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CASE REPORT – OPEN ACCESS

Human Herpesvirus 7-Associated Acute Longitudinal Myelitis in an Immunocompetent Patient: A Case Report

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ABSTRACT

Background: Human herpesvirus 7 (HHV-7) can cause a central nervous system infection in both immunodeficient and immunocompetent patients. This report describes a case of longitudinal myelitis due to HHV-7.

Case Report: A 56-year-old male presented with lower extremity weakness and the inability to walk, difficulty urinating, and numbness in lower chest region. Thoracic magnetic resonance imaging showed hyperintensity in the spinal cord below the T4 level in a T2 sequence. Polymerase chain reaction (PCR) analysis of the cerebrospinal fluid (CSF) revealed HHV-7. The clinical diagnosis was longitudinal myelitis and a positive PCR test confirmed acute viral longitudinal myelitis due to HHV-7. Treatment with intravenous immunoglobulin and ganciclovir was initiated. After a program of rehabilitation therapy, the patient demonstrated partial recovery at a 9-month follow-up assessment.

Conclusion: Acute transverse myelitis due HHV-7 has been reported, but clinicians should be aware that, while rare, longitudinal myelitis can also occur, even in an immunocompetent patient.

Keywords: Epstein-Barr virus, human herpesvirus 7, immunocompetent, viral myelitis

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INTRODUCTION

Human herpes virus 7 (HHV-7), a member of the family of herpes viruses, primarily targets CD4+ T-lymphocytes and cord blood mononuclear cells, and can induce pathological changes, including apoptosis (1). Some 80% to 90% of adults are infected with this virus in infancy (2). Following the early primary infection, HHV-7 can remain latent in CD4+ T-lymphocytes and macrophages and be reactivated (1). HHV-7 can be a cause of encephalitis, meningitis, and myeloradiculoneuropathy, particularly in adults with immune deficiency, however, rarely, HHV-7 may also cause central nervous system (CNS) infection in immunocompetent patients (3). This case report is a description of a rare clinical form of HHV-7 infection in immunocompetent patient and a brief review of the literature.

CASE REPORT

A 56-year-old male patient had presented at another hospital with complaints of an inability to walk and difficulty urinating for 10 days. The symptoms progressed to obvious lower extremity weakness and numbness in lower chest region. His medical records indicated a cerebrospinal fluid (CSF) protein level of 123 mg/dL and a glucose level of 46 mg/dL (simultaneous blood glucose [SBG]: 110 mg/dL). Cytomegalovirus immunoglobulin M (CMV IgM) results were negative, however, the CMV IgG level was 484 IU/mL. Acyclovir and ceftriaxone was administered with a preliminary diagnosis of CMV myelitis. The symptoms showed no regression after the seventh day of acyclovir therapy.

A neurological examination performed on admission to our department revealed hypoesthesia, pain, and reduced deep sensation below the T4 dermatome level. The Medical Research Council Manual Muscle Testing scale strength measurement was 0/5 in both proximal and distal lower limbs. Patellar, ankle, and plantar reflexes were absent on both sides. No other neurological deficits were observed. Thoracic magnetic resonance imaging (MRI) showed hyperintensity in the spinal cord below the T4 level in a T2 sequence, and edema in a T1 contrast sequence (Fig. 1). The patient was diagnosed with acute longitudinal myelitis and intravenous immunoglobulin (IVIG) 0.4 g/kg treatment was initiated.

CSF analysis on admission revealed a glucose value of 63 mg/dL (SBG: 156 mg/dL), chlorine 127 mEq/L (normal: 118–132 mEq/L), and protein 67 mg/dL (normal: 15–45 mg/dL). Cytological examination showed 280 lymphocytes/mm^3. Multiplex real-time polymerase chain reaction (PCR) testing of a CSF sample was positive for the Epstein-Barr virus (EBV) and HHV-7 (FTD Neuro 9, FTD Bacterial Meningitis, and FTD Neonatal Meningitis

