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Molecular detection of human herpesvirus 7 DNA in cerebrospinal fluid from adult patients with neurological disorders

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Abstract

Neurological manifestations associated with HHV-7 have been described in primary infection in children, and very occasionally in immunocompromised adult patients. However, the role of HHV-7 reactivation as a cause of central nervous system (CNS) diseases in immunocompetent adults has not yet been defined. We retrospectively analyzed clinical and microbiological features of adults with neurological symptoms who underwent lumbar puncture and a multiplex polymerase chain reaction (PCR) for herpesviruses (HHV-1–8) and enteroviruses performed in cerebrospinal fluid (CSF), during a 4-year period. A total of 251 subjects were included. Mean age was 55 years, ranging 15–89. Globally, HHV-7 DNA was detected in CSF in 14 patients (5.6%). It was detected in 1 of 36 patients with microbiologically confirmed CNS infections, and in 7 of 172 patients with diagnoses of non-infectious neurological disorders (Specificity 0.96, 95% confidence interval 0.93–0.99). Additionally, HHV-7 DNA was detected in 6 of 21 patients (28.6%) with probable CNS infections (compatible clinical syndrome and CSF changes) in the absence of other causative agent: four meningitis, one myelitis, and one encephalitis. Treatment with foscarnet was effective in achieving improvement of symptoms and clearance of HHV-7 DNA in CSF in the cases of encephalitis and myelitis, while ganciclovir was ineffective in the case of encephalitis. Our results show that HHV-7 reactivation may cause CNS disease in immunocompetent adults and that detection of HHV-7 DNA in CSF as a false-positive result or as asymptomatic reactivation in adult patients with neurological diseases is uncommon. Foscarnet seems the first-line treatment for HHV-7 CNS disease.

Keywords Human hervesvirus 7 · Polymerase chain reaction · Cerebrospinal fluid · Meningitis · Encephalitis · Myelitis

Introduction

Human herpesvirus 7 (HHV-7) is a lymphotropic virus that replicates in CD4+ T lymphocytes (Klussmann et al. 1997). HHV-7 infection is generally acquired during childhood, and therefore, most adults (between 96 and 100%) are seropositive (Wyatt et al. 1991; Ward et al. 2001). HHV-7 possesses neurotropism, and HHV-7 DNA may be detected post-mortem in brain tissue samples (Chapenko et al. 2016). Neurological disease associated with HHV-7 has been mainly reported in primary infection in children. Primary HHV-7 infection is found in a significant proportion of children with febrile seizures and febrile status epilepticus (Epstein et al. 2012; Ward et al. 2005). Neuroinvasion in primary infection in children has been documented (Van der Berg et al. 1999) and HHV-7 DNA has been detected in CSF in children with central nervous system (CNS) diseases (Pohl-Koppe et al. 2001; Yoshikawa et al. 2000), including cases of meningitis and meningoencephalitis. Delayed HHV-7 primary infection has occasionally been found to be the cause of encephalitis or meningoradiculopathy in immunocompetent children and also in a young adult (Schwartz et al. 2014; Ward et al. 2002; Fay et al. 2015; Rangel et al. 2017). HHV-7 reactivation might cause neurological disease in immunodepressed patients (Ward et al. 2002b; Chan et al. 2002). However, the role of reactivation of the virus as a cause of neurologic disease in immunocompetent adult patients has not been established (Ward et al. 2002). In this perspective, the clinical significance of HHV-7 DNA amplification from CSF is not clear yet, and the

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interpretation of this molecular amplification may pose difficulties in clinical practice, particularly in patients with suspected CNS infection. No study has ever yet addressed the prevalence and significance of HHV-7 amplification in CSF from patients with different neurological disorders.

In the present study, we analyzed the presence of HHV-7 DNA in CSF in a large series of patients with neurological symptoms with the aim of understanding better the role of HHV-7 reactivation as a cause of CNS disease in adults.

Material and methods

All patients older than 14 years with neurological symptoms, attended between October 2010 and December 2014 at our tertiary University Hospital, who had a search for herpesviruses and enteroviruses performed in CSF were included in the study.

