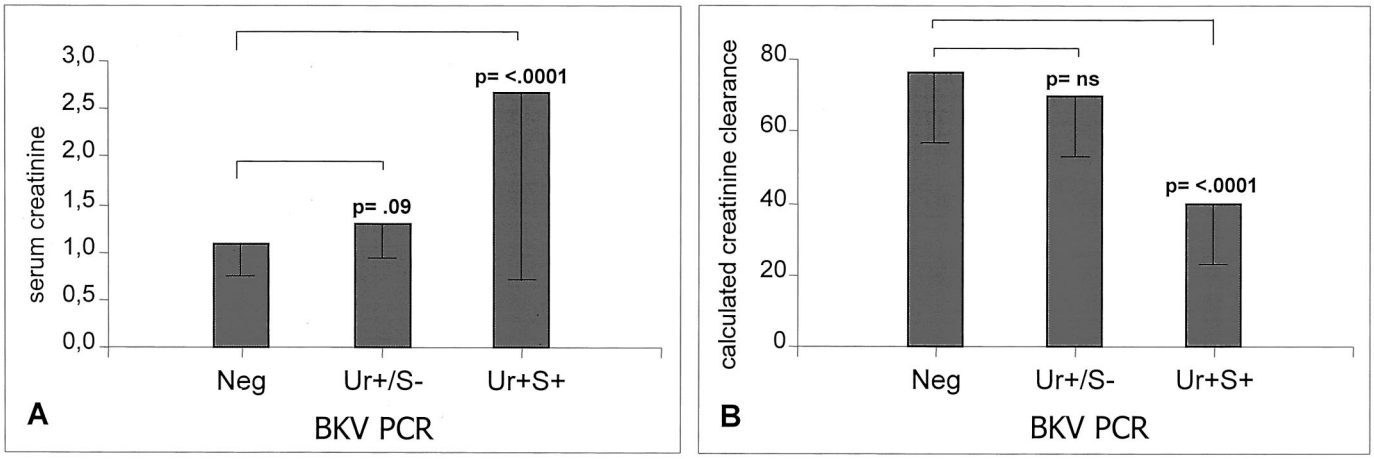

FIGURE 1. Renal function in pediatric kidney-allograft recipients with BK virus (BKV) infection. (A) Serum creatinine levels (mg/100 mL) in patients with BK viremia (Ur+/S+) (mean levels±SD 2.66±1.95) and BK viruria excluding the five patients with concomitant viremia (Ur+/S-) (mean levels±SD 1.30±0.39) compared with BKV DNA-negative patients (mean levels±SD 1.14±0.38). (B) Calculated creatinine clearance (mL/min per 1.73 m^2) in patients with BK viremia (Ur+/S+) (mean levels±SD 39.8±17.3) and BK viruria (Ur+/S-) (mean levels±SD 69.6±16.9) compared with BKV DNA-negative patients (mean levels±SD 76.1±19.1).

TABLE 3. Risk factors for BKV infection–reactivation: univariate analysis

	No. patients	Patients with BK viruria + (%)	Odds ratio	95% confidence	*P*
BKV serology[a]					
Recipient +	56	21			
Recipient −	24	58	4.9	(1.8–13.5)	$P < 0.005$
Donor −	26	31			
Donor +	54	32	1	(0.4–2.7)	*P*=NS
Cold ischemia					
<12 h	22	18			
12–18	63	27	1.5[b]	(0.5–5)	*P*=NS
>18 h	15	33	1.4[c]	(0.4–4.5)	*P*=NS
			2.1[d]	(0.5–9.2)	*P*=NS
ATN					
No	82	26			
Yes	18	28	1.2	(0.4–3.5)	*P*=NS
Baseline IS					
Anti-CD25 mAb: no	82	23			
Anti-CD25 mAb: yes	18	39	2.1	(0.7–6.1)	*P*=NS
CsA-based	79	23			
FK-based	21	38	2.1	(0.8–5.7)	*P*=NS
MMF: no	78	21			
MMF: yes	22	45	3.2	(1.2–8.5)	$P < .05$
IS at time of BKV analysis					
CsA-based	69	25			
FK-based	31	29	1.3	(0.5–3.2)	*P*=NS
MMF no	46	22			
MMF yes	54	30	1.5	(0.6–3.7)	*P*=NS
Acute rejection					
No	64	28			
Yes	36	22	0.75	(0.3–1.9)	*P*=NS

[a] Data on serology were available for 80/100 patients.
[b] Odds ratio:<12h vs. 12–18 h.
[c] Odds ratio: 12–18h vs. >18 h.
[d] Odds ratio: <12 vs. >18 h.
ATN, acute tubular necrosis; IS, immunosuppression; mAb, monoclonal antibody; CsA, cyclosporine A; FK, tacrolimus; MMF, mycophenolate mofetil, NS, not significant.

