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High-level JCPyV viraemia after kidney transplantation—Clinical and histopathological findings



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ABSTRACT

Background: The significance of JC polyomavirus (JCPyV) after kidney transplantation ranges from irrelevant to full-blown nephropathy or PML.

Objectives: To investigate the clinical significance of high-level JCPyV viraemia and JCPyV primary infections after kidney transplantation.

Study design: JCPyV viraemia was detected in routine screening by quantitative real-time PCR in 40/238 kidney transplant recipients and was high-level ($>10^7$ copies/ml) in 17 patients. A protocol biopsy at the time of JCPyV viraemia was available from 10 patients.

Results: Peak urine viral loads were 1.0×10^7 – 2.5×10^9 copies/ml in the 17 high-level viraemia patients. 6/15 (40%) patients with high-level JCPyV viraemia with pretransplant sera available were JCPyV IgG negative suggesting that JCPyV viraemia resulted from the donor graft in most cases. No acute graft dysfunction was associated with JCPyV viraemia. No positive SV40 staining was detected in protocol biopsies, and no specific histopathology was associated with high-level viraemia; JCPyV nephropathy was not found. No differences were seen in histopathology or graft function at 3 years in patients with high-level viraemia compared to non-JCPyV viraemic patients transplanted during the same time period, and outcome was similar in patients with presumably primary and reactivated JCPyV. The mean estimated GFR at last follow-up was 44 ml/min (range 12–60 ml/min). One graft with high-level viraemia was lost 9 years posttransplant due to recurrent IgA nephropathy.

Conclusions: High-level JCPyV viraemia seems to be associated with primary JCPyV infection reflecting the average seroprevalence of 60%, but is not stringently associated with inferior graft function or survival, or histopathological changes.

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Abbreviations: CADI, chronic allograft damage index; eGFR, estimated glomerular filtration rate; BKPyV, BK polyomavirus; JCPyV, JC polyomavirus; PML, progressive multifocal leukoencephalopathy; PyVAN, polyomavirus-associated nephropathy.

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1. Background

JC polyomavirus (JCPyV) was discovered already in 1964 in the brain tissue of a patient with progressive multifocal leukoencephalopathy (PML) [1], and it belongs to the few human polyomaviruses with documented pathology. Although the role of JCPyV in PML is well described [2], much less is known about JCPyV and pathology after kidney transplantation. Primary infection with JCPyV leads to life-long persistence in the renourinary tract. The seroprevalence of JCPyV ranges from 35% to 70% with

asymptomatic urinary shedding in approximately 30% of healthy individuals [2].

After kidney transplantation, urinary shedding of JCPyV appears slightly more frequently, but viremia is rare and of low level in 7–14% of patients [3,4]. While the role of BK polyomavirus (BKPyV) in polyomavirus-associated nephropathy (PyVAN) is well described [5], the role of JCPyV remains unclear. Several case reports including our own have associated JCPyV with PyVAN [6–9]: However, this seems to be a rare complication with an estimated incidence of less than 1% [3], and in larger studies no clear link of JCPyV viremia with inferior outcome has been detected [10]. Accordingly, current guidelines recommend screening BKPyV from blood or urine after kidney transplantation and prompt reduction of immunosuppression in case of significant BKPyV replication [11,12] whereas screening for JCPyV after kidney transplantation is currently not recommended [11].

However, in a recent case report we described a primary JCPyV infection developing into PyVAN after pediatric kidney transplantation [6], suggesting that JCPyV-specific pretransplant immunity may play a role in the association of JCPyV with PyVAN.

2. Objectives

Our aim was to examine the role of high-level JCPyV viremia in pathological changes in the transplanted kidney, and to examine whether pretransplant JCPyV seronegative patients are at increased risk of pathology associated with JCPyV replication.

3. Study design

3.1. Patients

Altogether 333 adult patients who received a kidney transplant between January 2004 and August 2011 with a graft survival over 6 months were followed up at Helsinki University Hospital Nephrology Clinic. Of these, a total of 238 patients were screened for polyomavirus viremia. Baseline immunosuppression was usually a triple-drug regimen with low-dose cyclosporine A, mycophenolate mofetil (MMF) and steroid. In patients with high immunological risk (long waiting time, poor HLA match, re-transplantation) cyclosporine was replaced by tacrolimus, and/or induction therapy with basiliximab was administered. Among patients with stable graft function, steroids were withdrawn slowly during the second post-transplant year. Biopsy-proven acute rejections were treated with high-dose intravenous corticosteroids and/or conversion of cyclosporine to tacrolimus.

