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Encephalitis associated with human herpesvirus-7 infection in an immunocompetent adult: a challenging case report

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ABSTRACT:

— ***Background:*** Primary Human herpesvirus-7 (HHV-7) infection usually occurs during childhood and mainly causes exanthema subitum *(Roseola infantum)*, followed by a lifelong latent state with possible reactivation in case of immunodeficiency. Occasionally, consequences of HHV-7 infection are reported in immunocompetent adults. The natural history of the infection is poorly studied, and little is known about its pathogenic role in central nervous system (CNS) disease in non-immune suppressed adults. Encephalitis results in substantial morbidity and mortality worldwide. Although rare, encephalitis follows infection with relatively common agents. CSF pleocytosis is suggestive of an inflammatory process and identification of a microorganism generally confirms a clinical diagnosis of encephalitis.

— ***Case presentation:*** We describe here a case of probable encephalitis associated to HHV-7 with seizures in an immunocompetent patient. Clinical presentation and evolution may contribute to a better understanding of HHV-7 related pathology.

— ***Conclusions:*** This case may alert clinicians to consider this specific etiology in the differential diagnosis of encephalopathy in patients with suspected infectious encephalitis. HHV-7 may be a pathological factor and this etiology could be underestimated.

— ***Keywords:*** Human herpesvirus-7 encephalitis, Immunocompetent adults, Clinical significance HHV-7 CNS infection.

INTRODUCTION

Human herpesvirus-7 (HHV-7) is a ubiquitous virus that belongs to the Roseolavirus, which is a genus of the herpes viruses subfamily (double stranded DNA genome of about 145 kb with homologies to human herpesvirus 6, HHV6, and cytomegalovirus). Primary HHV-7 infection usually occurs during childhood and causes exanthema subitum (*Roseola infantum*). Primary infection is followed by a lifelong latent state with possible reactivation in case of immunodeficiency[1,2]. The natural history of this infectious agent and the consequences of HHV-7 infection in immunocompetent adults are largely unknown; both late primary HHV-7 infection and reactivation of the virus from macrophages and/or CD4+ T cells can occur. In particular, little is known about its pathogenic role in central nervous system (CNS) disease in non-immunosuppressed adults. Specifically, in case of encephalitis, it is important to distinguish between infectious encephalitis and post infectious encephalomyelitis for the management of patients. We describe here a case of HHV-7 encephalitis with associated poly-myeloradiculopathy in an immunocompetent patient.

CASE PRESENTATION

A 20-year-old immunocompetent male presented partial

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seizure with secondary generalization. Admitted into the ER, the patient underwent a brain CT scan, a chest x-ray, complete blood count, creatinine and transaminase dosage, which turned out to be all normal. Therefore, he was referred to the Neurological Unit of our Hospital.

His neurological examination at the time of admission revealed a slight pronation of the left arm. An antiepileptic drug therapy with Levetiracetam 500 mg ½ table twice a day was started on admission with no reported adverse reactions. The rest of the neurological examination was unremarkable. The patient's father was affected by multiple sclerosis (MS), while his past clinical history was silent. At the admission, the patient did not show any major symptom and sign of meningeal irritation such as photophobia and nuchal rigidity. However, he complained of headache and asthenia. On day 4 of the admission, his body temperature reached 39°C. Physical examination did not reveal the presence of skin rash. The patient underwent a brain magnetic resonance imaging (MRI) and a lumbar puncture (LP). The cerebrospinal fluid (CSF) sample contained 132 leucocytes/µl (lymphocytes + monocytes) and 100 red blood cells/µl, 42 mg/dl of protein, and 60 mg/dl of glucose (blood glucose, 98 mg/dl). MS was ruled out by measuring oligoclonal immunoglobulin G. No progressive deterioration of the level of consciousness was reported. The patient was empirically treated with acyclovir, ceftriaxone, and corticosteroids. CT scanning ruled out space-occupying lesions. MRI of the brain highlighted T2 hyperintensity, with areas of restricted diffusion in left cerebral cortex and right periventricular and deep white matter.

Normal findings were obtained for a wide spectrum of antibodies (anti-Jo-1, anti-Sm, anti-SS-A, anti-SS-B, anti-nRNP, anti-Scl-70, anti-c-ANCA, anti-pANCA, anti-dsDNA, anti-amphiphysin, anti-CV2, antiPNMA2, anti-Yo (PCCA-1), anti-Hu (ANNA-1), anti-RI (ANNA-2), and anti-ganglioside). Cerebrospinal fluid (CFS), serum, and whole-blood samples were screened for the identification of possible etiologies.

Follow-up MRI, performed one month later, showed the persistence of T2 hyperintensity on the anterior temporal poles bilaterally, involving the frontal lobes and near by the corpus callosum body and left parietal lobe. None of those lesions showed enhancement after contrast-medium injection.

After treatment, the global performance status was improved. Therefore, the patient was discharged. However, low-grade fever persisted. Four months later, the patient had recovered completely. The results of the microbiological assessment, according to clinical and risk factors were the following. Gram stain and bacterial culture, alpha-herpesvirus (herpes simplex virus 1, herpes simplex virus 2, and varicella-zoster virus), and enterovirus were negative. Treponema pallidum and Cryptococcal neoformans (serum and CFS), Mycoplasma pneumoniae, Epstein-Barr virus, and Cytomegalovirus were negative. Screening for HIV (serology and RNA), hepatitis A, B, and C, and Mycobacterium tuberculosis (CSF) was also negative. Finally, human herpesvirus-6, HHV-7, and human herpesvirus-8 were suspected. HHV-7 DNA was detected in the first CSF sample by Multiplex Nested PCR. However, HHV-7 antibody and avidity testing, to determine primary infection *vs*. reactivation of HHV-7 in the nervous system, could not be performed. Acyclovir was discontinued after microbiological diagnosis and the patient was not treated with ganciclovir.