Detection and typing of eight DNA and three RNA neurotropic viruses, including the main human herpesviruses (HHV-1 to HHV-8) and human enteroviruses (polio-, echo-, and coxsackievirus), was performed by Clart® Entherpex kit (Genomica, Coslada, Spain), following the manufacturer's instructions. This assay is based on viral genome-specific fragments amplification (187 bp in HHV-7) via multiple reverse transcription-polymerase chain reaction (RT-PCR). The detection of amplified product is based on low-density microarray technology, using specific probes binding to solid surface. Briefly, the genetic material was extracted from 200 μl of CSF using NucliSens easyMAG (bioMerieux, Marcy l'Etoile, France), and 5 μl of total nucleic acid extract was used to amplify different specific fragments of the described viruses. An internal control is added in each amplification tube to control amplification efficiency. The biotinylated PCR products are hybridized to target specific binding probes. Finally, specific software coupled to a microarray reader allows the interpretation of the results (Leveque et al. 2011). This assay was evaluated in a previous work, using through QCMD program. This comparative study did not yield cross reactivity or misidentifications between herpesviruses, showing values of specificity ranging 98.3–100% (Leveque et al. 2011). The assay has also an excellent global sensitivity, except to enteroviruses ($>10^4$ copies/mL). The sensitivity for herpesviruses is ranging 10^2–10^3 copies/mL (Jääskeläinen et al. 2006; Leveque et al. 2011). Serology for HHV-7 was not available in our institution and was not performed in our patients.

For each patient, the clinical records and laboratory reports were retrospectively reviewed and the following data were recorded: age, sex, relevant past history, neurologic presentation, CSF parameters, and microbiological studies, including the results of the PCR assay, treatments received, course, and final neurological diagnosis.

Neurological diagnoses were classified in four groups: (1) confirmed infection of the CNS: patients with clinical presentation and CSF parameters compatible with CNS infection and a concordant positive microbiological result; (2) probable CNS infection of undetermined etiology: patients with clinical presentation and CSF parameters compatible with CNS infection, but without a concordant positive microbiological result; (3) other established neurological diagnoses, according to clinical criteria and results of complementary studies; and (4) neurological symptoms without an established neurological diagnosis. Amplification of HHV-7 was not considered for the classification of diagnosis. For the evaluation of the specificity of HHV-7 amplification in CSF, only patients with established diagnoses were included and only the first CSF sample was considered in patients with repeated lumbar punctures. Mann-Whitney was used for mean comparisons.

Because our study was based on a systematic and retrospective review of clinical records, no informed consent or approval from an institutional review board or ethics committee was needed, according to the local regulations.

Results

A total of 251 subjects were included in the study. Mean age was 55 years (range 15–89), and 121 (48.21%) were women. Twelve patients had factors for immunosuppression: four infections with human immunodeficiency virus (HIV), four malignancies, three cirrhoses, and one immunosuppressive therapy for rheumatoid arthritis. Globally, HHV-7 DNA was detected in CSF in 14 patients (5.6%), and only one of them had a factor for immunosuppression (HIV infection). HHV-7 DNA was detected in CSF from 1 of 36 patients with a diagnosis of microbiologically confirmed CNS infection. His diagnosis was meningitis by herpes simplex type 2. Among the remaining 35 patients, in six of them, a new CSF was obtained a mean of 11 days after the first lumbar puncture and PCR was repeated, with the same negative result.