3.2. Methods

The patients were screened for BKPyV and JCPyV from morning urine specimens by qualitative PCR at 3 and 12 months after transplantation as described previously [13]. From 2007 onwards, quantitative detection of BKPyV genomes in plasma was performed

as described previously [14] at three weeks, six and 12 months after transplantation, and also in case of unexplained graft dysfunction or diagnosis of biopsy-proven acute rejection. BKPyV was excluded as the aim was to investigate the significance of JCPyV viremia.

Quantitative JCPyV PCR from positive samples was retrospectively performed as described before [15]. High level viremia was defined as $>7 \log_{10}$ copies/ml, as suggested [16]. JCPyV serology was analyzed retrospectively from serum samples taken before transplantation as described [17,18]. JCPyVAN was defined by high-level JCPyV loads in urine, absence of BKPyV replication, and histopathological changes characteristic of PyVAN including a positive SV40 staining [16].

Protocol biopsies were routinely taken at 3 and 12 months (between 2004 and 2006) or at 6 months after transplantation (from 2007 onwards). All biopsies were scored according to the chronic allograft damage index (CADI) [19], with the individual parameters scored from 0 to 3 according to Banff classification [20]. All biopsies analyzed in this study were taken according to our clinical follow-up protocol.

Pre and post-transplant clinical and laboratory data were collected from patient files and from the laboratory database. Estimated glomerular filtration rate (eGFR) was calculated using plasma creatinine and the CKD-EPI equation [21]. Difference in the distribution of continuous variables was assessed using the nonparametric Mann–Whitney's *U*-test. Relation between binary variables was calculated with the Fisher's exact test. The calculations were performed with IBM SPSS statistics (version 19; IBM Corporation, NY, USA). Two-sided *P*-values <0.05 were considered significant.

4. Results

4.1. JCPyV viremia

Among the 238 screened kidney transplant recipients, JCPyV viremia was detected in 40 patients. Viremia was of high level with $>7 \log_{10}$ copies/ml by quantitative PCR in 17/238 patients (7%) ($1.0 \times 10^7 - 2.5 \times 10^9$ copies/ml). The urine viral loads of the other 23 patients varied between 1444 – 825318 copies/ml. The 17 patients with high-level viremia were further characterized (Tables 1 and 2) and compared with 221 patients transplanted between 2004 and 2011 with no evidence of high-level JCPyV viremia. None of the patients with JCPyV viremia had BKPyV viremia or viremia after transplantation.

4.2. Outcome of patients with high-level JCPyV viremia

During a follow-up of mean 77 months (\pm SD 27 months), one patient with high-level viremia returned to dialysis 9 years after transplantation. Kidney biopsy of the failing graft in this patient showed recurrence of IgA nephropathy as the cause for graft loss. In other patients the grafts were functioning at the end of follow-up, and mean eGFR at the end of follow-up was 44 ml/min

Table 1
Clinical characteristics of the patients with high-level JCPyV viremia ($>10^7$ copies/ml) detected after transplantation.

	Patients with high-level viremia ($>10^7$ copies/ml) N = 17
Age at transplantation (years)	50 \pm 14
Length of follow-up (months)	77 \pm 27
HLA AB mismatches	1.8 \pm 0.8
HLA DR mismatches	0.5 \pm 0.6
N: o of patients on cyclosporine/tacrolimus	10/7
Last eGFR at the end of follow-up	44 \pm 15 ml/min
Acute rejection	1/17 (6%)
CMV viremia after transplantation	6/17 (35%)

eGFR (estimated glomerular filtration rate using CKD-EPI equation (21).

Table 2Virological characteristics of patients with low-level vs. high-level JCPyV viraemia (>10⁷ copies/ml) after transplantation.

	Patients with high-level JCPyV viraemia (N = 17) ^a	Patients with low-level JCPyV viraemia (N = 23) ^b
JCPyV IgG positive before transplantation ^a	9/15 (60%)	8/8 (100%)
Level of peak JCPyV viraemia, median copies/ml (range)**	8.6 × 10 ⁷ (1.0 × 10 ⁷ – 2.5 × 10 ⁹)	2.3 × 10 ⁵ (1444 – 8.3 × 10 ⁶)

^a Pretransplant serum not available from 2 patients.^b Pretransplant serum not available from 15 patients.

** P < 0.001.

Table 3

Comparison of patients with high-level JCPyV viraemia with the background population of patients transplanted during 2004–2011 without evidence of JCPyV viraemia in screening.