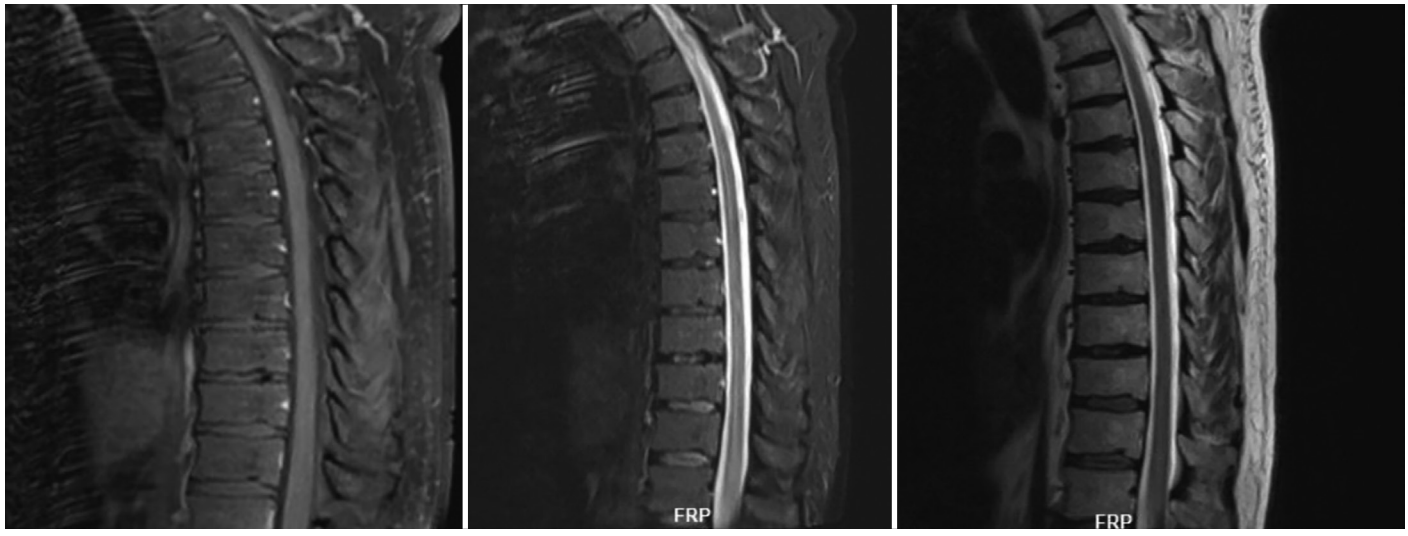

Figure 1. Thoracic magnetic resonance imaging revealing hyperintensity in the spinal cord below the T4 level in a T2 sequence and edema in a T1 contrast sequence

assays; Fast Track Diagnostics, Sliema, Malta). Test results were negative for human cytomegalovirus (CMV), enterovirus, *Streptococcus pneumoniae*, HHV-6, *Neisseria meningitidis*, *Haemophilus influenzae*, *Listeria monocytogenes*, and HSV 1–2.

A repeat CSF analysis was conducted. PCR testing was positive for HHV-7 DNA, anti-CMV IgM: 0.19 AU/mL (negative), anti-CMV IgG: 144.5 (positive), CMV DNA <42 copies/mL, EBV-viral capsid antigen (VCA) IgM: 0.05 S/CO (negative), EBV-VCA IgG: 57.2 (positive), EBV- Epstein–Barr nuclear antigen 1 IgG: 20.06 IU/mL, and brucella IgM/G: <0.01 S/CO, tuberculosis culture and PCR: negative.

The clinical diagnosis of acute longitudinal myelitis due to HHV-7 was confirmed by laboratory tests and radiological imaging. The patient completed 5 days of IVIG treatment. Acyclovir was exchanged for ganciclovir for 14 days. In the first week of treatment, his lower limb muscle strength improved noticeably, achieving a 3/5 score on discharge for rehabilitation therapy. At the follow up after 9 months, urinary incontinence persisted and intermittent catheterization was used for urination. Muscle strength in lower limbs was graded 4/5. He was able to walk 15 meters unsupported after rehabilitation therapy. Hypoesthesia was still present below the knees.

