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Original Article

Early HHV-6 replication is associated with morbidity non-related to CMV infection after kidney transplantation

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A B S T R A C T

Human herpesvirus type 6-(HHV-6) has been associated with morbidity after liver transplantation.

Objective: The aim of this study was to determine the HHV-6 seroprevalence among donor-recipient pairs, analyze the incidence of early active infection, its clinical manifestation, interaction with CMV, and the related morbidity in the first year after kidney transplantation.

Methods: 46 donor-recipient pairs had IgG evaluated by ELISA before transplantation: HHV-6-(Pambio – USA) and CMV-(Roche – USA). A frozen whole blood sample collected weekly (from the 1st to the 6th week) was retrospectively tested for HHV-6 viral load (VL) determination by real time quantitative PCR (qPCR, Nanogen – Italy). Patients were preemptively surveyed for CMV by pp65 antigenemia (Ag, APAAP, immunohistochemistry, Biotest – Germany) from the 4th to the 12th week after transplantation. Active infection was defined as qPCR-HHV6+ (viral-load/mL-VL) and Ag+ (+cells/100.000 granulocytes), for HHV-6 and CMV, respectively. DCMV was defined as simultaneous positive antigenemia and suggestive signs/symptoms. Concerning +qPCR-HHV6, associated factors, clinical manifestation, interaction with CMV and morbidity were searched.

Results: Pre-transplant HHV-6 seroprevalence was significantly higher among kidney recipients compared to their donors (82.6x54.8%; p = 0.005 [3.9 (1.4-10.4)]). Active infection by this virus occurred in 26.1% (12/46), with no association with previous IgG (p = 0.412). Median VL was 125 copies/mL (53-11.264), and the median Ag was 21 +cells (2-740). There was no association between HHV-6 and CMV activation after transplantation (p = 0.441), neither concerning DCMV (p = 0.596). Median highest Ag+ and days of ganciclovir treatment were similar between qPCR-HHV6 + or – (p = 0.206 and p = 0.124, respectively). qPCR-HHV6+ was associated with higher incidence of bacterial (p = 0.009) and fungal (p = 0.001) infections, and higher number (p = 0.001) of hospital admission and longer duration of hospitalization over the first 6 and 12 months post-transplantation (p = 0.033 and p = 0.001).

Conclusion: Latent HHV-6 infection is more common among recipients than donors before transplantation. Early active infection by this pathogen after transplantation does not increase DCMV incidence or severity during the first 3 months of follow-up. However, early HHV-6 replication is associated with other infections and hospitalizations in the first year.

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Introduction

Viral infections are one of the major causes of morbidity and mortality after organ and tissue transplants. Besides the etiological agent, the risk of a viral infection depends on the pathogen epidemiology and host's immunity. Because transplants imply the use of immunosuppressant drugs to avoid graft rejection, the diagnosis of a viral infection relies on its kinetics and clinical suspicion, frequently before signs/symptoms. One of the most studied families of virus in transplantation is the Herpesviridae, which encompasses eight different viruses. The majority of them are highly prevalent in the general population and shows an immunomodulatory effect.[1-5]

The deleterious role of the cytomegalovirus (CMV) after transplantation is well recognized, and its active replication is systematically checked. Initially, this active infection was associated with high mortality and morbidity.[1-10] These were the reasons that brought about the current practice of early diagnosis and treatment in risk populations. Nowadays, the morbidity and cost related to the specific antiviral treatment are still major concerns. In addition, late recurrences of CMV, slow decrease of viral replication rate, or even drug resistance have concerned clinicians.[11-15]

CMV replication has been surveyed after kidney, kidney-pancreas, lung, liver, heart, and hematopoietic stem cell transplantations in order to avoid end-organ disease.[3,13,15-21] In our hospital, a preemptive strategy for CMV was introduced in 1993 using antigenemia (Ag) from the 4th to 12th week post-solid organ transplantation and whenever there is clinical suspicion. Based on this, the cumulative incidence of probable CMV disease (pCMVD) in the first 3 months, among kidney recipients, has ranged from 27-38%, and severe cases have not been frequent.[3,13]

