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Clinical Significance of Human Herpesvirus 6 and 7 Infection in a Tertiary Hospital: a Case-Control Study

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Abstract

Background: Human herpesviruses (HHV)-6 and HHV-7 are ubiquitous viruses with a global seroprevalence of around 90%, but their pathogenic significance remains unclear.

Methods: For 2 years, at our center, the presence of HHV6 and 7 DNA was investigated by PCR assay in blood, CSF, or other fluids. Epidemiological and clinical variables were collected from these patients and compared with those obtained in a negative-control cohort. Molecular detection of herpesvirus was performed using The Clart Entherpex kit (Genomica, Coslada, Spain), allowing simultaneous detection and identification of the eight human herpesviruses (HSV-1 to HHV-8) and Enterovirus (echovirus, poliovirus, and coxsackievirus).

Results: All patients, cases, and controls were immunocompromised and had similar baseline clinical conditions. For all of them, molecular amplification of HHV-6 or 7 was requested as a diagnostic complement from different clinical pictures, mainly neurological symptomatology (80%). Corticosteroid treatment and viral or bacterial co-infection were independently associated with HHV-6 or 7 infections. When the impact of both viruses was analyzed independently, it was confirmed that HHV-6 was independently associated with higher 1-year mortality.

Conclusion: HHV-6 replication in CSF or blood may be a surrogate marker of mortality in the medium term in immunocompromised patients.

Keywords: Human Herpesvirus 6, Human Herpesvirus 7, Clinical significance, Immunocompromised patients

Introduction

HHV-6 and HHV-7 infections are more frequent in immunosuppressed patients and are associated with specific clinical syndromes. In vitro studies suggest that HHV-6 has immunomodulatory properties, including alterations in the expression of immune activation molecules (CD3, CD46, CCR7, or CXCR4) or cytokines (IL-2, interferon-gamma, tumor necrosis factor-alpha, IL-1beta, IL-10, IL-12, and IL-15), aspects that probably contribute significantly to the pathogenesis of the infection and especially to its immunosuppressive potential [1-3]. Like HHV-6, HHV-7 encodes genes capable of interfering with the host immune response, such as intense down-regulation of CD4 expression on T cells [3-7]. Like other herpesviruses, HHV-6 and HHV-7 are highly seroprevalent in the adult population and possess the ability to establish life-long latency and to reactivate in immune compromised settings [4-6]. Central Nervous System (CNS) infections have

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been the most frequently implicated for both viruses, although the role of HHV-7 reactivation within the CNS as a cause of the neurological disease is not clear [8]. HHV-6 encephalitis following allogeneic hematopoietic cell transplantation is a serious and often fatal complication accompanying reactivation of HHV-6B. The incidence varies among studies, with a higher risk among those receiving umbilical cord blood transplantation [9]. Magnetic resonance imaging (MRI) typically shows bilateral signal abnormalities in the limbic system. This complication is considered to represent acute encephalitis caused by direct virally induced damage to the central nervous system, but our understanding of the etiologies and pathogenesis is still limited [9].

HHV-6 infection has been associated with increased expression of adhesion molecules on vascular endothelial cells in liver allografts, eventually contributing to graft dysfunction and rejection [10]. Various studies have reported a higher risk of rejection in the presence of HHV-6 infection [11, 12], although the causal direction of this relationship may be confounded by the fact that viral reactivation is also more likely to occur after antirejection therapy [13]. HHV-7 reactivation has only occasionally been associated with neurological disease in immunocompromised adults [14] but possesses neurotropism, and HHV-7 DNA may be detected post-mortem in brain tissue samples [15]. The role of reactivation of HHV-7 as a cause of neurologic disease in immunocompetent adult patients has not been established [16]. Reactivation in CSF might be an epiphenomenon associated with other inflammatory or non-inflammatory diseases of the CNS, and we cannot entirely rule out the possibility that HHV-6 or HHV-7 reactivation simply represents a surrogate for overimmunosuppression and, therefore, a marker of increased risk for infection and other adverse events.

