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Case report

A rare case of recurrent HHV6 encephalitis in an immunocompetent adult

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ABSTRACT

Human Herpesvirus 6 (HHV-6) is a virus known to cause mild infection in children. In adults, HHV-6 reactivation has been described in immunocompromised individuals.Rarely, viral reactivation occurs in immunocompetent adults causing significant disease and morbidity. The use of certain medications, like amoxicillin, has been found to induce HHV-6 reaction in a number of cases. We report a 63-year-old immunocompetent female who presented with headache, fever and altered mental status. Past medical history included two bouts of HHV-6 encephalitis treated at external facilities. According to her medical history, both episodes of encephalitis were preceded by amoxicillin use. Her lumbar puncture analysis was consistent with viral etiology and a cerebrospinal fluid (CSF) PCR was positive for HHV-6. She was successfully treated with intravenous ganciclovir. It is important to keep a broad differential diagnosis in mind when approaching encephalitis in adults, and to be aware of unusual triggers for viral reactivation. Clinicians who suspect the infection in the correct clinical setting can successfully treat patients with recurrent HHV-6.

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Introduction

Human herpesvirus 6 (HHV-6), a member of the Betaherpesvirinae subfamily and Roseolovirus genus within the herpesvirdiae family, consists of two variants: HHV-6A and HHB-6B [1]. HHV-6B is responsible for the mild acute febrile disease generally presenting in the first three years of life known as roseola infantum (exanthem subitem or sixth disease). This self-limited disease usually lasts 3–5 days and later reverts to a latent phase [2]. HHV6-A usually presents as an acquired infection after HHV-6B has already been present and rarely presents as a primary infection [3]. Reactivation of HHV-6 may occur in immunocompromised patients such as those on chronic immunosuppressants and those with human immunodeficiency virus (HIV) [1]. Speculation exists of a connection between use of certain medications including amoxicillin and sodium valproate with reactivation of HHV-6, although a direct causal link has not been established [4]. We report a case of recurrent HHV-6 encephalitis in a 63-year-old immunocompetent female with a history of amoxicillin use.

Case presentation

A 63 year old female presented to the emergency department with aphasia, altered mentation, and headache. Medical history included two previous episodes of HHV6 encephalitis. Her initial episode in 2015 included similar presenting complaints and was treated in the intensive care unit (ICU) at an outside hospital with full recovery after the event. Her second episode occurred in 2016 where she was treated with valganciclovir and she again achieved complete resolution of symptoms within approximately 6 weeks.

Eight to ten days prior to onset of the current symptoms patient had presented to a dentist complaining of severe toothache and was prescribed amoxicillin. Over the coming days her dental pain improved but her mentation slowly declined and headache developed eventually prompting family to bring her to the hospital. Further review including outpatient pharmacy records revealed that her previous two episodes of HHV6 encephalitis were preceded by use of amoxicillin (initial episode for dental pain and subsequent episode in the form of amoxicillin-clavulanic acid for upper respiratory infection). She has no known history of immunosuppression or malignancy.

While in the ER, the patient was hemodynamically stable but with altered mental status. She had no nuchal rigidity and no skin rash. Her blood testing showed glucose level of 81 mg/dL, normal

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white cell count, electrolytes and liver functions. CT head and chest X-ray (CXR) were within normal limits. She received a lumbar puncture, cerebrospinal fluid (CSF) analysis showed glucose of 50 mg/dL with protein of 120 mg/dL and elevated WBC count at 178 with 97 % lymphocytes, consistent with viral etiology. CSF PCR was positive for HHV6. A blood culture revealed coagulase negative *Staphylococcus* species from one out of two blood culture bottles after 48 h of incubation, that was most likely skin flora. Infectious diseases (ID) service was consulted, intravenous (IV) ganciclovir was started and the patient got admitted to the medical floor. Testing for HIV and hepatitis B virus were negative and CD4 count was within normal limits at 841. Neurology service was consulted as well for concern of non-convulsive seizures. Electroencephalography (EEG) for 48 h showed mild encephalopathy without apparent seizure activity. MRI with and without contrast at that time showed mild punctate high-flair signals in the periventricular deep white matter consistent with HHV-6 encephalitis (Fig. 1).

Patient had worsening altered mental status followed gradually by fever, cough, and hypoxia. White cell count went up to 10,100 cell/cm, and CXR revealed mild airspace disease while CT of the chest with IV contrast was consistent with a moderate left lower lobe infiltrate. The patient was placed on oxygen and started by primary team on vancomycin and piperacillin/tazobactam. Her sputum culture grew methicillin-sensitive *Staphylococcus aureus* (MSSA). Thus she was de-escalated by the ID team to cefazolin, a non-penicillin antibiotic given consideration of penicillin antibiotics' potential role in the reactivation of HHV6. Patient's clinical and neurologic status significantly improved. She completed her course of IV ganciclovir for fifteen days and was discharged home without any neurological sequelae. She was counselled on discharge against using penicillin antibiotics without consulting with an infectious disease specialist first. At 2 months follow up in ID clinic, patient was doing well and afebrile without any recurrence of symptoms.

