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HHV-6 Infection in a Case of an Infant with Fever, Seizures, and Shock

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INTRODUCTION

Human herpesvirus 6 (HHV-6), commonly known to cause roseola, is a virus that often establishes latency in early childhood. It has been known to cause serious infection, and HHV-6 encephalitis frequently yields long-term neurologic sequelae. In this case, we discuss an infant who presented with seizures and shock secondary to acute HHV-6 encephalitis and subsequently returned to her neurologic baseline.

CASE DESCRIPTION

A previously healthy 10-month-old white girl presented to a community emergency department (ED) in status epilepticus. She had been in her usual state of health with the exception of rhinorrhea for several days prior to admission. On the night of admission, the patient had decreased appetite, tactile fever, and was fatigued. She was found in her crib covered in emesis with tonic-clonic movements of her extremities. Upon arrival to the ED, she was treated with diazepam and was loaded with fosphenytoin before seizure activity stopped. The patient was intubated for airway protection. Ceftriaxone and vancomycin were initiated for suspicion of sepsis. Blood and urine cultures were obtained, but a lumbar puncture was unsuccessful. She continued to seize and was treated with lorazepam and morphine sulfate, after which the movements resolved. In the pediatric intensive care unit, she received 2 normal saline boluses because of tachycardia and dusky appearance.

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The patient had no significant past medical history except for recurrent otitis media. She was born full-term, normal spontaneous vaginal delivery, and there were no complications with the pregnancy or delivery. She took no medications, had no allergies, and her immunizations were up-to-date. Her growth and development were appropriate for her age. She lived with her parents and 2 brothers, 1 of whom recently had a diarrheal illness. The family had 2 cats, 2 dogs, a turtle and fish. There was no recent travel. She attended day care.

Upon admission to the intensive care unit, she had a temperature of 39.1°C, blood pressure of 101/40, pulse of 164/minute, respiratory rate of 33/minute, and O_2 saturation of 100% on FiO_2 0.6. Her pupils were 1-2 mm and sluggishly reactive bilaterally. Her tympanic membranes were minimally erythematous bilaterally and non-opacified. She had coarse breath sounds throughout. Her extremities were cool bilaterally, and her distal extremities were significantly mottled. She was sedated, and there was no asymmetry on neurologic exam. She moved her extremities spontaneously and had a cough and gag reflex. The remainder of her physical exam was normal.

The patient's white blood cell count was 26.6 K/uL with 70% segmented neutrophils, 12% bands, 17% lymphocytes, and 1% monocytes. The hemoglobin was 12.4 g/dL, and the platelet count 469 K/uL. Blood and urine cultures were negative. Her cerebrospinal fluid (CSF), obtained approximately 24 hours after antibiotics were administered, had 7 total nucleated cells, 273 red blood cells with a differential of 9% neutrophils, 5% lymphocytes, 84% monocytes, and 2% macrophages. CSF glucose was 60, protein 24; gram stain was negative and culture showed no growth; herpes simplex virus (HSV) polymerase chain reaction (PCR) was negative. A head computed tomography scan was normal. Electrolytes, chemistry profile, and disseminated intravascular coagulation panel all were normal. Rapid

diagnostic viral antigen testing for respiratory syncitial virus, influenza A and B, parainfluenza, and adenovirus was also negative.

Because of widened pulse pressure, tachycardia, poor peripheral perfusion, and decreased systolic blood pressures, she was started on milrinone and norepinephrine. She was weaned off these medications by hospital day 2 and was extubated without further seizure activity. She was noted to be agitated at times and not at baseline neurologic status. She remained on cefotaxime and vancomycin because of initial concern for septic shock, but had no further fevers after her initial presentation.

She was transferred to the general medical unit on hospital day 4. At this time she developed a descending erythematous macular rash and had a focal seizure. She had subclinical electrographic seizures on electroencephalogram (EEG), which were successfully treated with phenytoin. A magnetic resonance imaging (MRI) scan of the brain revealed striking abnormalities in the white matter of the left temporal, frontal, and parietal lobes.

The patient underwent repeat lumbar puncture and acyclovir was added for empiric coverage of herpes simplex encephalitis. Subsequent serology was negative for parvovirus, rubella, and measles. CSF PCRs were again negative for HSV and enterovirus.

DENOUEMENT

Antibiotics were stopped on hospital day 6 because the patient did not appear to have a bacterial source of infection. The patient improved and was neurologically normal on hospital day 8. A third lumbar puncture revealed CSF that was negative for HSV, and acyclovir was stopped. She was discharged on hospital day 9, and she continued on phenytoin for seizure prophylaxis. On that day, the HHV-6 PCR from her second CSF collection returned positive. Due to her degree of clinical improvement, initiation of antiviral therapy with foscarnet or ganciclovir for the HHV-6 infection was deferred because the medication risks outweighed the uncertain benefits of treatment.