To date, the prognostic significance of such infections is not well known. This reactivation could hinder the control of the baseline disease and represent an additional factor of comorbidity and a more torpid progression in the short and medium term. The present study evaluated the clinical relevance of HHV-6 and HHV-7 viral load and its role as a surrogate marker of poor prognosis in immunocompromised patients. The confounding role of ciHHV-6 – a condition in which the complete HHV-6 genome is integrated into the chromosome of a host germline cell – may have led to the misdiagnosis of active HHV-6 infection. However, the estimated prevalence of ciHHV-6 in the general population is very low (≈1%–2%) [17], so it seems unlikely that this condition could have significantly impacted our findings.

Material and methods

This is a single-center case-control study in which the presence of HHV-6 or HHV-7 viral load in blood or other biological samples for 2 years (2019 and 2020) was analyzed. It was in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and after receiving approval from the institutional Research Ethics Board. A case was considered if DNA HHV-6 or HHV-7 or both were detected in blood or other biological samples. For each case, a control was chosen among those immunocompromised patients in whom HHV-6 or HHV-7 viral load detection was requested and was negative. Given the higher representation of CSF and blood in cases, controls were chosen with patients showing the absence of amplification of both viruses in CSF (two-thirds) and blood (one-third). Molecular detection of herpesvirus was performed using The Clart Entherpex kit (Genomica, Coslada, Spain), allowing simultaneous detection and identification of the eight human herpesviruses (HSV-1 to HHV-8) and Enterovirus (echovirus, poliovirus, and coxsackievirus). Briefly, total nucleic acids were extracted from 200 µl of serum sample using a MagPurix® Viral Nucleic Acid Extraction Kit instrument (Zinexts Life Science Corp., Taiwan) according to the manufacturer's instructions.

The genetic material was recovered in 50 µl of elution buffer and stored at -80°C before 5 µl of elution were added to two tubes with lyophilized amplification reagents for detection according to the manufacturer's recommendations, and the amplified product was visualized by hybridization in microarray support. Standard descriptive statistics were used to summarize the study population characteristics. Qualitative variables were expressed as absolute and relative frequencies. Categorical variables were compared using the chi-square or Fisher's exact test, whereas Student's t-test or Mann-Whitney U test was applied for continuous variables, as appropriate. Logistic regression was used to identify factors associated with HHV-6 and HHV-7 viral load and mortality predictors at 1 year. The Hosmer-Lemeshow test assessed the goodness of fit for logistic regression models. All statistical studies were performed using IBM® SPSS® Statistics version 19 (IBM®).

Results

HHV-6 and HHV-7 infections were documented in 15 patients each. Table 1 shows the compartments in which HHV-6 and/or HHV-7 were amplified. The most frequent sample analyzed was cerebrospinal fluid (CSF), tested in 14/30 (46.6%) cases and 20/31 (64.5%) controls. Blood was used in 9/30 (30.0%) cases and 11/31 (35.5%) controls. HHV-6 and HHV-7 were also amplified in pericardial and nasopharyngeal specimens in seven of the 30 cases (23.3%). Table 2 shows the clinical characteristics of patients in whom HHV-6 or HHV-7 were amplified. The most frequent symptomatology was neurological (meningo-encephalitis, encephalopathies, coma, bradypsychia), which were present

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in approximately 80% of both viruses. Fever (42.9% in both viruses) and hepatitis (35.7% and 21.4%, respectively) were also frequent. Significantly, clinical enteritis was only present in patients with HHV-6 infection (40%) and none with HHV-7 infection. Other viruses (not HHV-6 or HHV-7) were amplified in the previous 3 months (Table 3). Epstein Barr virus (EBV) was isolated in five cases, Enterovirus in two patients, and cytomegalovirus (CMV) in one patient.

