Case Report/Relato de Caso

# Human herpesvirus 6: report of emerging pathogen in five patients with HIV/AIDS and review of the literature

## Herpes virus humano 6: relato de patógenos emergentes em cinco pacientes com HIV/AIDS e revisão da literatura

**Marcelo Corti[1], Maria Florencia Villafañe[1], Norberto Trione[1], Lilia Mamanna[2] and Belén Bouzas[2]**

**ABSTRACT**

The reactivation of human herpesvirus 6 (HHV-6) in patients with AIDS can result in an acute and severe diffuse meningoencephalitis. We describe the epidemiological, clinical and outcome findings of five patients with diagnosis of HIV/AIDS and central nervous system involvement (CNS) due to HHV-6. Fever was present in all the patients. Meningeal compromise, seizures and encephalitis were present in some of the patients. Polymerase chain reaction (PCR) of cerebrospinal fluid (CSF) specimens was positive for HHV-6 in all the patients. HHV-6 should be included among opportunistic and emerging pathogens that involve the CNS in patients with AIDS.

**Keywords:** AIDS. HIV. Meningoencephalitis. Meningitis. HHV-6.

**RESUMO**

A reativação do herpesvírus humano 6 (HHV-6), em um hospedeiro com AIDS, pode resultar em meningoencefalite aguda difusa. Nós descrevemos a epidemiologia, a clínica e resultados encontrados em cinco pacientes com diagnóstico de HIV/AIDS e comprometimento do sistema nervoso central (SNC) devido ao HHV-6. Todos os pacientes apresentaram febre. Sinais e sintomas de comprometimento meníngeo, convulsões e encefalite podem ser encontrados. A reação em cadeia da polimerase (PCR) de amostras do líquor foi positiva para HHV-6 em todos os pacientes. O HHV-6 deve ser incluído entre os patógenos emergentes oportunistas que comprometem o SNC de pacientes com AIDS.

**Palavras-chaves:** AIDS. HIV. Meningoencefalite. Meningite. HHV-6.

## INTRODUCTION

Human herpesvirus 6 (HHV-6) is a member of the Betaherpesvirinae subfamily and was discovered to be a cause of a lymphoproliferative syndrome in 1986 by Salahuddin et al[1]. Like other members of this family, HHV-6 causes a primary infection during childhood that can be asymptomatic or can manifest as a febrile illness with or without exanthem subitum. The seroprevalence of HHV-6 IgG antibodies in children over two years of age is as high as 80%[2].

HHH-6 has been classified into two variants, A and B. Variant B is related to roseola infantum and febrile illness in children; variant A is generally associated with lymphoproliferative disorders and central nervous system involvement in immunocompromised patients[2].

1. Divisão de HIV/AIDS, Hospital de Enfermidades Infecciosas Francisco Javier Muñiz, Buenos Aires, Argentina. 2. Laboratório de Virologia, Hospital de Doenças Infecciosas Francisco Javier Muñiz, Buenos Aires, Argentina.

***Address to***: Dr. Marcelo Corti. Divisão HIV/AIDS/Hospital de Enfermidades Infecciosas Francisco Javier Muñiz Puan 381/2°C, 1406CQG Buenos Aires, Argentina. Tel: 54 11 4 432-3762

e-mail: marcelocorti@fibertel.com.ar

**Received in** 12/03/2010

**Accepted in** 25/01/2011

In immunocompetent adults, this herpesvirus is related to a mononucleosis-like syndrome, Sjögren syndrome, Hodgkin and Non-Hodgkin lymphomas and meningoencephalitis[2]. Recently, HHV-6 has been associated as an emerging pathogen in patients with AIDS and recipients of bone marrow and solid organ transplants. However, there are few reports related HHV-6 to the immunodeficiency caused by HIV/AIDS[4]. In patients with AIDS, reactivation of HHV-6 infection presents, generally, as an acute and fatal meningoencephalitis[2].

We present five patients with advanced HIV/AIDS disease who developed a severe meningoencephalitis due to HHV-6.

## CASE REPORT

The epidemiological, clinical, microbiological and virological characteristics of five AIDS patients with central nervous system (CNS) involvement caused by HHV-6 were retrospectively analyzed. Clinical and neurological examinations were performed on all the patients. All patients included in the study displayed neurological signs or symptoms during the physical examination and showed no contraindications for undergoing a lumbar puncture. All the samples of cerebrospinal fluid (CSF) were evaluated for white blood cell counts, protein level and glucose level, and also for common bacteria, mycobacteria, fungi, parasites, neuroherpesvirus and JC virus (JCV). Blood cultures for common bacteria, fungi and mycobacteria and CD4 + T cell counts were made for all the patients. Magnetic resonance image MRI was available from three patients.

