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10-Year-Old Male With Fever and Headache

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A 10-year-old African American male, with no significant medical history, presented with a 1-week history of fever and bitemporal headache. There was no history of rash, vomiting, or head trauma. The patient was seen by his pediatrician 2 days prior to admission and started on antibiotics for sinusitis. He took 3 doses of the antibiotic and stopped. On the day of admission, the patient was noticed to have an episode of eye fluttering, staring, and unresponsiveness lasting 5-10 minutes. The patient also had urinary incontinence during this episode.

The patient was taken to the emergency room of the referring hospital by ambulance, where he had a generalized tonic-clonic seizure lasting 1-2 minutes. He was treated with lorazepam. A complete blood count revealed a white blood cell count of 15,140 with a differential that consisted of 60% segmented neutrophils, 7% bands, and 23% lymphocytes. Serum electrolytes were within normal limits. Serum glucose was 293 mg/dL. A lumbar puncture was performed. Cerebrospinal fluid (CSF) revealed 2 white blood cells, 30 red blood cells, glucose of 103 mg/dL, and protein of 48 mg/dL. The Gram stain was negative. The patient was started on ceftriaxone and later acyclovir. The patient was also started on phenytoin. The CSF culture and blood culture sent on the date of admission were both negative. The patient also had a head computed tomography (CT), which was reported as normal. Magnetic resonance imaging (MRI) of the brain, which was performed soon after admission, was also reported as normal. The patient had routine electroencephalogram (EEG) that showed no spikes or other epileptiform activity.

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The patient continued to have seizure activity and was subsequently started on valproic acid. He was then transferred to our institution for video EEG telemetry. Upon arrival, the patient was febrile, with a temperature of 38.1°C. He had a blood pressure of 125/70 mm Hg and a pulse of 128. He had a respiratory rate of 24. He was awake, but disoriented to person, place, and time. He was also unable to answer simple questions. His pupils were equally round and reactive to light. There were sharp optic disc margins bilaterally on fundoscopic exam. Extraocular movements were intact. The patient had nuchal rigidity. Deep tendon reflexes were brisk throughout. Plantar reflexes were flexor bilaterally. The patient had intermittent myoclonic jerks of all extremities, especially the left lower extremity.

Hospital Course

A repeat lumbar puncture was performed and revealed 2 white blood cells, 30 red blood cells, glucose of 105 mg/dL, and protein of 41 mg/dL. The CSF Gram stain was negative. The CSF human herpesvirus (HHV)-6 polymerase chain reaction (PCR) was positive. The CSF was negative for herpes simplex virus (HSV)-1, HSV-2, *Mycoplasma pneumoniae*, varicella, Epstein-Barr virus, cytomegalovirus, and *Bartonella henselae*. The CSF culture was negative for bacterial and fungal organisms. A repeat head CT showed right sphenoid sinus thickening but was otherwise unremarkable. Video EEG showed generalized background slowing. An MRI of the brain performed 2 days after transfer showed an area of nonenhancing increased signal in medial temporal lobe bilaterally (Figure 1 and Figure 2).

The patient had a recurrence of seizures 5 days following transfer. Leviteracetam was added. Afterward, there was no further seizure activity noted. The patient was treated with acyclovir for a