On the other hand, in the control group, Epstein Barr virus was isolated in one patient and hepatitis B virus (HBV) in one patient. In 22 of the 30 cases, no new viral PCRs were performed in the following 3 months; but in the eight cases in which viral PCRs were repeated, HHV-6 was amplified in three patients (two of them in conjunction with CMV and EBV), CMV in one patient, and respiratory syncytial virus (RSV) in one patient. Another non-viral co-infection was confirmed in 16.1% of controls: four bacterial infections and one mycobacterial infection; however, this type of co-infection occurred in 48.3% of cases: seven bacterial infections and six fungal infections (p = 0.01). Non-viral co-infection was mostly in patients with HHV-6 infection (73.3% vs. 20% in HHV-7 infection). The frequency of non-viral infections in the following 3 months was also significant: 6.5% in controls and 33.3% in cases (p = 0.01).

There were eight hematologic diseases in the case group, five of them active. However, only one inactive disease was documented in the control group. Among cases, 31% were receiving corticosteroids (20.6%, with equivalent doses of prednisone ≥ 15 mg/d or had recently received them, 11%), while only one patient (3.2%) received corticosteroids, with doses < 15 mg/d of prednisone, in the control group. Previous or simultaneous chemotherapy was present in 20% of cases and none of the controls. There were also more treatments with biologic therapies among cases (23.3%) than among controls (6.5%). Thirteen percent of cases and none of the controls had had any episode of neutropenia (<500 cells/µl) in the last 3 months. The median lymphocyte count was also lower in cases (1416 lymph/µl) than in controls (2057 lymph/µl); 70.4% of cases had a lymphocyte count <1700 lymph/µl for only 41.4% of controls. There was 15% of hepatic injury (acute or chronic) in cases for none in controls. However, there was no difference between cases and controls in the development of renal failure (acute or chronic) or the control of the underlying disease. Finally, mortality was significantly higher in the case group (41.4%) than in the control group (13.3%) (p = 0.02). Among risk factors associated with HHV-6 or HHV-7 infections, according to other reports, the following variables were included in multivariate analysis: hematologic disease, corticosteroid therapy, treatment with biological therapies or other immunosuppressive drugs, viral co-infection in the previous 3 months, and bacterial or fungal infection in the previous 3 months or the following 3 months (table 3). Finally, the variables that were independently associated with HHV-6 or HHV-7 infection were: corticosteroid therapy (OR: 24.1; 95%CI 2.6–223.1), the development of bacterial or fungal infections in the following 3 months (OR: 10.9; 95%CI: 1.9–62.0), and co-infection by other viruses in the previous 3 months (OR: 7.3; 95%CI: 1.2–44.8). HHV-6 and/or HHV-7 infection was associated with a higher 1-year mortality (Tables 3 and 4). However, in multivariate analysis, factors independently associated with higher mortality were: age >60 years (OR 23.0; 95%CI: 1.9–269.8), no underlying disease control at 1 year (OR 17.2; 95%CI: 2.4–125.0), and bacterial or fungal infection in next 3 months (OR 14.6; 95%CI: 1.1–186.3). When HHV-6 and HHV-7 infections were analyzed separately, differences in mortality were observed (table 4). An analysis that excluded HHV-7 infections from cases and included them among controls showed a higher 1-year-mortality in patients with HHV-6 infection (66.7%). A second multivariate model, including HHV-6 infection and adjusted by the independent variables confirmed in model 1 (age > 60 years, other infections and no underlying disease control at 1 year), confirmed that only age >60 years (OR 12.0; 95%CI: 2.0–69.4)(p: 0.005) and HHV-6 infection (OR 16.8; 95%CI 3.0–93.6) (p = 0.001) were independently associated with 1-year mortality. Although a higher rate of HHV6 infection was documented among patients with age >60 years (35.7% in >60 years vs. 18.2% in <60 years), no collinearity was

