CASE IN POINT

PEER REVIEWED

# HHV-6 Encephalitis in an Immunocompetent Infant

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**Introduction.** Human herpesvirus 6 (HHV-6) encephalitis occurs primarily in individuals who are immunocompromised and is uncommon among immunocompetent children, with an incidence of approximately 2%.[1] The outcome of non-herpes virus encephalitis is usually favorable with complete recovery, but HHV-6 central nervous system infection can have severe neurologic injury, even in individuals who are immunocompetent. Neurologic manifestation ranges from simple febrile seizure to more severe necrotizing encephalitis. Antiviral use is usually reserved for immunocompromised individuals; however, a literature review describes its use in those who are immunocompetent with severe encephalitis. This case report describes an unusual instance involving an 8-month-old male infant who presented with clinical features of a complex febrile seizure but was subsequently found to have HHV-6 encephalitis and a secondary *E. coli* urinary tract infection.

**Case Description:** A previously healthy 8-month-old male infant born via vaginal delivery presented to the emergency department (ED) following a 1-minute episode of seizure-like activity at home. His mother witnessed bilateral hand shaking, generalized stiffness, lip cyanosis, drooling, and a blank stare. There was no eye up-rolling. Postictally, he was drowsy and remained asleep during transport to the ED. The child had just been breastfed, and he was awake and comfortable prior to the episode. The mother denied fever, upper respiratory symptoms, gastrointestinal symptoms, recent vaccinations, trauma, sick contacts, or developmental delays. She reported the child had been acting normally that morning and was feeding well with adequate urine and stool output. There was no family history of epilepsy, but the mother's brother had hydrocephalus in infancy. There was no history of sick contact, dysuria, vomiting, cough, runny nose, or increased frequency of urination. There was also no trauma or bruising. There was no recent travel history. He was exclusively breastfed.

During the initial day of the patient's hospital stay, he had another tonic-clonic seizure that lasted 1-2 minutes, requiring 1 dose of lorazepam. During the hospital stay, the mother noted that the patient had been sleepier and was not at baseline, but he continued to feed well and maintain saturations on

room air. Since admission, the patient had recurrent febrile episodes with a max temperature of 38.9°C (102°F).

The patient's physical examination on initial assessment was unremarkable, except for a tired-appearing infant. Neurologic status was assessed using the modified pediatric Glasgow Coma Scale. He scored a 13 (eye opening, 3 to pain; verbal response, 4; motor skills, 6). His reflexes and tone appeared normal.

The infant's initial laboratory tests in the ED showed a normal white blood cell (WBC) count of 7.3, microcytic anemia (Hgb 9.2, mean corpuscular volume 63), and mild thrombocytosis of 543. His comprehensive metabolic panel and lactic acid levels were unremarkable. The respiratory panel was negative for influenza A/B, COVID-19, respiratory syncytial virus, and the most common viruses, including adenovirus. Inflammatory markers were low, with a C-reactive protein of 0.92 and procalcitonin < 0.075. Iron studies showed a low iron level (20), a high total iron-binding capacity (TIBC) (525), and a low Ferritin (4), consistent with a diagnosis of iron-deficiency anemia. A peripheral blood smear showed microcytic, hypochromic anemia with anisocytosis, including polychromasia. His lead level was within normal range.

The infant had one more seizure during the hospital stay that lasted 1-2 minutes, which prompted further workup. His 1-hour electroencephalogram (EEG) was within normal range (a 24-hour EEG was unavailable). His head ultrasound showed no ventriculomegaly. Due to recurrent seizures and multiple febrile episodes with a maximum temperature of 38.9°C (102°F) and a physical examination finding that included episodes of lethargy, the initial diagnosis of febrile seizure was reconsidered. Given these findings, a lumbar puncture was performed, revealing cerebrospinal fluid (CSF) polymerase chain reaction positive for HHV-6 and elevated total protein, indicating HHV-6 encephalitis. Magnetic resonance imaging was performed under sedation, which was unremarkable.

The patient's urinalysis was negative, but the urine culture grew *E. coli* after 24 hours, whereas his blood culture remained negative throughout his hospital stay. His renal ultrasound was unremarkable except for bladder debris, suggestive of a urinary tract infection (UTI).

