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Editorial Open Access

JC Polyomavirus Infections in Transplant Patients

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Abstract

The polyomavirus JC virus (JCV) is a small nonenveloped DNA virus that asymptomatically infects about 80% of healthy adults and establishes latency in the kidney tissue. In case of immunodeficient hosts, JCV can lytically infect the oligodendrocytes, causing a fatal demyelinating disease, known as Progressive Multifocal Leukoencephalopathy (PML). Although the reactivation of another human polyomavirus, BK Virus (BKV), is relatively common and its association with the Polyomavirus Associated Nephropathy (PVAN) following renal transplantation is assessed, JCV replication and its impact on graft function and survival is less well studied. In addition, none of the performed studies ruled out the hypothesis that JCV could be associated with certain post-transplantation clinical syndromes. Thus, monitoring of Polyomaviruses infection, especially during the first 24 months post-transplantation, is recommended.

JC virus (JCV) is a member of the *Polyomaviridae* family, including naked DNA viruses with icosahedral capsids and small, circular, double-stranded DNA genomes. The natural hosts for polyomaviruses include humans, other primates, rodents, rabbits and birds [1].

Padgett et al. first isolated it in 1971 from the brain of a patient with the initial J.C., affected by Hodgkin's Lymphoma who died of Progressive Multifocal Leukoencephalopathy (PML), a demyelinating disease of the Central Nervous System (CNS) [2]. PML is a rare disease characterized by the lytic infection of glial cells and is often fatal. The disease occurs almost exclusively in patients with severe immunodeficiency; consequently the incidence of PML has increased dramatically, following the spread of HIV/AIDS. Nowadays, HIV infection is still the most frequent setting for PML, ~80% of the cases, followed by hematologic malignancies (~8%), solid cancers (~3%), organ transplantation and autoimmune diseases treated with immunomodulators [3]. Indeed, successful treatments for PML are not currently available.

JCV does not infect any species other than humans and its ability to infect human cells may be restricted at the level of viral early gene transcription and DNA replication, with the protein named Large T Antigen (Tag) interacting specifically with the human DNA polymerase [4].

JCV has a tropism for replication in human glial cells, kidney epithelial cells and, with a less efficiency, in B lymphocytes, and the restricted CNS tropism is confirmed by both experimental animals and in vitro analysis [4,5].

The transmission of JCV is not fully understood. JCV-specific antibodies are detected in approximately 80% of adults and the primary infection occurs in early childhood, usually in an asymptomatic way and results in a primary viremia. Afterwards, the virus produces a persistent latent infection in the kidney and is shed into the urine. Since JCV may be detected in the tonsillar stromal cells, viral transmission via the respiratory route has been hypothesized, and the virus isolation in B lymphocytes suggested the lymphoid tissue as another site of viral latency with lymphocytes involved in viral circulatory dissemination to other anatomic sites [6,7]. The virus has also been detected in the gastrointestinal tract and in the raw urban sewage suggesting a possible oral or fecal transmission of JCV [8,9]. In the context of an immunosuppressive condition, such as AIDS and transplantation, JCV disseminates to the CNS and litically infects oligodendrocytes, causing the PML. Another hypothesis that explains the pathogenesis of PML states that: JCV may establish latency in normal brain tissue and reactivates in non immunocompetent hosts [10-12].

Reports of JCV infection in renal transplant recipients have been published immediately after the first isolation of the virus [13,14]. Since those times, subsequent works have investigated both the silent and the symptomatic infection and/or reactivation of JCV in the setting of kidney transplantation, finding contradictory results. Gardner and colleagues performed a wide prospective, serological study for the evidence of JCV infection in forty eight renal transplant recipients, finding that 54% of the patients were seropositive already before the operation, and that in 23% of the seronegative patients JCV infection occurred within the first three months after transplantation [15]. Molecular analysis were also conducted, by means of specific *in situ* Hybridization, PCR and Quantitative PCR assays by different international groups: JCV has been identified in kidney biopsy tissue and/or urine within a range of 3.4% and 46% of kidney transplanted patients, while JCV viremia ranged from 0% and 25% [16-24]. The most recent surveys, that had the possibility to measure the amount of replicating JCV in the clinical specimens, reported a very wide range of viral loads, from 2.0×10^3 copies/ml to 1×10^7 copies/ml [17,19,21,22,24,25]. Only few studies analyzed also the molecular features of the isolated virus, observing that the JCV strains infecting the kidney transplantation recipients did not differ significantly from those infecting the immunocompetent subjects [21,25,26].