Table 1: Compartments in which HHV6 and/or HHV7 were amplified

	Cases (n: 30)		Controls (n: 31)
Blood	9 (30.0%)	(6: HHV-6; 3: HHV-7,	11 (35.5%)
CSF	14 (46.7%)	(4: HHV-6; 10: HHV-7)	20 (64.5%)
pericardial fluid	3 (10.0%)	(2: HHV-6, 1: HHV-7)	0
nasopharyngeal sample	4 (13.3%)	(3: HHV-6, 1: HHV-7)	0

CSF: cerebrospinal fluid,

Table 2: Clinical characteristics of patients with HHV-6 and HHV-7 infections

	HHV-6	HHV-7
Fever	6/14 (42.9%)	6/14 (42.9%)
Rash	1/14 (7.1%)	1/14 (7.1%)
Pneumonitis	2/14 (14.2%)	2/14 (14.2%)
Pericarditis	3/13 (23.0%)	1/11 (9.1%)
Hepatitis	5/14 (35.7%)	3/14 (21.4%)
Enteritis	6/15 (40.0%)	0/15
Neurological symptoms	12/15 (80.0%)	11/14 (78.6%)

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Table 3: Baseline and outcome conditions among cases and controls

	Univariate analysis			Multivariate analysis		
	Cases	**Controls**	**P**	**OR**	**IC95%**	**p**
Age, median age (range)	59 (4-84)	51 (17-78)	0.62	-	-	-
Other virus infection (previous 3 months)	8/30 (26.7%)	2/31 (6.5%)	0.04	7.3	1.2-44.8	0.03
Other infections (previous 3 months)	14/29 (48.3%)	5/31 (16.1%)	0.012	-	-	-
Other infections (next 3 months)	10/30 (33.3%)	2/31 (6.5%)	0.011	10.9	1.9-62-0	0.007
Diabetes	4/30 (13.3%)	6/31 (19.4%)	0.73	-	-	-
Baseline renal insufficiency	8/30 (26.7%)	8/31 (25.8%)	1	-	-	-
Baseline hepatic disease	8/30 (26.7%)	4/31 (12.9%)	0.21	-	-	-
Hematological disease	8/30 (26.7%)	1/31 (3.2%)	0.012	-	-	-
Bone marrow transplant	2/28 (7.1%)	0/31	0.22	-	-	-
Solid organ transplant	3/30 (10.0%)	0/31	0.11	-	-	-
Solid tumor	6/30 (20.0%)	3/31 (9.7%)	0.3	-	-	-
Corticosteroid therapy	9/30 (31.0%)	1/31 (3.2%)	0.006	24.1	2.6-223.1	0.005
Chemotherapy	6/30 (20.0%)	0/29	0.024	-	-	-
Biologic drug therapy	7/30 (23.3%)	2/31 (6.5%)	0.081	-	-	-
Neutropenia (last 3 months)	4/30 (13.3%)	0/31	0.53	-	-	-
Lymphocyte count <1700 lymph/ul	19/27 (70.4%)	12/29 (41.4%)	0.035	-	-	-
Antiviral therapy required	13/29 (44.8%)	5/29 (17.2%)	0.19	-	-	-
Long-therm (1-year) renal insufficiency	8/26 (30.8%)	8/28 (28.6%)	1	-	-	-
Long-therm (1-year) hepatic disease	4/26 (15.4%)	0/27	0.05	-	-	-
No underlying disease control (1-year)	13/26 (50%)	9/27 (33.3%)	0.27	-	-	-
1-year mortality	12/29 (41.4%)	4/30 (13.3%)	0.02	-	-	-

detected (p = 0.15). On the other hand, HHV-7 infection alone was not associated with a higher 1-year mortality in uni- or multivariate analysis (table 4).

Finally, there was no homogeneous criterion regarding antiviral treatment. Among patients who presented HHV-6 infection (n = 15): seven did not receive any treatment, five received acyclovir, and three received ganciclovir/valganciclovir (two of them in combination with foscarnet). Among patients with HHV-7 infection (n = 15): ten received no treatment, three received acyclovir, and one received ganciclovir/valganciclovir and foscarnet in combination. In the control group, in 26/31, no treatment was administered. However, four received acyclovir and one received ganciclovir. There was no difference in 1-year outcome (death, renal or hepatic failure or underlying disease control) among treated and untreated patients.