DISCUSSION

Our patient showed symptoms suspicious for encephalitis. Patients with encephalitis usually show an altered mental status ranging from subtle deficits to complete unresponsiveness. Seizures are common with encephalitis, and focal neurologic abnormalities can occur, including hemiparesis, cranial nerve palsies, and exaggerated deep tendon and/or pathologic reflexes. Diagnosis of encephalitis is difficult on clinical ground because it still lacks standardized case definition and diagnostic approaches. In 2013 the International Encephalitis Consortium proposed diagnostic criteria with major criterion (not satisfied by our case for short lasting of mental status alteration) and minor criteria (> 3 required for probable or confirmed encephalitis)[3]. Fever matched the major criteria, it was > 38 and within 72 hours after presentation. Seizures were generalized and not attributable to a pre-existing seizure disorder. CSF pleocytosis was present as the WBC of the CSF was > 5/mm^3. MRI had shown subtle CNS abnormalities. We believe the patient fulfilled the required criteria for at least probable encephalitis. Confirmed encephalitis required defined microbiologic evidence of acute infection with a microorganism strongly associated with encephalitis from CSF.

HHV-7 is a ubiquitous virus. More than 95 percent of adults are seropositive[4]. Infection with HHV-7 generally occurs during childhood. The role of HHV-7 in human disease is not clear. HHV-7infection is generally asymptomatic. It has been identified as one of the viruses causing exanthem subitum (ES, roseola), although HHV-6 is a more common cause. Hepatitis has been reported during HHV-7 infection, and a mononucleosis-like syndrome has been associated with HHV-7 with or without concurrent Epstein-Barr virus infection[5-7]. Several reports describe an association between HHV-7 and febrile seizures[8,9]. HHV-7 isolation has been described from infants with ES, including a report of two cases of seizures and acute hemiplegia complicating this entity.

In addition to febrile seizures, other central nervous system (CNS) manifestations have been described, such as encephalitis and Guillain-Barré syndrome. Isolated cases of encephalopathy and hemi-convulsion and hemiplegia syndrome have been reported during HHV-7 infection. Rare cases of acute myelo-radicular-neuropathy associated with HHV-7 have been reported[7]. In three adolescents, two of whom had encephalitis and one of whom had Guillain-Barré syndrome, primary HHV-7 infection was confirmed as the cause of the neurologic disease syndrome[10]. A case of hemorrhagic brainstem encephalitis has been described in an otherwise healthy child. After extensive investigation, only HHV-7 DNA was found in his cerebrospinal fluid (CSF)[11]. Cases of acute encephalitis occur rarely in immunocompetent

adults[12]. One patient with involvement of the nucleus of cranial nerve VI had only HHV-7 DNA found in the CSF. A second patient had ophthalmoplegia, HHV-7 DNA in the CSF, and increased HHV-7 antibody titers, although an antibody avidity assay was not performed. A third patient had limbic encephalitis with HHV-7 DNA in the CSF and an increase in HHV-7 IgG titers, believed to be due to HHV-7 reactivation[12].

Our approach to this patient included a differential diagnosis that excluded noninfectious CNS diseases such as structural lesions, brain abscesses, para-meningeal infections, and metabolic and toxic encephalopathies; however, a definitive diagnosis could not be established. The detection of HHV-7 DNA in the patient's CSF concomitant with neurological disease in association with the exclusion of all alternative etiological causes supported HHV-7 as the possible cause of the encephalitis. Since antibody avidity could not be determined, we cannot confirm whether encephalitis associated to HHV-7 infection in our patient was secondary to late primary infection or a reactivation. Conversely, HHV-7 is a virus that is highly prevalent and has been detected in normal brain tissue[9]. Therefore, CSF PCR has a low positive predictive value.

No clinical settings in which treatment for HHV-7 infection is required have been identified. *In vitro*, foscarnet, cidofovir, and tenofovir inhibit HHV-7 replication. On the other hand, the virus is relatively resistant to acyclovir, penciclovir, and ganciclovir. Small clinical studies suggest that HHV-7 is resistant to ganciclovir at levels that were effective for prevention and treatment of cytomegalovirus. Sensitivity of HHV-7 to the guanine analogs was different from human herpesvirus 6, suggesting a difference in selectivity of specific viral enzymes.

In fact, the patient had already improved before acyclovir therapy was administered, making HHV-7 the most probable responsible for the immunological response, taking into account our patient's clinical improvement. The case presented here contributes to the delineation of the approach to a patient profile with a similar clinical presentation and evolution to those presented in the literature[9-14]. Notably, these findings are similar to those of the HHV-7 encephalitis cases previously published, which occurred in both immunocompetent and non-immunocompetent adults; this may alert clinicians to consider this specific etiology. It is worthwhile to mention that Multiple sclerosis's etiology is thought to have a possible viral component and that some studies seem to indicate the possible involvement in MS of HHV-7[15].

CONCLUSIONS

HHV-7 should be considered in the differential diagnosis of encephalopathy in patients with suspected infectious encephalitis. A timely diagnosis is crucial for the early administration of new specific treatments.

Future studies need to be done to better understand the potential effect of HHV-7 infection in the etiology of MS.

Conflict of Interest:
The Authors declare that they have no conflict of interests.

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