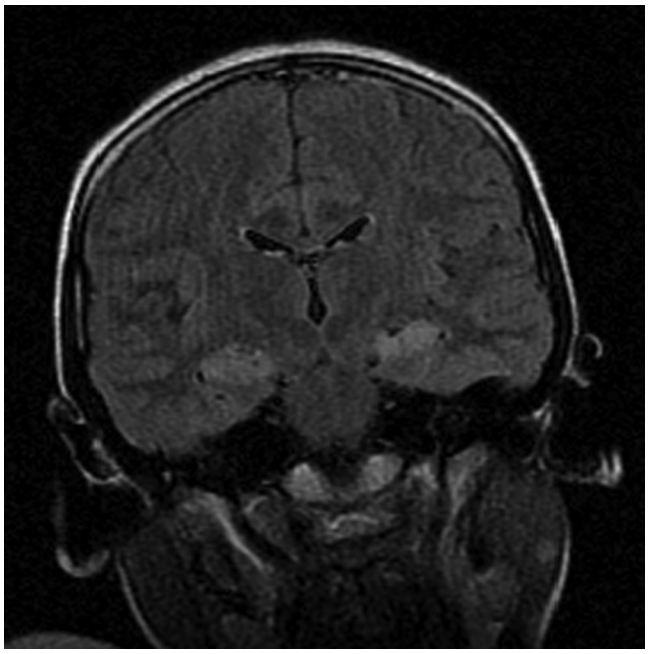

Figure 1. Coronal fluid attenuation inversion recovery (FLAIR) image showing increased signal in medial temporal lobes.

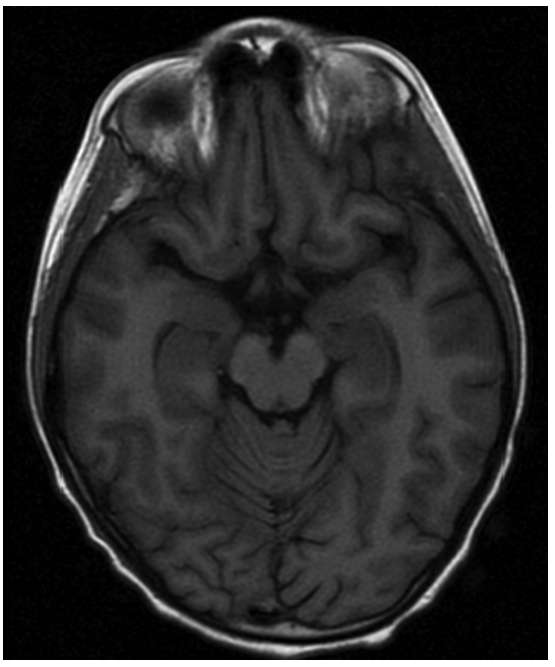

Figure 2. Transverse T1 weighted image.

14-day course. He was left with residual dyscalculia and short-term memory impairment. His neurological exam was otherwise negative. The patient was discharged home 16 days after admission. He was to receive a formal neuropsychologic evaluation as an outpatient.

Discussion

Human herpesvirus-6, a member of the herpes virus family, is a large, enveloped double-stranded DNA virus.[1] Human herpesvirus-6 infects nearly all children by 3 years of age.[2] Primary infection is usually mild, but encephalitis and other neurologic complications have been reported.[3] Clinical manifestations of primary infection with HHV-6 include roseola in approximately 20% of infected children. In roseola, a macularpapular rash erupts coincident with defervescence, although it may be present earlier.[1] Additional clinical manifestations of HHV-6 infection include undifferentiated febrile illness without rash or localizing signs and other acute febrile illnesses such as febrile seizures, encephalitis, and mononucleosis-like syndrome. Fever is characteristically high, often 39.5°C or more. Fever often persists for 3-7 days.[4] Seizures are one of the characteristic features of severe HHV-6 infection, and these seizures are often prolonged and complicated.[3] Seizures occur during the febrile period in approximately 10% to 15% of primary infections.

Humans are the only natural hosts of HHV-6. Transmission is via secretions. During the febrile phase of primary infection, HHV-6 can be isolated from peripheral blood lymphocytes, saliva, and CSF. The mean incubation period may be 9 to 10 days. Diagnosis is confirmed by isolation of the virus from peripheral blood or CSF.[4] Serum can also be tested for IgG and IgM to HHV-6. Treatment is generally supportive.[4] Ganciclovir, foscarnet, and cidovir inhibit HHV-6 replication in vitro and are currently used for patients experiencing HHV-6–associated end organ disease.[5]

One prospective study included 21 children with suspected HHV-6 infection. Nine previously healthy, immunocompetent children, ages 3-24 months, had positive HHV-6 PCR in the CSF. Primary infection was confirmed in 6 children by seroconversion of specific antibodies.[3] Clinical manifestations in these patients included seizures (6), rash (4), ataxia (4), and gastroenteritis (4). All but 2 had high fever. At follow-up, 4 had residual neurologic sequelae, including ataxia and developmental delay.

