Severe Encephalomyelitis in an Immunocompetent Adult with Chromosomally Integrated Human Herpesvirus 6 and Clinical Response to Treatment with Foscarnet plus Ganciclovir

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Human herpesvirus 6 has rarely been identified as a cause of encephalitis in immunocompetent adults. We describe a patient who had severe encephalomyelitis, hypoglycorrhachia, and human herpesvirus 6 identified in his cerebrospinal fluid and serum and who recovered after treatment with foscarnet and ganciclovir. Human herpesvirus 6 should be considered in immunocompetent patients with encephalitis.

Human herpesvirus 6 (HHV-6), the causal agent of roseola infantum, infects almost all children by 2 years of age [1]. HHV-6 subsequently latently infects PBMCs, salivary glands, and brain tissue [1]. HHV-6 type B is associated with most cases of roseola, although the pathologic role of the more neurotropic HHV-6 type A is less well defined [2]. HHV-6 has been associated with encephalitis during primary infection in children and during reactivation in immunocompromised individuals. Encephalitis due to HHV-6 in immunocompetent adults has been reported but is more controversial [1].

Case report. A previously healthy 34-year-old man presented with a 1-week history of sore throat, vomiting, fever, and headache. He was a married software engineer with 2 young children and had traveled to China 7 months before presentation (he received no vaccinations before traveling to China). A lumbar puncture at hospital admission revealed a WBC count of 331 cells/μL (76% lymphocytes), a protein level of 119 mg/dL, and a normal glucose level. Initial MRI findings were normal. Treatment with vancomycin, ceftriaxone, and acyclovir was initiated, but the patient's mental status deteriorated, and he developed myoclonus.

One week after presentation, the patient became comatose and was intubated. His antibiotic regimen was changed to vancomycin, cefepime, and ampicillin-sulbactam. Acyclovir treatment was changed empirically to ganciclovir. An electroencephalogram on hospital day 14 revealed bifrontal epileptiform discharges and an evolving run of stimulus-induced seizures. Brain MRI on hospital day 12 revealed small areas of restricted diffusion, possibly indicating small ischemic strokes in the bilateral cerebral hemispheres. Findings of a brain magnetic resonance angiogram were normal. The patient developed acute renal failure and autonomic dysregulation.

A lumbar puncture 2 weeks into the patient's course revealed a WBC count of 127 cells/μL (87% lymphocytes), an RBC count of 3355 cells/μL, a protein level of 92 mg/dL, and a glucose level of 36 mg/dL . Because of the hypoglycorrhachia, empirical therapy was initiated for tuberculous meningitis (isoniazid, rifampin, ethambutol, pyrazinamide, and dexamethasone) and for *Coccidioides* meningitis (fluconazole); treatment with the other antibacterial agents and ganciclovir was continued.

Results of a PPD skin test were negative, and chest radiograph findings were not consistent with pulmonary tuberculosis. Results of 4 sputum acid-fast bacillus smears and cultures were negative. Results of multiple studies of serum and CSF samples were negative (table 1). Testing for Japanese encephalitis was not performed, because the 7-month period between the patient's trip to China and the onset of illness made this diagnosis highly unlikely.

Brain MRI on hospital day 21 revealed diffuse, symmetric foci of abnormal diffusion signal throughout the subcortical white matter and middle cerebellar peduncle. Fluid-attenuated inversion-recovery imaging also revealed patchy abnormal signal in the bilateral insular cortices, basal ganglia, and thalamus. No abnormal brain enhancement was seen. Spine MRI revealed multifocal, intramedullary T2 hyperintensities throughout the spinal cord without enhancement. These changes were considered to be most consistent with a diffuse process, such as a toxic-metabolic derangement or an infectious encephalomyelitis.

A CSF sample obtained on hospital day 12 was positive for HHV-6 by PCR (viral load, 30,000 copies/mL). The patient had

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Table 1. Negative results of CSF and serologic examinations during hospitalization.