The definitive diagnosis was made by DNA detection of HHV-6 in CSF by polymerase chain reaction (PCR). Aliquots of CSF samples were stored at -70°C until they were analyzed by HVM (Herplex, Genomica, Spain). Specimens were tested by HVM following the manufacturer's instructions. The HVM is a multiplex PCR device that amplifies and detects the genomes of *Herpes simplex*-1 (HSV-1) and 2 (HSV-2) and Herpes varicella-zoster (HVZ) in a single tube as well as the genomes of cytomegalovirus (CMV), Epstein-Barr virus (EBV) and HHV-6. Every tube has an internal amplification control, and the amplified products are detected by hybridization with specific probes in a microplate. The analytical sensitivity reported by the manufacturer is two genome equivalents for HSV-1, HSV-2 and EBV, and between 2 and 20 genome equivalents for HVZ, HHV-6 and CMV[4].

Four patients were male and one female. The median age at the time of HHV-6 meningoencephalitis diagnosis was 42 years, and the median CD4 T cell counts was 70 cells/μL. The primary risk factor for HIV (human immunodeficiency virus) infection was intravenous

drug use (IVDU) in 2 patients, unprotected homosexual contact in two and unprotected heterosexual contact in one. All patients had been diagnosed with AIDS because of their clinical histories of AIDS defining illnesses. Two of them presented histories of disseminated cryptococcosis with meningeal involvement; the other three had been diagnosed with disseminated tuberculosis, and one of them had had meningeal involvement. Laboratory findings confirmed that there was no evidence of activity associated with these AIDS-defining illnesses. None of the patients had received antiretroviral therapy. Clinical examination revealed fever in all the patients at the time of admission. Three of them had signs and symptoms of meningeal compromise (headache, photophobia, vomiting and neck stiffness). Only one of them presented seizures, and another one had signs of encephalitis (agitation, confusion and temporo-spacial disorientation). Biochemical examination of CSF samples showed hyperproteinorrachia in three of them, and there were normal levels between 15 and 45mg in the other two. Examinations of the CSF samples for common bacteria, fungi and parasites were negative. The polysaccharide cryptococcal capsular antigen in the CSF was negative in the two patients with a history of meningeal cryptococcosis. Imaging techniques like MRI were available for three of the patients. The images showed cortex and cerebellar atrophy related to advanced HIV/AIDS in two patients, and in one of them, the neuroimages were compatible with vasculitis. PCR by the HVM of CSF specimens was positive for HHV-6 and negative for HSV-1, HSV-2, VZV, EBV and CMV in all the patients. PCR was also negative for JCV. After PCR confirmed the presence of HHV-6, only one patient was able to receive specific treatment with ganciclovir plus foscarnet during a six-week course of both antiviral treatment, resulting in the improvement of neurological symptoms. After that, this patient was started on a secondary prophylaxis regimen with the same two antiviral drugs and highly active antiretroviral therapy (HAART). At that time, PCR of the patient's CSF was negative for HHV-6.

Two years later, this patient remains in good clinical condition; the secondary prophylaxis can be interrupted, the CD4 T cell count is >350 cells/μL and the plasma RNA-HIV viral load is undetectable.

The human herpesvirus 6 meningoencephalitis diagnosis was confirmed postmortem by PCR of CSF samples in patients 2, 3 and 4. For this reason, it was not possible to initiate antiviral therapy. Intravenous acyclovir therapy plus ceftriaxone was initiated for possible HSV-1 meningoencephalitis in patient 1, who died four days after admission (**Table 1**).

**TABLE 1 - Epidemiological, clinical and immunological characteristics and cerebrospinal fluid findings in a series of 5 patients with CNS involvement due to HHV-6.**

| | **Patient 1** | **Patient 2** | **Patient 3** | **Patient 4** | **Patient 5** |
|---|---|---|---|---|---|
| Gender | female | male | male | male | male |
| Age (years) | 55 | 30 | 42 | 43 | 37 |
| Risk factor | IVDU | unprotected homosexual contact | unprotected heterosexual contact | unprotected homosexual contact | IVDU |
| Previous | meningeal | meningeal | meningeal | disseminated | disseminated |
| Opportunistic diseases | criptococosis | tuberculosis | criptococosis | tuberculosis | tuberculosis |
| Neurological | meningeal | meningeal | meningeal | encephalitis | seizures |
| symptoms | syndrome | syndrome | syndrome | | |
| Fever | yes | yes | yes | yes | yes |
| CD4 cell count | 70sep/μL | 131cell/μL | 54cell/μL | 46cell/μL | 144cell/μL |
| CSF | ↑ proteins | ↑ proteins | ↑ proteins | normal | normal |
| PCR HHV-6 CSF | + | + | + | + | + |
| Neuroimages | MRI: cerebral and cerebella atrophy without contrast enhancing | MRI: cerebral atrophy. hipointensity in white matter | ND | ND | MRI: periventricular pinted images: vasculitis |
| HAART in the onset of symptoms | no | no | no | no | no |
| Treatment | aciclovir + ceftriaxone | no | no | no | ganciclovir/ foscarnet + HAART |
| Survival | died | died | died | died | good response to therapy |