Eighty of the 100 patients included in the study had pretransplant and donor's sera available. Fifty-six of the 80 (70%) evaluated patients and 54 (67.5%) donors were found to be BKV seropositive. In the univariate analysis, negative antibody status of the recipient was the most important predictor of BKV infection (Table 3). In detail, 14 of 24 seronegative recipients had BKV infection–reactivation as compared with 12 of 56 seropositive recipients (58.3% vs. 21.4%, $P<0.005$). Conversely, no statistically significant correlation with BKV infection was observed in recipients of seropositive as compared with seronegative graft (31.5% vs. 30.8%, *P*=NS). Within the seronegative recipient population, patients receiving a seropositive graft had a higher probability of BKV infection than those transplanted with a seronegative organ (69% vs. 37%).

The presence of MMF in immunosuppression regimens at baseline, but not at the time of BKV viruria testing, was the other significant risk factor of BKV infection (Table 3). The use of anti-CD25 mAb, and the presence of tacrolimus rather than CsA in immunosuppressive regimens at baseline or at the time of BK viruria, were not found to have significant impact on BKV shedding.

In regards to the association between the risk factors positively correlated with active BKV infection and BKV disease as diagnosed by biopsy, it is noteworthy that three of three patients with BKV nephropathy were BKV-seronegative recipients receiving the graft from a seropositive donor, and two of three received MMF as part of their baseline immunosuppressive regimen.

DISCUSSION

Our retrospective analysis shows that BKV infection is an emerging complication in the setting of pediatric kidney transplantation. Indeed, as reported for cohorts of adult recipients (*1*, *5*, *9*), we found a 26% incidence of BKV infection–reactivation, with histologically documented interstitial nephritis in 3% of the overall population.

With respect to the course of BKV infection, our study confirms the data reported by Nickeleit et al. (*2*) on the positive relationship between the presence of viral DNA in blood and impairment of renal-allograft function, thus indicating viremic patients as a cohort at high risk of progression to BKV-related interstitial nephritis. Moreover, a recent prospective study has shown how plasma viral load is significantly higher in patients with biopsy-proven BKV nephropathy than in patients without histologic evidence of nephropathy (*5*). However, data from both our study and the literature (*1*, *2*) suggest that viremia is a late event in BKV infection, mostly associated with the presence of graft dysfunction. Consequently, a therapeutic intervention at this

stage might be too late to avoid graft-damage progression, or require too prompt a reduction of immunosuppression, with consequent increased risk of graft rejection (*3*). Our preliminary data on quantitative urinary BKV DNA seem to suggest that patients with viremia have higher levels of urinary BKV DNA as compared with viremia-negative recipients, although some overlap in viruria levels between viremic and nonviremic subjects was observed. Therefore, further prospective studies are warranted to determine whether urinary DNA quantitation can be predictive of viremia and graft damage occurrence to obtain indication for preemptive therapeutic intervention.

In our study, negative antibody status of the recipient was the most important predictor of active BKV infection, whereas seropositivity of the donor was not a risk factor per se but only in association with recipient seronegativity. This finding is apparently in contrast with previous observations in adult cohorts, notwithstanding the comparable percentage of seronegative recipients in our population (*10*, *11*). A hypothetical explanation for this discrepancy is that some of the adults found seronegative have in fact been exposed to the virus but have subsequently experienced a waning of antibody titers. Alternatively, as also observed for Epstein-Barr virus (EBV) (*12*), because of the increased exposure of adults to environmental antigens, a cross-reactive immune response in true BKV-seronegative individuals could account for the lack of risk for BKV infection shown by seronegative adult-recipient populations.

A role for immunosuppression in the development of BKV infection has been indicated by a number of reports (*1*, *3*, *5*, *6*, *9*, *13*). As reported for an adult cohort (*9*), MMF, in the initial immunosuppressive regimen, but not at the time of BKV DNA testing, was positively associated with occurrence of BK viruria in our pediatric series. Another risk factor that has been suggested to favor polyomavirus replication is tissue injury inherent in transplantation (*14*). However, in line with previous observations (*15*), we did not find a correlation between BK viruria and either duration of cold ischemia or acute tubular necrosis or with acute rejection episodes.

Our findings seem to indicate that, at least in the pediatric kidney-transplant population, a deficient immune response to BKV caused by iatrogenic alteration of immune function is the main initiating cause of BKV infection–reactivation and is likely enhanced by the allogeneic environment of the graft. The progression of infection to BKV disease indeed may correlate not only with persistent heavy immune deficiency but also with other independent risk factors, such as rejection episodes, concomitant viral infections, and various forms of renal parenchymal damage.

Because onset and persistence of active BKV infection seem to be dependent on an altered specific immune function, we are assessing the feasibility of reducing the incidence of active BKV infection and related interstitial nephropathy through induction or restoration of protective immunity to BKV in renal-transplant recipients. It has been recently reported that cellular immunotherapy has proven to be a successful and safe approach to augment virus-specific immune responses and reduce EBV viral load in organ-transplant recipients (*16*). Preliminary data from our group indicate that it is possible to reactivate and expand in vitro autologous BKV-specific cytotoxic T-cell lines from kidney-graft recipients with evidence of active virus replication. Thus, we intend to verify whether an immunotherapy approach based on infusion of autologous BKV-specific cytotoxic T lymphocytes, following a strategy of preemptive therapy guided by BKV DNA levels, could induce control of BKV infection in vivo without increasing the probability of graft rejection or graft damage.

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