Test	Negative results, by sample type		
	CSF		
	Day 1	Days 10, 12, and 15	Serum, days 10–25
Antibody	To WNV	To Rubeola, WNV, *Mycoplasma* species, LCV, *Toxoplasma gondii, Borrelia burgdorferi, Coxiella burnetii, Bartonella* species, Spotted Fever and Typhus Fever group *Rickettsia* species, *Coccidioides* species, and cysticercosis	To Coccidiodes, WNV, Western Equine encephalitis virus, St. Louis encephalitis virus, Eastern Equine encephalitis virus, California encephalitis virus, *Brucella* species, *Legionella* species, HIV, HBV, HCV, LCV, HSV-1, HSV-2, Spotted Fever and Typhus Fever group *Rickettsia* species, poliovirus, coxsackie virus, echovirus, and adenovirus
PCR	For HSV-1, HSV-2, and *Mycobacterium tuberculosis*	For cytomegalovirus, HSV-1, HSV-2, VZV, enterovirus, EBV, *Toxoplasma gondii, Tropheryma whipleii,* and *Bartonella* species	For WNV, human metapneumovirus, HSV-1, and HSV-2
Smear and/or culture	Bacteria, *M. tuberculosis,* and fungi	Bacteria, viruses, CMV, *M. tuberculosis* (3 times), and fungi	6 Blood cultures
Serologic examination	…	…	For EBV, measles, adenovirus, *Chlamydia pneumoniae,* influenza A and B, and *Mycoplasma pneumoniae* (consistent with past infection or immunization)
Other	…	VDRL test and latex *Cryptococcal* antigen	RPR test

NOTE. CMV, cytomegalovirus; EBV, Epstein Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus; LCV, lymphocytic choriomeningitis virus; RPR, rapid plasma reagin; VDRL, Venereal Disease Research Laboratory; VZV, varicella zoster virus; WNV, West Nile virus.

received empirical intravenous therapy with ganciclovir starting on hospital day 10. On hospital day 26, foscarnet was added according to a dosing regimen published elsewhere [3]. Fluconazole therapy was stopped after 4 days, and antituberculous therapy was stopped after 9 days of therapy.

One day after starting foscarnet and ganciclovir combination therapy, the patient's mental status improved substantially. This improvement continued; however, coincident with inadvertent discontinuation of ganciclovir therapy, his mental status transiently worsened. Shortly after reinstitution of ganciclovir therapy, his mental status improved again.

The patient received combination therapy with foscarnet and ganciclovir for 26 days. Analysis of a CSF sample on hospital day 40 revealed an increase in the glucose level to 47 mg/dL, a decrease in the level of pleocytosis (WBC count, 6 cells/μL), and a decrease in the HHV-6 load to 4400 copies/mL (by PCR). The patient received intravenous ganciclovir monotherapy, followed by oral valganciclovir therapy for 2 additional months. His serum HHV-6 load decreased from 93,000 copies/mL on hospital day 31 to 17,000 copies/mL 3 months after presentation; by that time, he had experienced nearly complete clinical recovery. MRI of his brain and spine 4 months after hospital admission revealed improvement in the areas of white matter, restricted diffusion in the brain, and a normal spinal cord.

The patient's serum HHV-6 IgG titer was 1:160, and his serum HHV-6 IgM titer was undetectable on hospital day 20, which indicated chronic infection. His CSF HHV-6 IgG titer was 1:1, and his CSF HHV-6 IgM titer was undetectable. The HHV-6 in his CSF and serum samples was type A (HHV-6 Variant Subtyping; ViraCor). His mother had a whole blood HHV-6 (type A) load of 46,500 copies/mL. Hair follicles from the patient, his mother, and his daughter had detectable HHV-6 (by HHV-6 PCR of the hair follicles; Bioworld Consulting Labs), which suggested chromosomally integrated HHV-6 infection. His other family members were not tested in this manner.

Discussion. This immunocompetent 34-year-old man developed severe encephalomyelitis and subsequently experienced almost complete recovery. Results of an extensive etiologic analysis were negative, except for the finding of HHV-6 type A in CSF and serum samples. The patient's clinical symptoms were accompanied by CSF pleocytosis, hypoglycorrhachia, and markedly abnormal brain and spine MRI findings. Slow or inapparent response to 2 weeks of ganciclovir monotherapy was followed by dramatic clinical improvement after the addition of foscarnet.

There are <30 reported cases of suspected HHV-6 encephalitis in immunocompetent adults in the literature [1, 4–6]. Similar to our patient, some patients in the literature had hypoglycorrhachia [5], perhaps indicating that this is a characteristic finding for HHV-6 encephalitis. HHV-6 was most frequently identified in these patients by CSF PCR, although several patients received a diagnosis based on detection of intrathecal HHV-6–specific IgG and/or IgM, transiently elevated serum HHV-6–specific antibody levels, or brain immunohistochemistry of HHV-6 early protein at autopsy. The clinical spectrum ranged from mild encephalitis with complete recovery to death [1, 4–6].

