CASE REPORT

HHV-6 Encephalitis Associated With Acute Disseminated Encephalomyelitis (ADEM) in an Immunocompetent Child

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ABSTRACT

Human herpesvirus-6 (HHV-6), is classically known as the causative agent of roseola infantum, which is a self-limiting illness in younger children. Rarely, it causes encephalitis, with most cases occurring in immunocompromised individuals. We report an unusual case of an eight-year-old healthy boy with HHV-6 encephalitis that progressed to acute disseminated encephalomyelitis (ADEM). His cerebrospinal fluid (CSF) analysis indicated a viral etiology and a Meningitis/Encephalitis Panel PCR confirmed the presence of HHV-6. The patient's condition significantly improved following treatment with intravenous acyclovir and intravenous immunoglobulin. HHV-6 encephalitis in immunocompetent children is rare but can lead to serious sequelae. The QIAstat-Dx Meningitis/Encephalitis Panel is a timely diagnostic method valuable for detecting 15 types of pathogens causing CSF infection. Therefore, it enables clinicians to initiate targeted treatment strategies promptly. This case highlights that HHV-6 encephalitis can occur in immunocompetent pediatric patients and underscores the importance of early diagnosis and treatment.
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INTRODUCTION

HHV-6 is a ubiquitous pathogen, that belongs to the Roseolavirus genus of the beta-herpesvirus subfamily. HHV-6 is classically known as the causative pathogen in Roseola infantum or erythematous subitem or the sixth disease, a common childhood disease that resolves spontaneously (1). HHV-6 can also manifest as a febrile illness without rashes and other rare complications such as seizures. Primary HHV-6 infection is commonly seen in children under three years old (2). Rarely primary infections occur in older children and adults. The virus can establish latency in various tissues, which allows for reactivation in immunocompromised host (1). We describe a case of an eight-year-old healthy boy with HHV-6 encephalitis and rapidly progressing to acute disseminated encephalomyelitis (ADEM).

CASE REPORT

An eight-year-old male presented to the emergency department with a complaint of prolonged fever for ten days and visual hallucinations for two days. He had no prior medical history and had never been under medical follow-up for treatment. His family history was unremarkable. His vaccination status was up-to-date, and there was no history of recent travel, trauma, or falls. On arrival, the patient was fully alert, mildly dehydrated, and experiencing chills and rigor. His temperature was raised at 38.2°C, but his heart rate (98 beats per minute) and blood pressure (100/60 mmHg) were within normal ranges for his age. Physical examination revealed an optimal Glasgow Coma Scale score of 15 out of 15, equally reactive pupils, and normal chest examination findings. CNS examination noted neck stiffness, but Kernig and Brudzinski's signs were negative. Other systemic examinations were unremarkable. A computed tomography (CT) scan of the brain showed no abnormalities, intracranial bleed, or mass. The patient was treated for meningitis and empirically started on intravenous acyclovir 420 mg every eight hours and intravenous ceftriaxone 2 g once daily.

Routine laboratory tests, including full blood count, renal function, electrolytes, and liver function tests, were within normal ranges. His random blood glucose was 5.1 mmol/L. Lumbar puncture demonstrated an

elevated protein concentration of 1.45 g/L (normal range: 0.15-0.45) with a CSF-to-blood glucose ratio within normal limits. The CSF cell count for WBCs was unremarkable, and bacterial culture of the CSF showed no growth. The CSF sent for Meningitis/Encephalitis Panel genome detection (MPGD) test was positive for Human Herpesvirus 6 (Table I).

Table I: Test Result from Qiastat-Dx Meningitis/Encephalitis panel

Types	Microorganism	Result
Virus	Enterovirus	Not detected
	Herpes simplex virus 1	Not detected
	Herpes simplex virus 2	Not detected
	Human parechovirus	Not detected
	Human herpesvirus 6	Detected
	Varicella zoster virus	Not detected
Bacteria	*Streptococcus pneumoniae*	Not detected
	Neisseria meningitidis	Not detected
	Streptococcus agalactiae	Not detected
	Listeria monocytogenes	Not detected
	Hemophilus influenza	Not detected
	Escherichia coli K1	Not detected
	Streptococcus pyogenes	Not detected
	Mycoplasma pneumoniae	Not detected
Fungi and Yeast	*Cryptococcus neoformans/gattii*	Not detected