	High-level JCPyV viraemia (N = 17)	No high-level JCPyV viraemia (N = 221)
Graft survival at three years after transplantation	17/17 (100%)	212/221 (96%)
eGFR at three years after transplantation ml/min	61 ± 18	57 ± 23
CADI at the time of JCPyV viraemia or at 6 or 12 months after transplantation in patients with no JCPyV viraemia	1.1 ± 1.7	1.3 ± 1.5

Mean ± SD. All differences are nonsignificant.

CADI (Chronic allograft damage index).

eGFR (estimated glomerular filtration rate using CKD-EPI equation (21)).

(range 12–60 ml/min). High-level JCPyV viraemia was asymptomatic in all patients, and no graft dysfunction was associated with JCPyV viraemia.

4.3. Histopathological findings in patients with high-level JCPyV

Of the 10 protocol biopsies taken at the time of high-level viraemia, eight were considered normal or nearly normal (CADI 0 or 1), whereas two biopsies showed chronic changes (mild interstitial fibrosis, vascular intimal sclerosis, CADI 3 and CADI 5 respectively). These two biopsies with chronic changes also showed an unspecific inflammatory infiltrate. Mean CADI in all biopsies taken during high-level JCPyV viraemia was 1.1 (range 0–5). SV40 staining was negative in all biopsies, and no specific histopathological lesions were associated with high-level viraemia. No cases of JCPyV nephropathy were confirmed. No differences were seen in CADI score or graft function at 3 years in patients with high-level viraemia compared to the background population of patients without high-level JCPyV viraemia transplanted between 2004 and 2011 (Table 3).

4.4. Primary JCPyV infections

Pretransplant sera for JCPyV IgG antibody analysis were available from 15/17 patients with high-level viraemia, and from 8/23 patients with low-level JCPyV viraemia. Of the patients with high-level viraemia, six out of 15 (40%) were JCPyV seronegative before transplantation, whereas 0/8 patients with low-level viraemia were JCPyV seronegative pretransplant (P = 0.06). Mean OD levels of JCPyV IgG antibodies in seropositive patients with high-level viraemia

was 0.54 ± 0.50 compared to 0.68 ± 0.38 in patients with low-level viraemia (P = 0.5). Mean peak viral load in urine among the 15 patients with high-level viraemia was similar in patients with primary JCPyV infection after transplantation compared to seropositive patients with JCPyV reactivation (2.89 × E8 (8.46 log₁₀) vs. 1.98 × E8 (8.30 log₁₀) copies/ml, P = 1.0). No difference was seen in graft function at the end of follow-up (mean eGFR 42 ± 20 vs. 43 ± 14 ml/min respectively). Comparison of patients with primary JCPyV infection and those with JCPyV reactivation, including all the 23 patients from whom pretransplant sera were available for analysis, is presented in Table 4. Patients with primary JCPyV infections were younger, and they were more frequently on tacrolimus, but no differences were seen in graft function or survival in follow-up.

5. Discussion

Among a population of 238 kidney transplant recipients screened for JCPyV in the urine, we could identify 17 patients with high-level viraemia. No specific histopathological features or increased frequency of chronic changes could be identified among these 17 patients. High-level viraemia was not found to be associated with inferior graft function or survival in follow-up. Our results suggest that the role of JCPyV in chronic damage to the transplanted kidney, even with highly active replication, seems to be minimal, and JCPyV only rarely causes pathology after kidney transplantation. However, there was a trend towards low or undetectable JCPyV pretransplant antibody levels in patients developing high-level viraemia, suggesting that the JCPyV-specific immune memory might be a determinant for better posttransplant immune control.

Table 4

Comparison of patients with JCPyV primary infection compared to patients with JCPyV reactivation.

	Patients with JCPyV primary infection (N = 6)	Patients with JCPyV reactivation (N = 17)
Age at transplantation (years)	43 ± 14	55 ± 11
HLA AB mismatches	1.8 ± 1.2	1.7 ± 0.7
HLA DR mismatches	0.7 ± 0.8	0.5 ± 0.5
N:o of patients on tacrolimus	4/6 (66%)	2/17 (12%)*
Acute rejection	1/6 (17%)	1/17 (6%)
Median JCPyV load in urine (range), copies/ml	2.9 × 10 ⁸ (6.3 × 10 ⁷ – 2.1 × 10 ⁹)	1.5 × 10 ⁷ (1444 – 2.5 × 10 ⁹)
Graft survival at the end of follow-up	5/6 (83%)	17/17 (100%)
Last eGFR at the end of follow-up	43 ± 20 ml/min	48 ± 16
CADI at the time of JCPyV viraemia	0.5 ± 1.0	1.4 ± 1.5

CADI (Chronic allograft damage index).

eGFR (estimated glomerular filtration rate using CKD-EPI equation (21)).