Discussion

Latent HHV6 infection is highly prevalent in the majority of the population approaching nearly 100 % seroprevalence. The initial infection with HHV6 occurs primarily in childhood as an acute infection that can later recur in healthy children and adults without causing any obvious symptoms. Once the primary infection is resolved the virus remains latent in the body with predominance in lymphocytes and monocytes. However, in immunocompromised patients the virus can be reactivated from latency [1,2].

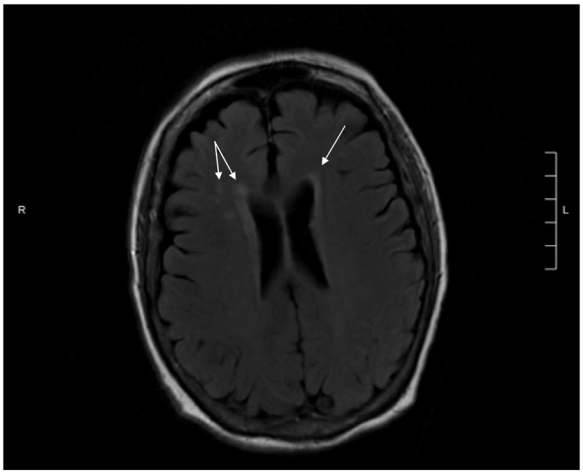

Fig. 1. Brain MRI with contrast showing mild punctate high-flair signals in the periventricular deep white matter consistent HHV-6 encephalitis.

According to the CDC, HHV6 infection in immunocompetent patients occurs due to viral replication in the salivary glands, as observed in HHV6-B, and scarcely cause lymphadenopathy, fulminant hepatitis, mononucleosis-like disease, or generalized infection. The latent infection most likely persists due to the HHV6 genome integration into the host's chromosomes. However, the mechanism for which the virus spreads to other organs and can remain latent is unclear. In contrast, immunocompromised patients with reactivation of HHV6 may develop encephalitis, bone marrow suppression, and rejection of transplanted organs. Moreover, the incidence of HHV6 encephalitis has been mostly documented in patients who are immunocompromised such as history of solid organ transplantion, HIV, or other immunodeficiencies [1]. This case highlights the unique presentation of recurrent HHV6 encephalitis in an immunocompetent patient.

Thirty-nine percent of patients evaluated for HHV6 primary infection had the viral DNA in both peripheral blood mononuclear cells and CSF samples, but is detected more frequently in the CSF [3]. This viral chromosomal integration makes the diagnosis of recurrent HHV6 encephalitis more challenging. It needs the presence of appropriate clinical context, more often than not an immunosuppressed state, and significant clinical response after antiviral therapy [5]. It is noteworthy that presence of HHV6 on PCR assessment of CSF does not always occur. HHV6 DNA was detected in 61 % of children assessed after primary HHV6 encephalitis. Hence, the possibility exists of HHV6 encephalitis with negative CSF PCR [6].

The limited occurrence of recurrent HHV6 encephalitis in immunocompetent patients has been documented in the literature with seizure activity and encephalomyelitis. This case is rare due to recurrent HHV6 encephalitis presenting as altered mental status without seizure activity, CSF positive for HHV6-DNA, and MRI findings consistent with HHV6 encephalitis. With each recurrent episode of HHV6 encephalitis patient reported preceding use of amoxicillin. Recent studies have associated Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) with active HHV-6 and has been suggested that drugs that induce DRESS are capable of inducing viral multiplication [4]. A further study cited amoxicillin and sodium valproate as capable of causing DRESS and inducing HHV6 replication [6]. This provides insight into possible triggers for HHV6 encephalitis and the need for consideration of antibiotic choices in the future.

Due to the scarcity of cases, clinical guidelines for the treatment of HHV6 encephalitis have not been developed. The use of foscarnet, cidofovir, and ganciclovir have all been described in the treatment of HHV6 with favorable outcomes; however, multiple cases have involved switching the patient from foscarnet or cidofovir to ganciclovir after an adverse reaction in the patient [7–9]. Thus, ganciclovir is a reasonable first choice of therapy for HHV6 encephalitis due to its efficacy and favorable side effect profile.

Conclusion

This case report highlights the unusual presentation of HHV6 encephalitis in an immunocompetent adult. It sheds light on the importance of considering such a diagnosis in patients that may present similarly, possible triggers, and future modification in the way we assess and treat such cases.

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Ethical approval

The design of the work has been approved by our local ethical committee: Marshall University Institutional Review Board (IRB) committee number 1 (Medical). It conforms to standards currently applied in Huntington, West Virginia.

Consent

The patient's written consent was obtained.

Author contribution

Each author has contributed to the literature review, and writing of the manuscript and abstract of this case report.

Authors statement

Rania Al Asmar, Kara Willenburg: Conceptualization, Resources.

Jamila Ranavaya, Noor Mozahem, Scott Thiesfeldt: patient's data collection, chart reviewing and writing. Original draft preparation.

Kara Willenburg, Rania Al Asmar, Ryan Carroll: Supervision.

Rania Al Asmar, Ryan Carroll: Writing- Reviewing and Editing.

Declaration of Competing Interest

The authors report no declarations of interest.

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