In reports of HHV-6 encephalitis in immunocompetent patients, patchy abnormal MRI signal in the cerebral cortex and white matter has been described, as has diffusion abnormality in the absence of other findings [7, 8]. Our patient demonstrated extensive white matter involvement and corticolimbic abnormalities on T2 and diffusion-weighted imaging, consistent with previous reports of HHV-6 encephalitis. Pathologically, oligodendrocytes and astrocytes are thought to be a target for lytic HHV-6 infection in the CNS of patients with HHV-6 encephalitis. This may explain the characteristic extensive white matter signal abnormality. Whether this stems from direct cytotoxic injury or secondary demyelination remains unclear.

There have been no in vivo studies—except for case reports—that have addressed treatment of HHV-6 infection. However, many antiviral agents that are active against cytomegalovirus are also active against HHV-6 in vitro [1]. A recent study found that, in HHV-6–infected PBMCs, foscarnet and ganciclovir demonstrated the most antiviral activity, but only foscarnet and cidofovir were effective at inhibiting HHV-6 replication in glial cells [2]. This could explain why our patient did not respond to ganciclovir alone but experienced subsequent marked improvement after the addition of foscarnet. Ganciclovir-resistant HHV-6 has been reported; thus, resistance is another possible reason for nonresponse to ganciclovir monotherapy [1]. Ganciclovir plus foscarnet has shown synergy even against ganciclovir-resistant cytomegalovirus in vivo [3]; this could also apply to HHV-6.

There has been debate regarding the clinical relevance of HHV-6 in the CSF of immunocompetent adults, even in the presence of encephalomyelitis [9]. The virus has a tropism for glial cells and PBMCs and remains latent in all infected individuals. Therefore, the presence of HHV-6 does not necessarily establish a pathogenic role. However, in several autopsy specimens from immunocompetent patients with encephalitis, either HHV-6 early protein was localized by immunohistochemistry or HHV-6 nucleic acid was localized by in situ hybridization, specifically to involved portions of the brain [1, 6]. This suggests that HHV-6 was etiologic in these cases and, thus, has the potential to cause severe encephalitis in immunocompetent persons.

Detection of HHV-6 in hair follicles obtained from the patient, his mother, and his daughter suggests chromosomally integrated virus in all 3 individuals. Because HHV-6 exists latently only in PBMCs, salivary glands, and brain tissue, detection in hair fol-

licles indicates HHV-6 presence in all cells of the body, which in turn indicates chromosomal integration and, arguably, vertical transmission [10, 11]. The relevance of chromosomally integrated HHV-6 is controversial. Although some authors believe that chromosomal integration must be excluded before a diagnosis of HHV-6 encephalitis can be validated [11], the prevalence of chromosomally integrated HHV-6 in encephalitic patients in Britain is reported to be 4 times higher than that in healthy British blood donors (3.3% vs. 0.8%) [12], which suggests that HHV-6 reactivation in patients with chromosomal integration may play a role in some cases of encephalitis.

Our report has limitations. Although it appears that our patient had HHV-6 encephalomyelitis and responded to antiviral agents, patients with chromosomally integrated HHV-6 infection can have detectable virus in CSF or serum at any time [11]. A PCR result positive for HHV-6, therefore, does not establish this agent as causal, even in a patient with encephalitis. The decrease in HHV-6 load in temporal association with our patient's treatment and clinical recovery could be explained, in part, by the decreasing level of CSF pleocytosis. It is also possible that an infection-induced vasculitis or acute disseminated encephalomyelitis supervened and that, therefore, dexamethasone could have driven his recovery. Despite these limitations, the combination of severe encephalomyelitis with CSF lymphocytic pleocytosis, negative results of an extensive etiologic analysis, and improvement after administration of treatment with foscarnet plus ganciclovir strongly suggests that HHV-6 was the cause of our patient's syndrome. Additional studies are needed to define the role of HHV-6 in immunocompetent encephalopathic adults, but based in part on the data presented here, HHV-6 should be considered in the differential diagnosis of patients with encephalitis, and if found, antiviral therapy should be strongly considered.

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