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Table 4: One-year mortality. Uni- and multivariate analysis

	Univariate analysis		Multivariate analysis		
	Global mortality 16/59 (27.1%)	P	OR	IC95%	p
Age > 60 y-o	13/27 (48.1%)	0.001	23	1.9-269.8	0.012
HHV-6 or HHV-7 infection	12/29 (41.4%)	0.02	-	-	-
HHV-6 infection*	10/15 (66.7%)	0.001	16.8*	3.0-93.6*	0.001*
Other virus infection (previous 3 months)	4/9 (44.4%)	0.23	-	-	-
Other infections (previous 3 months)	11/19 (57-9%)	0.001	-	-	-
Other infections (next 3 months)	5/12 (41-7%)	0.27	14.6	1.1-186.3	0.038
Diabetes	2/10 (20.0%)	0.71	-	-	-
Baseline renal insufficiency	10/16 (62.5%)	0.001	-	-	-
Baseline hepatic disease	6/12 850.0%)	0.069	-	-	-
Hematological disease	4/9 (44.4%)	0.23	-	-	-
Bone marrow transplant	1/2 (50.0%)	0.48	-	-	-
Solid organ transplant	3/3 (100%)	0.017	-	-	-
Solid tumor	7/9 (77.8%)	0.001	-	-	-
Corticosteroid therapy	4/10 (40.0%)	0.43	-	-	-
Chemotherapy	5/6 (83.3%)	0.005	-	-	-
Biologic drug therapy	5/9 (55.6%)	0.052	-	-	-
Neutropenia (last 3 months)	3/4 (75.0%)	0.057	-	-	-
Lymphocyte count <1700 lymph/ul	2/25 (8.0%)	0.006	-	-	-
Long-therm (1-year) renal insufficiency	10/16 (62.5%)	0.001	-	-	-
Long-therm (1-year) hepatic disease	4/4 (100.0%)	0.002	-	-	-
No underlying disease control (1-year)	10/22 (45.5%)	0.002	17.2	2.4-125.0	0.01

1º model including HHV-6 or HHV-7 infection: for multivariate analysis the following variables were included: hematologic disease, corticosteroid therapy, treatment with biological therapies or other immunosuppressive drugs, viral co-infection in the previous 3 months, and bacterial or fungal infection in the previous 3 months or in the following 3 months. Multivariate result: age >60 y-o (OR 23.0; 95%CI:1.9-269.8), no underlying disease control at 1 year (OR 17.2; 95%CI 2.4-125.0), and bacterial or fungal infection in next 3 months (OR 14.6; 95%CI 1.1-186.3).

*2º model including HHV-6 infection and independent variables confirmed in model 1: age > 60 y-o, other infections (next 3 months) and no underlying disease control at 1 year confirmed that only age >60 y-o (OR 12.0; 95%CI:2.0-69.4)(p: 0.005) and HHV-6 infection (OR 16.8; 95%CI 3.0-93.6) (p: 0.001) were independently associated with 1-year mortality

Discussion

Although there is controversy about the pathogenicity of HHV-6 and HHV-7, the present work suggests that HHV-6 may be a surrogate marker of poor prognosis and even mortality in medium to long-term immunosuppressed patients. Infection by both viruses is associated with a clinical scenario of greater immunosuppression and, in the present study, was significantly associated with corticosteroid therapy and viral, bacterial or fungal co-infection simultaneous or before infection by HHV-6 or 7. The most relevant aspect of the study is the independent association with higher mortality at 1 year in patients with HHV-6 infection, a circumstance that was not confirmed after HHV-7 infection. Other authors have confirmed that HHV-6 is associated with lower absolute lymphocyte count and platelet count in the first year post-HCT. Similar to our results, these authors confirmed that HHV-6 was independently associated with higher mortality by 1-year post-HCT after adjusting for age, antiviral treatment, and absolute lymphocyte count (18). Acute limbic encephalitis has been reported in the setting of treatment-related immunosuppression and attributed to HHV-6 infection