DISCUSSION

HHV-7 was first isolated from CD4+ lymphocytes of a healthy adult in 1990. Primary infection generally occurs during childhood; seropositivity has been reported to be >75% in children over the age of 2 years. Primary HHV-7 infection is typically responsible for a subset of exanthem subitum and other exanthema cases in childhood. Cases can sometimes be complicated by seizures and CNS disease, including acute hemiplegia, suggesting that HHV-7 may also infect the brain (4).

Acute myelitis, encephalitis, and flaccid paralysis have been reported in immunocompromised individuals. The first case of acute myelitis due to HHV-7 was reported in a 47-year-old male patient who underwent bone marrow transplantation (5). Encephalitis and flaccid paralysis associated with primary HHV-7 was also reported in a 19-year-old immunocompetent male patient in 2002 (6). Acute transverse myelitis that involves a contiguous lesion of the spinal cord is referred to as longitudinal myelitis. This case was diagnosed as longitudinal myelitis.

A diagnosis of myelitis due to HHV-7 can be made using radiological imaging and a positive PCR test for HHV-7 (3). In this case, the diagnosis was based on clinical and MRI findings as well as a positive PCR result for HHV-7.

A search of the PubMed and the Web of Science databases with the keywords "HHV-7" and "viral myelitis" yielded 8 results. Seven reports are summarized in Table 1. One was excluded because it was published in Spanish.

MRI is the preferred imaging tool to demonstrate HHV-7-related myelitis. Patients with normal brain and spinal MRI results when there is spinal cord, cauda equina, or conus medullaris involvement have been reported (3). The involvement may manifest as hyperintense and gadolinium-enhanced lesions in T2 and fluid attenuated inversion recovery sequences (8–10) In this patient, longitudinal gadolinium-enhanced intraspinal cord involvement was present below the T4 level.

Serology, cultures, and PCR testing are also used to diagnose HHV-7 infection, as with other types of HHV. The greatest challenge is the differentiation between active and latent infection and reactivation (2).

Since HHV-7 does not contain thymidine kinase, acyclovir treatment is not effective, and it has also proven to be resistant to penciclovir (2). Ganciclovir, cidofovir, and foscarnet have been found to inhibit the DNA polymerase of HHV-7. These 3 drugs can be used to treat HHV-7 infection (4, 2). In addition to ganciclovir and immunoglobulin treatments, methylprednisolone can be used alone or in combination with foscarnet (3). As seen in this patient, complete or partial recovery can be achieved.

Table 1. Clinical and laboratory characteristics of some selected cases associated with HHV-7 infection

Reference	Immune status	Age (years)	Gender	Clinical diagnosis	HHV-7 diagnosis	CSF	Radiology	Treatment	Prognosis
Ward and White et al. 2002 (5)	Bone marrow recipient	47	Male	Acute myelitis	HHV-7 DNA in CSF and high avidity HHV-7 IgG before transplant (PCR)	48 leucocytes/µL (predominantly lymphocytes), 235 red blood cells/µL, elevated protein of 1.22 g/L, and 52.2 mg/dL glucose (blood glucose 99 mg/dL)	Normal MRI of brain and spinal cord	Methylprednisolone (1 g/day)	Full recovery
Ward and Kalima et al. 2002 (6)	Immunocompetent	19	Male	Encephalitis and flaccid paralysis	HHV-7 DNA in CSF and low avidity HHV-7 IgG (PCR)	65 leucocytes/µL (63 lymphocytes + 2 neutrophils) and 2 red blood cells/µL, elevated protein of 80 mg/dL, and 48.6 mg/dL glucose (blood glucose 90 mg/dL)	Normal MRI of brain and spinal cord	Not reported?	Not reported
Mihara et al. 2005 (7)	Immunocompetent	26	Male	Acute myeloradiculopathy	HHV-7 DNA in CSF by real time-PCR and increase in anti-HHV-7 titers from 1:16 to 1:64 (IFA)	Normal at admission with an increase in protein of 89 mg/dL and modest pleocytosis (8 cells/µL) by day 20	Normal MRI of brain and spinal cord	Intravenous immunoglobulin (400 mg/kg/day) for 5 days	After 8 months, muscle strength returned to subnormal levels (4/5 on the Medical Council Scale)
Ginanneschi et al. 2007 (8)	Immunocompetent (HHV-7/ CMV co-infection)	51	Male	Encephaloradiculomyelitis	HHV-7 DNA in CSF (nested PCR) and anti-HHV-7 IgG but no IgM in serum (IFA)	Pleocytosis (250 cells/µL) with 93% lymphocytes, 10 red blood cells/µL, high protein level (950 mg/dL) and normal glucose	MRI showed signal hyperintensity around the spinal cord and localization of contrast medium in the conus medullaris and cauda equine; brain MRI showed small areas of contrast medium in subcortical	Ganciclovir and dexamethasone	Walk with support, urinary retention, constipation, numbness of the lower limbs (after 4 months)