Regarding the non-kidney solid organ transplants (SOT), the incidence and clinical manifestation of JCV infection have been poorly investigated. In 2005, two independent groups published very different results about JCV infection in liver transplant patients, reporting 1.7% and 22.7% of patients excreting the virus, respectively [24,27]. More recently, Kusne and colleagues observed that 71% of the studied patients excreted JCV after liver transplantation, with very high viral load (1.6×10^6 copies/ml) [28]. Studies on the association between JCV infection and lung, pancreas and heart transplantations are even rarer.

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Although the different experimental approaches and the various results reported by the analyzed studies, they all agree that strict attention should be paid to monitoring JCV infection, especially during the first 24 months post-transplantation. In fact, even if JCV replication was mostly silent, it was not ruled out the hypothesis that it could be associated with certain clinical syndromes.

In particular, infection by JCV has been observed in renal allograft recipients as both nephropathy and/or PML. PML occurs rarely in renal transplant patients and it is typically associated with high levels of viral genome found in the cerebrospinal fluid [29]. However, recent reports suggest that another polyomavirus, closely related to JCV, the BK Virus (BKV), can also cause a PML-like disease [30,31]. BKV was isolated in the VERO cell line from the urine of a renal transplant recipient and it was also named after the initials of the patient from whom it was isolated. In immunodepressed patient, BKV is responsible for severe diseases such as: upper respiratory tract infections, pneumonia, hemorrhagic cystitis, interstitial kidney disease, ureter stenosis, meningitis, encephalitis, retinitis, colitis and vasculitis. Furthermore, its reactivation may be associated with the onset of Polyomavirus Associated Nephropathy (PVAN), a serious complication of transplantation [32].

Renal transplant recipients have the highest risk of developing PVAN in comparison to other organ recipients because of the presence of ongoing graft injury due to drug toxicity, rejection episodes, cold ischemia and donor/recipients HLA mismatch [33-36]. PVAN with graft dysfunction and premature graft loss has been markedly increased since the 1990s [37,38], therefore a pathogenic potential of JCV should be taken into account. In contrast to the closely related BKV, to date, only few cases of nephropathy have been attributed to JCV [39-44]. Low level of JCV replication and shedding are common in immunocompetent individuals [45,46] but surprisingly the incidence of asymptomatic viruria is not increased in renal allograft recipients [47,48]. This suggests that immunosuppressive state is not as strictly related to development of PVAN as it is for BKV [49,50]. In addition, the immunosuppressive regimen does not play any important role and once JCV PVAN has established, the reduction of immunosuppression has a controversial impact on the clinical course [51]. However, a profound immunosuppressive state is required for a pathological and potentially threatening JCV replication. In fact, patients with PML have significant JCV viruria and PML and JCV PVAN have been reported to occur concurrently [43,52-54]. This arise the question whether anti-CD20 biological therapy with Rituximab in kidney transplant recipients is potentially cumbersome, because of a rapid depletion of pre-B and mature B-cells that lasts for at least six months upon its administration. Our recent report in a small cohort of pediatric kidney transplant recipients showed that rituximab treatment had no effect on susceptibility to JCV replication [25]. These findings confirm some reports on adult population treated with either rituximab [55] or different immunomodulator drugs such as natalizumab [56,57], where the risk of JCV new infection or reactivation was found inconsistent.

In a recent paper by Drachemberg and colleagues based on urine cytology and prospective protocol kidney biopsy in a cohort of hundred kidney transplant recipients, the incidence of JCV PVAN was reported as low as 0.9% despite the fact that a significant proportion of the patients displayed JCV viruria or decoy cell shedding [17]. Interestingly, the majority of JCV PVAN was diagnosed in patients with a normal renal function suggesting an apparently less aggressive or more protracted clinical course when compared with BKV PVAN. This was recently confirmed by Cheng et al. in a larger cohort of kidney transplant recipients where the clinical outcome of JCV viruric patients was reported to be favorable up to five years post transplant [58]. Compared to non-JCV viruric patients, rejection rate, graft survival and death-censored graft survival were lower and patient survival was similar. Based on their results, they also suggested that JCV reactivation occurs in the native kidney on immunosuppression rather than in the donor-derived graft in contrast to BKV [36]. Another important difference between BKV PVAN and JCV PVAN is the strong association with viremia and the severity of histological pattern in the former [59]. On the contrary, low level of JCV viremia has been reported either in patients shedding large amounts of JCV in urine or in patients with parenchymal involvement and this may be related to fundamental differences between BKV and JCV biology, which remain presently unexplained [16,27].

In conclusion, JCV PVAN is a unique clinical entity that needs to be differentiated from BKV PVAN. This requires viral typing methods that are not widely available and this should accounts for an underestimation of its incidence in kidney transplant recipients. However, the protracted and non-aggressive clinical course of the disease and the favorable outcome should be considered once this form of PVAN is diagnosed. Thus, monitoring of JCV infection, especially during the first 24 months post-transplantation, is recommended and the development of new, more sensitive technologies will be advantageous.

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