On day three of admission, the patient suddenly became drowsy and only responded to pain stimulus. Glasgow Coma Scale fluctuated from seven to nine out of 15, with bilateral pinpoint pupils. Intermittent periodic breathing was observed, and arterial blood gases showed respiratory acidosis. The patient was promptly intubated and transferred to the intensive care unit (ICU). Electroencephalogram (EEG) findings were suggestive of encephalopathy with intermittent delta slowing. Magnetic resonance imaging (MRI) revealed multiple foci of T2-weighted/FLAIR hyperintensity in the brain consistent with acute disseminated encephalomyelitis (ADEM) (Figure 1). Intravenous methylprednisolone at 10 mg/kg/dose was administered every eight hours daily for five days. The patient was successfully extubated following completion of methylprednisolone therapy. However, 24 hours post-extubation, the patient could only articulate a few words and was mostly incomprehensible. Bilateral upper and lower limb weakness was noted, with power graded at 2/5, accompanied by hypotonia and hyperreflexia. Intravenous immunoglobulin at 2 g/kg was infused over 24 hours, leading to a positive response as second-line treatment for ADEM. A 14-day course of intravenous acyclovir was completed for HHV-6 encephalitis. After 18 days of comprehensive treatment, significant improvement was observed, and discharge was recommended. The final diagnosis was HHV-6 encephalitis complicated by ADEM.

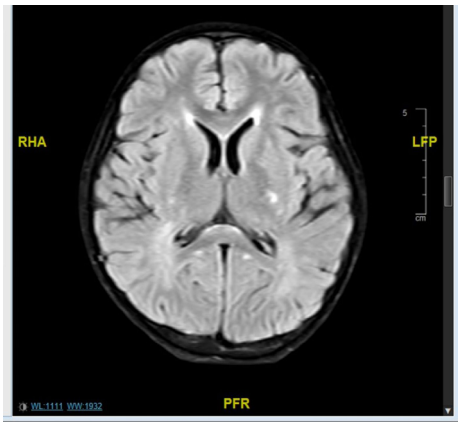

Figure 1: Brain MRI showing multiple foci of T2W/FLAIR hyperintensity which may represent acute disseminated encephalomyelitis (ADEM).

DISCUSSION

HHV-6 belongs to the Roseolavirus genus of the beta-herpesvirus subfamily (2). Like other beta-herpesviruses, HHV-6 can establish latency after primary infection and may reactivate later, especially in immunocompromised hosts such as those undergoing hematopoietic stem cell transplantation (HSCT) or solid organ transplant recipients (1,3). This case highlights the unique presentation of HHV-6 encephalitis in an eight-year-old healthy boy.

Typical infection with HHV-6 is commonly characterized by a high fever lasting three to five days, usually resolving on its own. In contrast, the patient presented with a prolonged fever for 10 days and had a recorded temperature of 38.2°C upon arrival, indicating persistent infection. HHV-6 infection is typically associated with benign illnesses such as fever, fussiness, rhinorrhea, cough, diarrhea, and roseola infantum (4). Its role in causing encephalitis is less frequent and rarely occurs in immunocompetent patients, as seen in our case. Visual hallucinations and neck stiffness in this patient suggest a high likelihood of CNS involvement.

Humans become infected with HHV-6 through contact with infected saliva. The virus can actively replicate in salivary glands or remain dormant in lymphocytes and monocytes, persisting in various tissues including neuroglial cells in the CNS, which may reactivate later. Infection of brain tissue triggers activation of the immune systems, leading to increased production of proinflammatory cytokines (3). The autoimmune response further exacerbates brain inflammation and injury, a pathogenesis that likely contributed to our patient's rapid progression to ADEM.

Encephalitis is a serious medical emergency associated with serious sequelae and fatal outcomes, especially in

the pediatric population. Therefore, timely diagnosis is crucial for providing effective treatment. The microbiology laboratory has an essential role in the early diagnosis of CNS infection and in identifying the causative pathogen. The etiological agents can be viruses, bacteria and fungi, requiring a diverse set of tests including bacterial culture, fungal culture, real-time PCR, and antigen tests and as a consequence, a final result may take days. An excellent technology; QIAstat-Dx Meningitis/Encephalitis Panel, leveraging qualitative multiplex PCR, which can detect 15 types of pathogens (as listed in Table 1) within just eighty minutes (5). This rapid and accurate diagnostic tool facilitates accurate diagnosis and enables clinicians to initiate targeted treatment strategies promptly.

Other diagnostic modalities include serological testing for antibodies against HHV-6 which is commonly used. IgM antibodies indicate recent infection, while IgG antibodies indicate past exposure. Although viral culture is less commonly used now due to lower sensitivity and longer turnaround times compared to PCR, viral culture can still be employed for vaccine production, research purposes and antiviral susceptibility testing including plaque reduction assay or viral cytopathic reduction assays (1).

CT scans may show nonspecific findings such as brain edema, mass effect, or intracranial hemorrhage in severe cases of HHV-6 encephalitis. However, MRI is typically more sensitive for detecting specific changes as in this case, which indicate inflammation and demyelination by showing multiple foci of T2W/FLAIR hyperintensity (2), as in this case.

CONCLUSION

This case report highlights the unusual presentation of HHV-6 encephalitis in immunocompetent children. It sheds light on the serious neurological complications that could occur following HHV-6 infection. Timely diagnostic tools are essential for effective treatment and good outcomes.

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