Since he continued to be febrile with an identified source of infection, antipyretics (acetaminophen) were scheduled for 24 hours. The pediatric infectious diseases service was consulted regarding HHV-6 encephalitis, and they recommended supportive management. They advised against ganciclovir due to its inconsistent efficacy in an immunocompetent infant with a normal MRI. Pediatric neurology was also contacted since his seizures were likely due to his encephalitis and not a complex febrile seizure. They recommended starting levetiracetam (30mg/kg once then 15mg/kg twice daily), discharging the patient on this medication, and to be weaned as tolerated in the outpatient setting, which was done. Long-term seizure control was to be followed up with pediatric neurology. The infant also received ceftriaxone for his UTI, which was pan sensitive, and he was discharged home with the medication for a total of 7 days of antibiotics. Prior to discharge, the infant was more active, with decreased episodes of lethargy.

**Discussion:** HHV-6 includes distinct species, HHV-6A and HHV-6B, both of which are lymphotropic members of the Herpesviridae family. These viruses share close genetic ties with cytomegalovirus and can thereby reactivate with immunosuppression. HHV-6B is frequently associated with primary infections that manifest with symptoms, such as fever, irritability, and a runny nose. In 33% of affected children, a widespread rash appears, and about a quarter develop roseola infantum, also known as exanthem subitem.[1] During acute HHV-6B infection, patients may also present with swollen cervical and postauricular lymph nodes, gastrointestinal or respiratory symptoms, and eardrum inflammation. Fever can be quite high, exceeding 39.5°C (103°F), persisting for several days.[1] Notably, 20% of emergency visits for febrile children aged 6 to 12 months are linked to primary HHV-6B infection.[1] Febrile seizures are the most common complication, sometimes progressing to status epilepticus, requiring hospitalization. Other neurologic manifestations include bulging fontanelle, encephalopathy, and, in rare instances, severe encephalitis. These neurological manifestations are more frequently observed in infants in Japan than in western countries.[1]

There have been documented cases of acute disseminated encephalitis (ADEM) and acute necrotic encephalomyelitis (ANEC) linked to HHV-6 infection, with MRI scans revealing characteristic changes.[2] Generally, HHV-6 encephalitis occurs predominantly in patients with compromised immune systems, and it is rarely seen in otherwise healthy individuals. In contrast, conditions such as ADEM and ANEC predominantly affect immunocompetent patients.[3] Although primary HHV-6 encephalitis is uncommon in children with normal immune function, it can be a highly aggressive and fatal neurological disorder with significant long-term consequences when it is associated with acute necrotizing encephalopathy, including epilepsy and ataxia.[5] Therefore, prompt testing and diagnosis are critical, and initiating antiviral treatment early may improve outcomes in selected cases.

Diagnostic testing for HHV-6 is performed by detection of viral DNA using a nucleic acid amplification test (NAAT) in blood, CSF, other body fluids, or tissue specimens. Detection of HHV DNA by NAAT might not reliably differentiate between new infection, persistence, or reactivation of the virus from past infection. Detection of immunoglobulin M (IgM) antibodies against HHV is unreliable for establishing infection, as these antibodies may not be detectable during primary infection and may also be present in asymptomatic individuals. Also, a fourfold increase in IgM antibodies does not necessarily indicate an acute HHV-6 infection, as these antibodies also rise with reactivation and other beta-herpesvirus infections. However, documented seroconversion is considered evidence of recent infection.

Management of HHV-6 infection is largely supportive, although evidence to guide treatment remains limited. Antiviral agents such as ganciclovir (and therefore valganciclovir) or foscarnet may provide benefit for individuals who are immunocompromised and have HHV-6 or HHV-7 disease. These agents are also recommended for the treatment of HHV-6 encephalitis in individuals who have undergone hematopoietic cell or solid organ transplantation. The use of antiviral therapies depends on multiple factors, including the patient's age, immune status, infection severity, and medication

interactions. Case reports noting the use of antiviral therapies in immunocompetent individuals with severe encephalitis and associated MRI changes have been reported,[4,5,6] which led to rapid recovery and prevented long-term sequelae.[4] One of the case reports highlighted the effectiveness of cidofovir in clearing HHV-6 from the CSF; however, the data is limited.

In this case, complex febrile seizure was the initial clinical diagnosis of HHV-6 encephalitis in an 8-month-old male infant. Clinicians should maintain a high index of suspicion for central nervous system infections in infants with atypical or prolonged seizures and initiate prompt evaluation and treatment. Supportive care, including rest and hydration, is the recommended treatment approach in this population.[5] The use of antiepileptic drugs is controversial; however, it has been used in severe encephalitis with associated changes. Long-term neurological monitoring and close attention to developmental milestones are crucial in such patients.

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