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(19). In accordance with the neurotropism of both viruses documented in the literature, it is not surprising that in the present study, the most frequent symptoms for which HHV-6 or -7 DNA amplification was requested were neurological, which were present in approximately 80% of both viruses. The most frequent sample analyzed was cerebrospinal fluid (CSF), tested in 46.6% of cases. In addition to HSCT patients, HHV-6 reactivation leading to CNS disease also occurs in settings such as following adoptive T cell therapy or biologic immunotherapy (20). HHV-6 has also been implicated in autoimmune-caused events. HHV-6 infection may play a role in multiple sclerosis pathogenesis by changing cytokine signaling that may lead to peripheral inflammation (21). HHV-6 DNA-emia occurred more frequently in seronegative pediatric LT recipients, and HHV-6 cannot be ruled out as a cause of hepatitis in the absence of allograft tissue testing (22).

In this study, co-infection with other viruses was frequent in patients with HHV-6 or HHV-7 infection. Epstein Barr virus (EBV) was isolated in five cases, Enterovirus in two patients, and cytomegalovirus (CMV) in one patient. The incidence of non-CMV opportunistic infection at year 1 in patients with HHV-6 infection has been documented. Previous studies showed an association between HHV-6 infections after LT, as assessed by PCR in whole blood and the development of CMV disease and other opportunistic infections and severe hepatitis C virus recurrence (23). The indirect effects potentially attributable to HHV-7 have been less characterized, with some studies suggesting that HHV-7 reactivation may increase the risk of CMV infection (24). However, Fernandez-Ruiz et al. found that HHV-7 infection had no apparent impact on post-transplant adverse outcomes (25). Apart from their pathogenic role, the possibility of intervening in the replication of both viruses is relativized by the low activity of the available antivirals. Although there is more experience with the treatment of HHV-6 infections, in this series, there were no differences between treated and untreated patients, and the literature does not clarify this need very well either. Fernández-Ruiz et al., in a study carried out on solid organ transplant recipients and which analyzes the need to monitor the replication of HHV-6 or 7, concluded that an attitude of intervention on both viruses with antivirals or reduction of immunosuppression in SOT does not reduce the number of infectious events or rejection (25). They found a significant trend suggesting an increased incidence of biopsy-proven acute graft rejection at year 5 in the presence of HHV-6 infection; however, there were no significant differences in outcome between patients with or without HHV-7 infection at either time point (25).

Among the limitations of the study is its retrospective nature, the reduced sample size, the single-center setting, the use of different compartments for viral amplification, and the absence of a follow-up protocol for replication control in these patients. In contrast, this is a study that provides data of prognostic interest in this type of viral infection where clinical and prognostic evidence is limited. In conclusion, the present work suggests that the request for amplification of HHV-6 or 7 in clinical practice is especially required in patients with central nervous system pathology or immunosuppressed patients. Its replication is more frequent in patients receiving corticosteroid treatment or with viral, bacterial, or fungal co-infections. When the impact of both viruses was analyzed independently, it was confirmed that HHV-6 was independently associated with higher 1-year mortality. In conclusion, although it is necessary to confirm this data in prospective series with a greater number of patients, this work suggests that HHV-6 replication may be a surrogate marker of mortality in the medium term in immunocompromised patients.

Ethics approval: This study was approved by the institutional ethics board of Hospital Universitario Ramón y Cajal, Madrid

Consent to participate: Due to the nature of the retrospective chart review, the need for informed consent from individual patients was waived.

Consent for publication: All authors accept the terms and conditions of the editorial for publication.

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Conflicts of Interest: The authors declare no conflicts of interest.

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