Nevertheless, there can be sporadic patients subjected to more than 21 days of intravenous ganciclovir; cases with low cellularity on Ag showing signs/symptoms; and, sometimes, unusual clinical manifestations for patients being preemptively surveyed (as severe bone marrow suppression or central nervous systems involvement). These observations raised the hypothesis that another viral agent could be implicated, such as HHV-6, which also has a known immunomodulatory potential.[1,5,7,18-23]

HHV-6, as other herpesviruses, can remain latent in the host's cells and reactivate as soon as the immunosuppression starts. Usual sites for latency after primary infection include salivary glands, lymph nodes, mononuclear cells, and liver and renal parenchyma.[6] Clinically, HHV-6 causes a mononucleosis-like syndrome, lymphadenopathy, hepatitis, bone marrow suppression, interstitial pneumonitis, and severe focal encephalitis, well-reported in liver transplant recipients.[4,7,8]

Understanding that the epidemiology and the clinical role of the latent and early-active HHV-6 infection after kidney transplantation are not clear, we designed this study. The purpose was to determine HHV-6 seroprevalence in donor-recipient pairs, the incidence of early viral replication after kidney transplant, its clinical repercussion, interaction with CMV, and association with morbidity during the first year after transplantation.

Patients and methods

This was a cohort study that included all the adult kidney transplants performed between April and September/2002 in a tertiary hospital, which is a national reference for transplants (n = 46).

There, donor's and recipient's serology, collected before transplantation, were analyzed for latent infection determination. HHV-6 active infection was described as viral load (VL) measured by real time quantitative polymerase chain reaction (qPCR-HHV6) in peripheral blood collected between the 1st and 6th weeks and frozen at –80°C.

Patients were surveyed preemptively, as routine, with serial CMV-Ag from the 4th to the 12th week post-transplantation. Intravenous ganciclovir was administered prophylactically during 14 days in CMV-IgG negative recipients (n = 3). CMV active infection was defined as CMV-Ag+, and pCMVD was defined as more than ten +cells on Ag independent of the signs/symptoms or increasing number of +cells combined with signs/symptoms, according to our previous study.[13] Treatment was also performed using intravenous ganciclovir for 14 days or more, until Ag became negative.

Donor and recipient demographic data (age and gender) and transplant characteristics (donor source, isolated kidney/simultaneous pancreas-kidney, cold ischemia time, initial immunosuppression, induction therapy and delayed graft function) were analyzed. Delayed graft function was defined as the necessity for dialysis in the first week post-transplantation.

Clinical and laboratory parameters studied that could be associated with HHV-6 included: total leukocytes and lymphocytes (1st-6th week), liver enzymes (aspartate- and piruvate-amminotransferase, 1st-12th week). Serum creatinine levels were evaluated as a graft function marker (1st-12th weeks, monthly until the 6th month, and annually until 4th year). Morbidity in the first year was evaluated by: biopsy-proven acute graft rejection, development of other infections (non-HHV-6 and non-CMV), hospital admission (number and duration), and graft loss and death. Information was taken from medical records.

The variables above described were compared, qualitative and quantitatively, as indicated, between patients who developed HHV-6 active infection (+qPCR-HHV6) and those who remained negative. In order to avoid a bias due to CMV infection, all comparisons were performed between positive and negative patients, as follows: a) HHV-6 active infection (qPCR-HHV6+), b) CMV active infection (CMV-Ag+) and c) active infection by both viruses (qPCR-HHV6 + CMV-Ag+) after transplantation, each one analyzed during its higher risk period.

For the study of HHV-6 latent and early replication effects upon CMV infection, the following associations were analyzed: a) incidence of CMV active infection, b) incidence of pCMVD and c) pCMVD severity (highest Ag+ and days of ganciclovir treatment).

This study was approved by the institutional Ethics Committee, and all patients included signed an informed consent.

HHV-6 and CMV serology

Immunoenzimatic test (ELISA) for specific IgG was performed in the sera of all donor-recipient pairs collected before the