HHV-7 DNA was detected in 7 of 172 patients with a diagnosis of other non-infectious neurological conditions (Table 1). Among the 165 patients of this group without HHV-7 amplification, a second CSF PCR was performed in 15 patients after a mean of 14 days, also with negative results. The final diagnoses of patients with HHV-7 amplification were first relapse of relapsing–remitting multiple sclerosis (two patients), psychogenic hemiparesis (two patients), syndrome of headache with neurological deficits and CSF lymphocytosis (HaNDL), diabetic polyneuropathy, and idiopathic facial palsy. In the case of the patients with psychogenic hemiparesis, lumbar puncture was reported as traumatic (red cell count in CSF 4.240 and 13.680/mm^3). No amplification of HHV-7 was obtained in CSF from 22 patients without specific neurological diagnosis. Considering all 208 patients with an established diagnosis (infectious or non-infectious), the specificity of HHV-7 amplification in CSF was 0.96% (95% confidence interval 0.93–0.99). There were no significant differences in mean CSF white cells (p 0.086) or CSF

Table 1 Characteristics of patients with specific neurological diagnoses and false-positive amplification of HHV-7

Age/sex	Previous history	Neurological diagnosis	CSF lymphocytes (cells/mm^3)	CSF proteins (mg/dL)
16/M	No	Multiple sclerosis (first relapse)	2	37.98
31/F	No	Multiple sclerosis (first relapse)	6	52.97
39/F	No	Psychogenic hemiparesis*	0	76
22/M	No	Psychogenic hemiparesis*	0	23
25/F	No	HaNDL	351	40
50/F	No	Diabetic polyneuropathy	5	73
68/M	No	Idiopathic facial palsy	0	36

HaNDL, headache with neurological deficits and CSF lymphocytosis

CSF cerebrospinal fluid, *M* male, *F* female

*Traumatic lumbar puncture;

proteins (p 0.348) among patients with and without detection of HHV-7 in CSF.

Among 21 patients with probable CNS infections (compatible clinical syndrome and CSF changes, in the absence of demonstrated causative agent), HHV-7 DNA was detected in CSF samples from six patients (28.6%): four had aseptic lymphocytic meningitis, one had encephalitis, and one had myelitis. A summary of these cases is presented in Table 2. Case 5 has been previously reported (Escobar et al. 2016) and case 6 is reported below.

The reproducibility of the results of HHV-7 amplification in CSF shown in our study was high. Twenty-four patients had two consecutive CSF examinations during the same neurologic process and 23 (95.8%) had concordant PCR results in both samples. All 21 cases with a first negative result had a second negative one. Among three patients with an initial amplification, the result of the repeated assay (mean 14 days after the first) was negative in one case of meningitis, but positive in the cases of encephalitis and myelitis.

Case report. HHV-7 encephalitis

A 44-year-old man without significant past medical history was admitted to the neurology ward for a 4-day history of progressive gait impairment, anxiety, and urinary urgency. He had preceding flu-like symptoms with inguinal adenopathies 10 days before admission. There was no history of recreational drugs, contact with animals, or foreign travel. On examination, temperature was 37.5 °C. There were no meningeal signs. The patient showed mild inattention and slow mentation, but higher cortical functions were otherwise normal. He had a spastic gait, with generalized hyperreflexia and bilateral Babinski signs. The patient presented episodes of paroxysmal cervical and upper limb dystonia. Cranial computed tomography was normal. Cranial magnetic resonance imaging (MRI) showed bilateral hyperintensities involving pyramidal tracts and basal ganglia with mild enhancement after intravenous gadolinium (Fig. 1). Spinal MRI was normal. Cerebrospinal fluid (CSF) contained 60 lymphocytes/mm^3, 44.9 mg/dL proteins, and normal glucose. Considering a diagnosis of acute disseminated encephalomyelitis and the progressive gait deterioration, therapy with high-dose intravenous methylprednisolone (1 g daily for 5 days) was initiated, followed by oral prednisone 60 mg/day tapered over 28 days, without significant improvement. Serologies for human immunodeficiency virus and syphilis, and antineuronal antibodies were negative. CSF cultures for bacteria, mycobacteria, and fungi were negative. After HHV-7 amplification in CSF, the patient was treated with intravenous ganciclovir 300 mg bid for 10 days. However, the patient suffered neurological