All other differences are nonsignificant.

* < 0.05.

The lack of outright progression to JCPyVAN in these cases argues that additional factors are required for progression to nephropathy. Some of the differences to the previously reported cases of primary JCPyV infection could be the level and duration of viremia, the intensity of immunosuppression, and the cross-protection by BKPyV-specific T-cells as described previously [22–25]. None of the patients with JCPyV viruria in this material had any evidence of BKPyV replication after transplantation.

As we recently described in a case report of JCPyV seronegative kidney transplant recipient developing JCPyV associated PyVAN [6], patients at risk of primary infection may also be at greater risk of abnormal pathology associated with JCPyV. In our material, forty percent of the patients with high-level viruria were JCPyV seronegative before transplantation, suggesting that primary infection after kidney transplantation may more often lead to extensive virus replication in the renourinary tract. However, even in these JCPyV primary infections, no pathology could be associated with JCPyV viruria. In the general population, the seroprevalence of JCPyV seems to increase with age [18]. In a study of pregnant women in Finland, JCPyV IgG seroprevalence was found to be 72% [26], whereas among healthy blood donors in a Swiss study it increased with age and was found to range between 50% and 68% [18].

The outcome of patients with high-level JCPyV viruria was excellent in our material, with only one graft loss due to recurrent glomerulonephritis nine years after transplantation. However, only patients with a functioning graft 3 or 12 months after transplantation were screened for JCPyV replication, and patients with early graft loss were not included in the study explaining the good outcome also in the patients with no evidence of JCPyV viruria. Otherwise the 17 patients with high-level JCPyV were comparable to our transplant population with regard to the frequency of acute rejections, CMV infections, or the immunosuppression used.

Although some previous reports exist on the lack of association between JCPyV infections and inferior outcome or histopathological changes after kidney transplantation [4,10,13,27], to our knowledge the specific impact of high-level viruria or primary JCPyV infections has not been assessed previously in detail. Several case reports have described that JCPyV is able to cause PyVAN after kidney transplantation [6–9], but our present findings together with previous reports suggest that JCPyV is not associated with extensive pathology after kidney transplantation in the majority of cases. In general, less than 5% of PyVAN is estimated to be caused by JCPyV, and in contrast to BKPyV, JCPyV viremia is rare and of low-level even in cases of PyVAN and cannot be used as a sensitive marker for monitoring [16]. Thus, results of the present study suggest that routine screening for JCPyV replication after kidney transplantation does not seem justified, in agreement with current guidelines [11].

This study has some limitations. Firstly, this was a retrospective study, and the level of JCPyV viruria was not available to the clinician at the time of urine sampling. However, as these data were not available, no modifications to immunosuppression were made due to JCPyV findings, which enabled us to explore the natural course of JCPyV infections. The results of JCPyV urinary loads were expressed as copies per millilitre, and not normalized to the possibly changing concentrations of urine. Although for this study, the first morning urine was used, we cannot exclude that the varying concentration of urine might have an effect on JVPyV loads. In addition, no follow-up samples were available from all patients, and thus duration or persistence of high-level JCPyV replication could not be assessed in all cases. The analysis of primary JCPyV infections was limited as pretransplant sera were not available from all patients, and no true control group was available as only a limited number of patients with JCPyV viruria detected after transplantation were analysed for pretransplant JCPyV antibodies. However, to our knowledge,

our material is the largest so far describing the natural course of the transplanted kidney with high-level JCPyV replication.

In conclusion, high-level JCPyV replication is seen in less than 10% of patients after kidney transplantation. Patients who are JCPyV seronegative before transplantation seem to be at a higher risk of high-level JCPyV viruria after transplantation, but high-level JCPyV viruria is not associated with inferior graft function or survival, or histopathological changes in protocol biopsies.

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Competing interests

None declared.

Ethical approval

The study was approved by the Institutional Review Board and the Ethics Committee of Helsinki University Hospital.

Authorship

IH: Study design, data collection and analysis, preparation of the manuscript, principal investigator.

HHH: Study design, virological methodology, data analysis, preparation of the manuscript.

EA: Virological methodology, preparation of the manuscript.

LM: Virological methodology and analyses, data collection.

MN: Virological methodology and analyses, data collection.

MW: Virological methodology and analyses, data collection.

FO: Data collection.

AR-S: Pathological analyses.

ML: Data collection.

IL: Study design, data analyses, preparation of the manuscript.

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