Another study looked at infants and children under the age of 3 years presenting to the emergency room with acute illnesses. Of those presenting with acute

febrile illnesses, 9.7% had primary HHV-6 infection, as documented by viremia and seroconversion. Human herpesvirus-6 infections accounted for one-third of all febrile seizures in children up to the age of 2 years. In follow-up studies over a period of 1 to 2 years, the HHV-6 genome persisted in blood mononuclear cells after primary infection in 37 of 56 children (66%).[6]

In a 3-year prospective study in Britain and Ireland, 205 children hospitalized with suspected encephalitis and/or severe illness with fever and convulsions were tested for primary HHV-6 and HHV-7 infections. Of children aged 2-23 months, 17% had primary infection coinciding with the acute illness. All children found to have primary HHV-6/7 infection were under 2 years old. Each virus contributed equally. Of these 26 affected patients, 25 had convulsions (18 status epilepticus).[7]

Human herpesvirus-6 has been associated with a broad range of common neurologic disorders including multiple sclerosis, temporal lobe epilepsy, and encephalitis, especially in immunocompromised hosts.[2] After resolution of primary infection, HHV-6 remains latent in the host and may reactivate. Encephalitis is the most frequently reported clinical manifestation of HHV-6 reactivation.[7] In one study, post-transplant acute limbic encephalitis (PALE) was described in 9 patients. Clinical symptoms of PALE include acute onset of fever, confusion, anterograde amnesia, and seizures. Mild CSF pleocytosis with lymphocyte predominance was present in all but 1 patient. Electroencephalogram showed temporal or frontotemporal lobe abnormalities. All patients who underwent MRI showed focal medial temporal lobe abnormalities. Cerebrospinal fluid PCR assays for HHV-6 were positive in 6 of 9 patients on initial lumbar puncture.[2]

In another case report, presenting symptoms of HHV-6 encephalitis in a neutropenic stem cell transplant recipient included persistent headache, discrete tremor, confusion, short-term memory dysfunction, and altered mental status. Cerebrospinal fluid revealed mild pleocytosis, and MRI of the brain revealed high signal intensity in bilateral hippocampus and parahippocampus, which was slightly more pronounced on the left.[7]

Human herpesvirus-6–related meningoencephalitis, especially of older children and adults, in immunocompetent hosts is less frequently reported, and the pathogenesis of these cases remains unclear. In one case report, severe meningoencephalitis was caused by HHV-6 in an immunocompetent 21-year-old woman, who presented with auditory hallucinations, labile affect, disorientation, and intermittent agitation. She later developed generalized tonic-clonic seizures. Findings of an MRI were normal. Electroencephalogram first showed epileptic focus in the right frontal lobe, then later bilateral temporal slowing.[8] The patient was left with neuropsychologic deficits including amnesia, aphasia, and apaxia, which persisted for weeks.

To date, the majority of case reports regarding HHV-6 meningoencephalitis in older children and adults involve immunocompromised hosts such as stem cell transplant recipients. Since 98% are HHV-6 seropositive, cases of HHV-6 meningoencephalitis in older children and adults are unlikely to result from primary infection and more likely represent reactivation of the virus.

In summary, we report a case of a 10-year-old immunocompetent host with HHV-6 meningoencephalitis. Although HHV-6 usually causes a mild, nonspecific, febrile illness, encephalitis and other neurologic complications can occur in both primary infection and reactivation. Although reactivation causing HSV encephalitis is more common in immunocompromised patients, it can occur in an immunocompetent host.

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