Table 2 Characteristics of patients with probable CNS infection caused by HHV-7

Case	Age/sex	Previous history	Clinical syndrome	CSF lymphocytes (cells/mm^3)	CSF proteins (mg/dL)	Antiviral treatment	Outcome
1	50/F	No	Aseptic meningitis	560	138	No	Full recovery
2	33/M	No	Aseptic meningitis	116	25	No	Full recovery
3	16/F	No	Aseptic meningitis	595	71	No	Full recovery
4	20/F	No	Aseptic meningitis	115	85	No	Full recovery
5	40/M	HIV stage A1	Myelitis	1	26	Foscarnet	Full recovery
6	44/M	No	Encephalitis	60	45	Ganciclovir Foscarnet	Mild sequelae

CSF cerebrospinal fluid, *M* male, *F* female

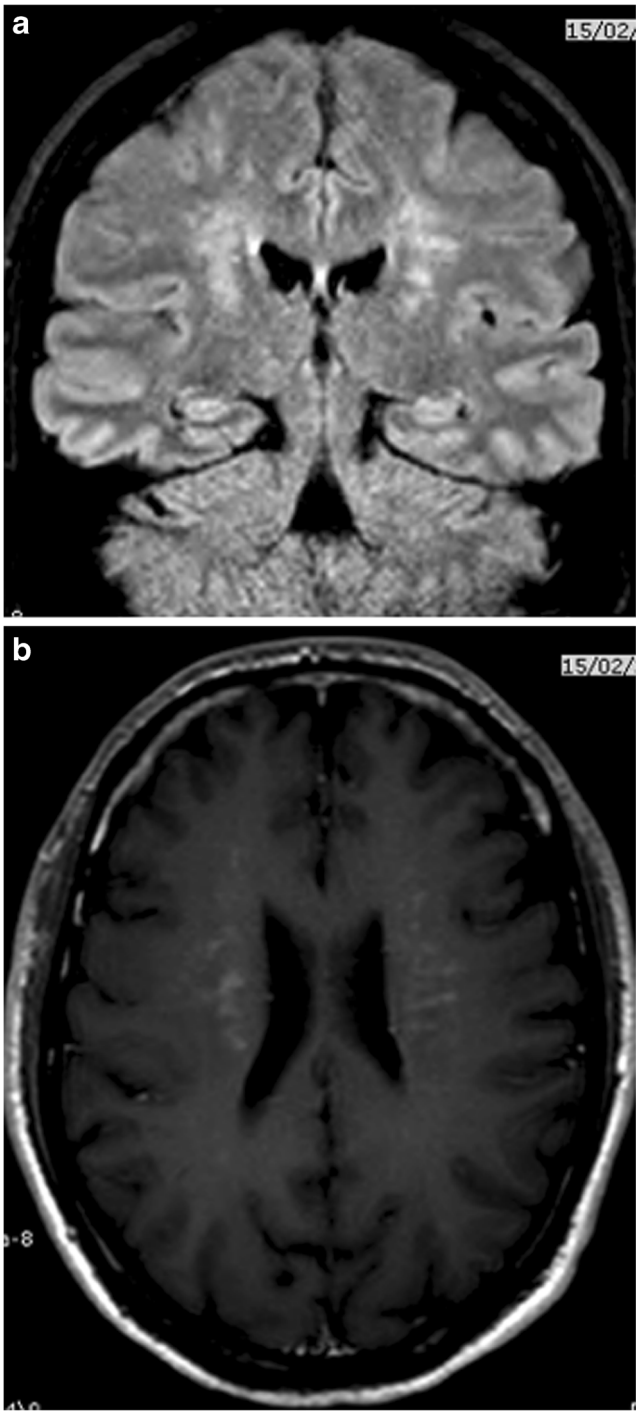

Fig. 1 Cranial magnetic resonance imaging of case 6. **a** Fluid attenuation inversion recovery-weighted coronal image showing bilateral white matter hyperintensities. **b** T1-weighted image after intravenous gadolinium, with slight enhancement of white matter lesions