Table 1 (cont.). Clinical and laboratory characteristics of some selected cases associated with HHV-7 infection

Reference	Immune status	Age (years)	Gender	Clinical diagnosis	HHV-7 diagnosis	CSF	Radiology	Treatment	Prognosis
							and periventricular white matter.		
Miranda et al. 2011 (9)	Immunocompetent	34	Male	Acute myelitis	HHV-7 RNA in CSF (PCR-microarray)	35 leucocytes/µL (predominantly monocytes) and elevated protein of 75 mg/dL	Cervical spine MRI showed hyperintense images in 2 extensive segments compatible with inflammatory lesions	Methylprednisolone (1 g/day) and ganciclovir	Full recovery (after 6 months)
Miranda et al. 2011 (9)	Immunocompetent	27	Male	Neurological disorder	HHV-7 RNA in CSF (PCR-microarray)	160 leucocytes/µL (predominantly monocytes) and elevated protein of 75 mg/dL	Normal MRI of brain	Analgesia and rest	Full recovery (after 6 months)
Escobar-Villalba et al. 2016 (10)	HIV-infected	40	Male	Acute myelitis	HHV-7 DNA in CSF (PCR-microarray)	1 lymphocyte, 0 erythrocytes, 25.88 mg/dL proteins and 59 mg/dL glucose	Spinal MRI showed gadolinium-enhanced intra-spinal lesions at thoracic vertebrae 6–7	Foscarnet	Full recovery (after 1 month)
Parra et al. 2017 (3)	Immunocompetent	26	Male	Encephalitis with polymyeloradiculopathy	HHV-7 DNA in CSF (Multiplex nested PCR)	110 leucocytes/µL (lymphocytes + monocytes) and 100 red blood cells/µL, elevated protein of 82 mg/dL, and 60 mg/dL glucose (blood glucose, 108 mg/dL)	MRI showed presence of cervical and dorsolumbar myelitis	Intravenous immunoglobulin and ganciclovir	Not reported
Current case	Immunocompetent	56	Male	Acute longitudinal myelitis	HHV-7 DNA in CSF (real time-PCR)	280 leucocytes/µL (lymphocytes), elevated protein of 67 mg/dL, and 63 mg/dL glucose	Spinal MRI showed gadolinium-enhanced intra-spinal lesions at thoracic vertebrae 4–12	Intravenous immunoglobulin and ganciclovir	Partial improvement (after 9 months)

CMV: Cytomegalovirus; CSF: Cerebrospinal fluid; HHV: Human herpesvirus; IFA: Indirect fluorescent antibody; Ig: Immunoglobulin; MRI: Magnetic resonance imaging; PCR: Polymerase chain reaction

CONCLUSION

HHV-7 infection with neurological involvement in an immunocompetent patient is rare. Nonetheless, physicians should be aware of the etiological agent of HHV-7 when presented with cases of acute transverse or longitudinal myelitis. The diagnosis is based on isolation of the virus or demonstration of HHV-7 antigens in the CSF.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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