She was seen in Neurology Clinic 6 weeks post-discharge and at 1 year of age. She had no further seizures and had a normal neurologic examination. Developmentally, she was crawling, cruising on furniture, babbling, and manipulating objects in an age-appropriate manner. These were all tasks she was able to perform prior to her illness. Her EEG was normal in the awake, drowsy, and sleep states. MRI showed resolution of the diffusion-weighted signal abnormalities, and improvement in the T2 signal abnormalities. The phenytoin was tapered, and she remained seizure free. A repeat MRI 8 months post-discharge, when the patient was 19 months, showed no new lesions with very minimal residual T2 changes in the left hemisphere and no diffusion-weighted image abnormalities. Again, the patient had a completely normal examination and was walking and running, had bilateral pincer grasp, was using utensils, and had a 20-word vocabulary.

DISCUSSION

HHV-6 is in the betaherpes subfamily and is a DNA virus that is expressed as 2 variants, A and B.[1] HHV-6B is more prevalent and is commonly recognized as the cause for roseola infantum,[2] while clinical disease manifestations for HHV-6A are not well-defined. Infection with HHV-6 has been associated with neurological sequelae in children.[2] By age 3, HHV-6 has infected most children and is able to persist and establish latency in the monocytes and macrophages.[1]

Primary HHV-6 infection can manifest in different ways. Most commonly, symptoms include fever, irritability, and rash. HHV-6 infection is also frequently associated with the first manifestation of benign febrile seizures in childhood. While these seizures are more commonly related to the febrile response to HHV-6 infection, we speculate that there is a subset of patients who have direct central nervous system HHV-6 infection accounting for the seizures. The frequency of such cases of encephalitis and meningoencephalitis is unclear due to the lack of baseline testing for HHV-6 in children with simple and complex febrile seizures. Additionally, the exact role that HHV-6 plays in neurological infections is not well understood.[3] Neurologic manifestations of the disease can include generalized, repetitive, and prolonged seizures. Ataxia, weakness, hemiplegia, and disturbances in consciousness can also occur. Complications such as meningoencephalitis and encephalopathy can be severe and lead to poor outcomes.[4]

There are various reports of acute encephalitis and meningitis occurring in immunocompetent patients with HHV-6.[5] Crawford et al reported 3 cases of children, 2 of which were documented as previously healthy, with HHV-6 causing rhombencephalitis. Long-term outcomes showed significant volume loss of cerebral hemispheres and cerebellum in 1 child who was ultimately diagnosed with juvenile rheumatoid arthritis-like chronic idiopathic childhood arthritis. One of the previously healthy children suffered asym-

metrical tonicity and reflexes and had pronounced cerebellar atrophy at 1 year after diagnosis. Another child demonstrated significant behavioral difficulties and delayed speech and development at 1-year follow-up.

Yoshinari et al studied 10 children between 8 and 26 months of age, all with previously normal development, who had HHV-6 encephalopathy based on clinical, seroimmunologic, and virologic findings. Of these children, all had seizures before and after their fevers subsided. Long-term outcomes showed 4 patients had intellectual impairment, while 2 developed quadriplegia.[6]

Conclusive laboratory diagnosis of HHV-6 encephalitis may be difficult at times. Elevated serum IgMs may be suggestive of recent infection and possible post-infectious encephalitis, but also may not be causally related to CNS disease. Even positive blood PCRs for HHV-6 do not confirm the presence of this agent in the CNS. To be certain of the diagnosis of active CNS infection with HHV-6, CSF sampling is required, and positive CSF PCRs likely indicate active CNS infection with HHV-6. While CSF PCR is definitive, serum IgM and PCR can be used to help assure the diagnosis prior to starting toxic therapy.

The International Herpes Management Forum recommends the use of foscarnet and ganciclovir, either individually or combined, to treat progressive neurologic disease due to HHV-6 infection.[7] Cidofovir, an acyclic nucleoside phosphonate, has been found to be more inhibitory than ganciclovir or foscarnet in vitro.[8] However, it is unclear how well it crosses the blood brain barrier and has associated drug toxicities, so at this time it is not recommended for treating HHV-6 related infections.[9]

Compared to the poor outcomes demonstrated by the children reported thus far in our references with HHV-6 encephalitis, our patient has exhibited no apparent long-term sequelae. This suggests that HHV-6 encephalitis can be associated with a wide range of clinical outcomes, from long-term neurologic sequelae to a benign post-infectious clinical course. Further baseline testing for HHV-6 in children with suspected encephalitis will need to occur to determine the spectrum of disease associated with HHV-6 CNS infections. Improved knowledge of the spectrum of disease and neurologic outcomes for HHV-6 encephalitis will also help to guide antiviral therapy decisions based on clinical severity.

CONCLUSION

It is important to consider HHV-6 encephalitis as a diagnosis in children who present with fever, convulsions, and symptoms of shock. Timely diagnosis may prevent unnecessary prolonged treatment with empiric antimicrobials, and also guide the appropriate acute and long-term follow-up plan.

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