deterioration, with severe inattention, painful spastic tetraparesis, and paroxysmal opisthotonus. He was bedridden and completely dependent for basic daily activities. CSF at day 16 contained 13 lymphocytes/mm^3, 33 mg/dL proteins, and normal glucose. Amplification of HHV-7 in CSF persisted and treatment with 7200 mg of intravenous foscarnet bid for 14 days was prescribed. A slow but progressive improvement during foscarnet treatment was observed. At the end of the antiviral trail (at day 32), the patient was alert, with moderate tetraparesis and spasticity, able to walk with unilateral assistance, and partially dependent for basic daily activities. At day 34, CSF analysis showed four cells/mm^3, normal proteins (33 mg/dL), and negative PCR for HHV-7. Control MRI was performed at 6th week after the onset of the disease showing established and confluent lesions without contrast enhancement. CSF analysis and immunologic tests were also negative. After 6 months of rehabilitation, he was able to walk with unilateral assistance with mild spasticity, hyperreflexia, and manageable sporadic urinary urgency.

Discussion

Primary HHV-7 infection occurs usually in children and is frequently asymptomatic or causes minor symptoms. It has been associated with neurological manifestations in children, such as febrile seizures and febrile status epilepticus (Epstein et al. 2012; Ward et al. 2005), and neuroinvasion during primary infection has been documented through the detection of HHV-7 DNA in CSF in children with CNS diseases (Van der Berg et al. 1999; Pohl-Koppe et al. 2001; Yoshikawa et al. 2000). Delayed primary HHV-7 infection has been reported to cause encephalitis or meningoradiculitis in immunocompetent children and a young adult (Schwartz et al. 2014; Ward et al. 2002; Fay et al. 2015; Rangel et al. 2017).

Most adults are seropositive for HHV-7 (Wyatt et al. 1991; Ward et al. 2001). In adults, the role of HHV-7 reactivation within the CNS as a cause of neurological disease is not clear. HHV-7 reactivation has only occasionally been associated with neurological disease in immunocompromised adults, as was the case of myelitis in an HIV-infected patient included in the present study: a case of acute myelitis in a bone marrow transplant recipient (Ward et al. 2002b), and a case of encephalitis in a peripheral blood stem cell transplant recipient (Chan et al. 2002). A pathogenic role of viral HHV-7 reactivation in immunocompetent adult patients has not been definitely established yet (Schwartz et al. 2014, Ward 2005). A case of encephalitis and myeloradiculitis associated with HHV-7 has been recently reported in an immunocompetent adult (Parra et al. 2017). Our experience with five cases of probable neurological disease caused by HHV-7 in immunocompetent adults adds new evidence supporting the concept that HHV-7 reactivation may also cause neurologic disease in this population.

In clinical practice, the diagnosis of a possible CNS disease caused by HHV-7 is usually based on the detection of HHV-7 DNA in CSF by molecular approaches. However, it may be difficult to proof a pathogenic role of this amplification. HHV-7 reactivation in CSF might be an epiphenomenon associated

with other inflammatory or non-inflammatory diseases of the CNS. Our study shows that detection of HHV-7 DNA in CSF has high specificity (0.96) in patients with other neurological diseases, which suggests that in clinical practice unspecific reactivation of HHV-7 within the CNS is uncommon in the context of other inflammatory and non-inflammatory neurological diseases. This is of particular importance for patients with confirmed infections of the CNS with different etiologies, where reactivation of the virus would be more frequently expected, in whom HHV-7 was only amplified in 1 of 36 cases. The high rate of reproducibility of the results shown for patients with two consecutive CSF examinations, especially for those with negative results, supports the clinical validity of this high specificity.

False-positive results for HHV-7 amplification in CSF might in some cases be the consequence of detection of blood HHV-7 in traumatic lumbar punctures, as shown in two of the cases of the present series. However, it is improbable that most cases of false-positive amplification of HHV-7 could be explained by the transference of infected blood cells into CSF, since the mean lymphocyte count in CSF did not differ among patients with and without amplification. Other cases of false-positive amplification occurred in patients with non-infectious inflammatory diseases: first relapse of multiple sclerosis and HaNDL. HHV-7 has not been detected in CSF fluid of multiple sclerosis patients (Taus et al. 2000). A report has recently shown amplification of HHV-7 in CSF from a patient with HaNDL (Stelten et al. 2016), so a pathogenic role of HHV-7 in this disease cannot be completely ruled out.