**IVDU:** intravenous drugs users , **CSF:** cerebrospinal fluid, **PCR:** polymerase chain reaction, **HHV-6:** human herpesvirus 6, **ND:** not done, **MRI:** magnetic resonance image , **HAART:** highly active antiretroviral therapy.

## DISCUSSION

To our knowledge, there are only a few reports of HHV-6-induced meningoencephalitis in HIV patients in the medical literature. However, the role of HHV-6 in the pathogenesis of CNS disease remains unclear[4,5]. Bossolasco et al.[5] evaluated the frequency of HHV-6 DNA detection in the CSF of patients infected with HIV/AIDS and its possible relation to neurological disease. HHV-6 was found by PCR in only 2.2% of 365 patients. The detection rate was substantially lower than those found for CMV, EBV and JCV (16%, 12% and 9%, respectively)[4]. Liedke et al.[6], in contrast, reported that HHV-6 DNA was found in the CSF samples of 30% of HIV-infected patients with neurological disease. Even though two of the patients in our series had histories of cryptococcal meningitis and three had previous diagnoses of disseminated tuberculosis, no evidence of these pathogens was found in the laboratory specimens. The evidence suggesting a relation between HHV-6 and CNS disease is based on the detection of HHV-6 DNA in the CSF. If well in our series, only patient 5 can be fully classified as having HHV-6 meningoencephalitis according to Koch's postulates; HHV-6 was the only pathogen isolated from the patient's CSF at the time of the acute neurological illness. The fact that HHV-6 was found in all of the CSF samples taken from our patients suggest that, at least in these patients, this finding is not incidental. HIV and HHV-6 may have a synergistic activity; both of them infect and replicate in T CD4 lymphocytes, and furthermore, HIV may enhance the replication and dissemination of HHV-6[2]. In this context, the main difficulty is the interpretation of the pathogenic role of HHV-6 in patients with AIDS who have CNS involvement because this virus, HHV-6 is frequently identified with other opportunistic pathogens. HHV-6 may be considered an emergent pathogen in AIDS patients that can act directly or indirectly or can interfere in different components of the immune system[4-6]. Moreover, infection with HHV-6 may predispose patients to superinfection with other viruses, especially EBV, CMV and HHV-7[5,6].

Clinical reactivation in the CNS leads to an asymptomatic infection or a severe meningoencephalitis with fever, headache, seizures, demyelinating lesions and, rarely, an acute transverse myelitis with dysesthesia of the lower extremities, dysuria and dyschezia. The majority of immunodepressed patients with HHV-6-induced meningoencephalitis presented with fever, seizures, focal neurological signs and varying degrees of altered consciousness[5]. This is the most frequent clinical presentation of HHV-6 neurological involvement in this kind of patients. The most common clinical picture in our series was meningeal syndrome associated with fever and seizures. Diagnosis of HHV-6 meningoencephalitis includes neurological manifestations, CSF analysis positive for HHV-6 DNA and the absence of any other identifiable pathogens. All of the patients described in this report presented these three clinical and laboratory findings. Less frequently, HHV-6 infection of the CNS can present with neuropsychiatric manifestations, including dementia[3].

MRI generally reveals the meningeal contrast-enhance signal intensity abnormality in the medial temporal lobe and hyperintense lesions in the insula region, the amygdale and the inferior frontal lobe similar to herpes simplex type 1. Some patients can present periventricular lesions hypointense in T1 and hyperintense in T2 compatible with vasculitis damage[7,8]. However, MRI brain findings might be completely normal in some cases, especially in immunocompromised patients. This is probably due to a limited inflammatory response in this kind of patients. If MRI changes of hypointensities in T1 and hyperintensity in T2 are not specific for vasculitis, the pathogenic effect of all neuroherpesvirus infections is consistent with these findings.