While amplification of HHV-7 in CSF was rare in patients with demonstrated infections or other CNS diseases, we found it frequently in patients with suspected infections of the CNS of unknown etiology (28.6%). In the cases of aseptic lymphocytic meningitis, a causative role for reactivation of HHV-7 is possible, although not proven. The alternative explanation seems more difficult to accept: the amplification of HHV-7 DNA in these cases would be an epiphenomenon in a patient with lymphocytic meningitis of unknown etiology, and the virus is secondarily reactivated but not actually contributing to the meningitis. It is plausible that reactivation of HHV-7 within the CNS in adults might cause aseptic meningitis as do other herpesviruses, like herpes simplex type 2 and varicella-zoster, because the presence of HHV-7 DNA and antigens has been demonstrated in brains of patients with unspecific encephalopathy and controls (Chapenko et al. 2016). Aseptic lymphocytic meningitis caused by HHV-7, would behave, as other viral meningitis, with a favorable course and spontaneous improvement in days without specific treatment.

In the cases of acute myelitis and encephalitis reported here, the etiologic role of HHV-7 as the cause of the neurological disease is supported by the sustained amplification of HHV-7 in two separate CSF samples, by the rapid clinical improvement and negativization of PCR only after specific antiviral treatment, and by the exclusion of other causes of myelitis and encephalitis. We cannot definitely exclude a delayed primary infection by HHV7 in these six patients, because serology for HHV-7 was not available. But primary infection seems very improbable because of patients' age, as most cases of primary infection with HHV-7 occur in childhood (Wyatt et al. 1991; Ward et al. 2001) and positive HHV-7 serology in adults always shows evidence of past infection (Ward et al. 2001).

Clinical experience in the treatment of HHV-7 CNS disease is limited. Improvement without specific antiviral treatment has been reported in cases of meningitis, meningoradiculopathy, myelitis, encephalitis, and Guillaín-Barré syndrome (Pohl-Koppe et al. 2001; Schwartz et al. 2014; Fay et al. 2015; Rangel et al. 2017). This was also the case with our patients with aseptic meningitis and HHV-7 amplification. An 11-year-old patient with brainstem encephalitis improved with high-dose corticosteroids, intravenous immunoglobulins, and plasma exchange (Fay et al. 2015). Acyclovir has no in vitro activity against HHV-7 (Zhang et al. 1999), but has been used in cases of encephalitis (Ward et al. 2002; Ward et al. 2002b), with apparent success. Foscarnet possesses potent in vitro activity against HHV-7, higher than ganciclovir (Zhang et al. 1999). In renal transplant recipients, ganciclovir prophylaxis did not influence the prevalence of HHV-7 viremia (Galarraga et al. 2005). In our experience, treatment with ganciclovir did not result in clinical improvement in the patient with encephalitis, nor did it control HHV-7 replication in CSF. Instead, foscarnet treatment was associated with neurological improvement and successful control of CSF viral replication in both patients with encephalitis and myelitis. These results support that foscarnet is probably the first therapeutic option for the treatment of severe HHV-7 infections.

The main limitation of the present study is its retrospective nature. However, it analyzes a representative large series of neurological patients studied in daily clinical practice without any selection bias.

In summary, HHV-7 reactivation may cause neurological disease in immunocompetent adult patients. Detection of HHV-7 DNA in CSF in adults has high specificity and, therefore, a pathogenic role of a positive result should be considered in patients with suspected CNS infections of unknown etiology, particularly if sustained amplification is demonstrated and blood contamination of CSF excluded. Cases of lymphocytic meningitis may resolve without treatment, but specific antiviral therapy is indicated in more severe CNS infections. In our experience, foscarnet is the drug of choice in severe CNS infections associated with HHV-7.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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