Since its introduction in 1990, the PCR technique has contributed to the diagnosis of neurological infection caused by herpesvirus and is the standard method for the diagnosis of this agent. This is a very sensitive and specific technique with fast results than can be faster with RT-PCR[6]. The profit advantage with this technique is increased when affected patients have CSF alterations such as pleocitosis and protein elevation. However, there are some reports of meningoencephalitis in immunosuppressed hosts with normal CSF. For all these reasons, PCR has displaced the serological tests and the intratecal synthesis of antibodies for the diagnosis of neuroherpesvirus infections. When the sample is taken within the first ten days of the onset of the neurological symptoms, the rate of PCR-positive results is higher than after ten days have elapsed. In relation to the diagnosis of CNS infection due to HHV-6, PCR is highly sensitive and specific for the detection of etiological agents, nearly 98% and 94%, respectively[9].

HHV-6 is often detected in plasma, suggesting that the virus may spread to the CNS from the blood. However, Bossolasco el al.[5] affirm that the target discrepancies between the CSF and plasma HHV-6 findings support the hypothesis of an active brain infection by herpesvirus, rather than a spread across the blood-brain barrier. Also, these authors hypothesize that HHV-6 may be found after reactivation.

If all the patients included in this series had been given HAART, it was their own decision not to follow the indicated treatment. The last patient was started on HAART after the acute period of HHV-6 disease, and he presented a good virological, clinical and immunological response with immune restoration. He can stop the secondary prophylaxis for HHV-6.

Ganciclovir and foscarnet, either alone or in combination, proved to be the most effective therapy for immunosuppressed patients with HHV-6 related to neurological disease[9]. Some authors report that the administration of cidofovir followed by foscarnet was associated with clinical improvement of HHV-6 infection[9,10]. None of our patients were treated with cidofovir, because this antiviral agent is not available in Argentina.

In our opinion, CNS involvement due to HHV-6 should be considered in all patients with a diagnosis of meningoencephalitis, advanced HIV/AIDS disease and T CD4 cell counts less than 200 cells/μL. CSF examination is very useful for diagnosis, especially when it is abnormal, as it was in all the patients included in our series.

MRI can show, in some cases, vasculitic lesions or demyelination of the white matter, as can be seen with other neuroviruses. The diagnosis is confirmed by the detection of the genome of HHV-6 by PCR. Early diagnosis followed by specific therapy based on ganciclovir and foscarnet plus HAART can improve the poor prognosis of this type of patient.

## REFERENCES

1. Salahuddin SZ, Ablashi DV, Markham PD, Josephs SF, Sturzenegger S, Kaplan M, et al. Isolation of a new virus, HBLV, in patients with lymphoproliferative disorders. Science 1986; 234:596-601.

2. Okuno T, Takahashi K, Balachandra K, Shiraki K, Yamanishi K, Takahashi M, et al. Seroepidemiology of human herpesvirus 6 infection in normal children and adults. J Clin Microbiol 1989; 27:651-653.

3. Méchaï F, Boutoulleau D, Manceron V, Gasnault J, Ouertainmont Y, Brosseau JP, et al. Human Herpesvirus-6 asociated retrobulbar optic neuritis in an HV-infected patient: response to antiherpes therapy and long term outcome. J Med Virol 2007; 79:931-934.
4. Cinque P, Vago L, Dahl H, Brytting M, Terreni MR, Fornara C, et al. Polymerase chain reaction on cerebrospinal fluid for diagnosis of virus associated opportunistic diseases of the central nervous system in HIV-infected patients. AIDS 1996; 10:951-958.
5. Bossolasco S, Marenzi R, Dahl H, Vago L, Terreni MR, Broccolo F, et al. Human herpesvirus 6 in cerebrospinal fluid of patients infected with HIV: frequency and clinical significance. J Neurol Neurosurg Psyquiatry 1999; 67:789-792.
6. Liedtke W, Malessa R, Faustman PM, Eis-Hubinger AM. Human herpesvirus-6 polymerase chain reaction findings in human immunodeficiency virus associated neurological disease and multiple sclerosis. J Neurovirol 1995; 1: 253-258.
7. Corti ME, Villafañe MF, Palmieri OJ. Viral Opportunistic Infections. *In*: Corti ME, Villafañe MF, Palmieri OJ, editors. Atlas of neuroimages and neuropathology of HIV/AIDS disease. 1st ed. Buenos Aires, 2007. p. 29-35.
8. Dewhurst S. Human herpesvirus type 6 and human herpesvirus type 7 infections of the central nervous system. Herpes 2004; 11:105A-111A.
9. Pöhlmann C, Schetelig J, Reuner U, Bornhäuser M, Illmer T, Kiani A, et al. Cidofovir and foscarnet for treatment of human herpesvirus 6 encephalitis in a neutropenic stem cell transplant recipient. Clin Infect Dis 2007; 44:118-120.
10. Yoshikawa T. Human herpesvirus 6 encephalitis. Brain Nerve 2010; 62:869-875.