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Limbic Encephalitis Associated with Human Herpesvirus-7 Infection in an Immunocompetent Adolescent

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Abstract

Despite the ubiquitous nature of human herpesvirus-7 (HHV-7) infection, its clinical significance in the central nervous system (CNS) is poorly understood. However, the related human herpesvirus-6 (HHV-6), which has remarkable genomic similarity to HHV-7, is linked to encephalitis. We present the case of a 17-year-old immunocompetent male with remote history of seizure who arrived in status epilepticus. Upon resolution, he required hospitalization for worsening encephalopathy. Electroencephalogram (EEG) revealed bilateral temporal lobe dysfunction and magnetic resonance imaging (MRI) showed increased signaling in bilateral medial temporal lobes with hippocampal microhemorrhages. Empiric intravenous (IV) acyclovir was initiated despite initially negative cerebrospinal fluid (CSF) studies due to concern for herpes simplex virus (HSV) encephalitis. The patient improved and was discharged on hospital day 13 (HD13). After discharge, a human metagenomics CSF panel resulted positive only for HHV-7, making a case for possible etiology and empiric treatment of HHV-7 despite delayed CSF and serum studies.

Keywords

encephalitis, epileptic encephalopathy, pediatric, seizures, status epilepticus, treatment

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Background

Human herpesvirus-6 (HHV-6) and human herpesvirus-7 (HHV-7) are part of the Roseolovirus genus and the Herpesviridae family, which also includes herpes simplex virus (HSV), varicella-zoster, and cytomegalovirus. HHV-7 is widely distributed in the population, with most individuals infected by the age of 6 through contact with saliva of an infected individual[1]; primary infection is followed by lifelong latency with possible symptomatic reactivation, typically in immunocompromised individuals. While encephalitis with predilection to temporal lobe dysfunction has been linked to both HSV and HHV-6, the CNS sequelae of the closely related HHV-7 remain poorly understood. However, a recent study found immunoexpression of both HHV-6 and HHV-7 to be significantly increased in temporal gray matter of patients with unspecified encephalopathy, and to a lesser degree, the control group.[2] More research is needed to determine the extent to which HHV-7 contributes to human disease and to establish the most effective diagnostic approach and treatment.

Case Presentation

A 17-year-old immunocompetent male was transferred from an outside hospital (OSH) with status epilepticus consisting of three seizures lasting 3–4 min each without a return to baseline in between seizures. Medical history included well-controlled epilepsy, diagnosed one year prior after two instances of generalized tonic-clonic seizures, spaced a month apart. After the second seizure, the patient was prescribed and compliant with 0.5 gram of levetiracetam twice daily, resulting in no

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subsequent seizure occurrences until the time of hospital presentation. Notably, EEGs conducted ten months and one month prior to presentation were normal. No previous imaging studies were available. The patient's mother reported he used marijuana regularly though she was unaware of any other substance use.

Preceding his acute presentation, the patient was without infectious symptoms though did have vague abdominal pain and headache that morning which kept him home from work. That afternoon, he was witnessed having a convulsion with head deviation to the right and stiffness of the lower extremities. At the outside emergency department, the patient received lorazepam and was intubated. He also received midazolam, etomidate, succinylcholine, levetiracetam, and piperacillin/tazobactam and was then transferred to our pediatric intensive care unit (ICU). During transport, he had a fever of 38.3 °C. Thirty-six hours later, he was extubated and transferred out of the ICU. Upon admission to wards, the patient was oriented to self, place, and year, but not to month, and his short-term memory was significantly impaired. Confabulations were present and corroborated by the patient's mother, who remained at bedside. His mental status at that time was attributed to medication side effects, history of marijuana use, and postictal state.

Labs were notable for mild leukocytosis (13.9 K/mm^3). HIV and syphilis testing were negative. Complete metabolic panel, blood gases, and respiratory virus panel were non-diagnostic. Blood cultures showed no growth throughout admission. The toxicology screen was positive only for midazolam.

Head computed tomography (CT) performed at OSH on hospital day 1 (HD1) was normal. Non-contrast brain MRI on HD2 (within 6 h of admission to our hospital) demonstrated minimally increased fluid-attenuated inversion recovery (FLAIR) signal abnormality within bilateral mesial temporal lobes, left greater than right (Figure 1A). Cortical diffusion restriction was present in the hippocampi and lateral aspects of the bilateral temporal lobes. Abnormal signal extended into the left parahippocampal gyrus and medial aspect of the left thalamus (Figures 1A and 2A). There was no evidence of masses, shift, or extra-axial fluid collection. Hemorrhages were not appreciated on susceptibility weighted angiography (SWAN) MRI. Imaging with contrast was not performed at that time. Findings were attributed to seizure activity.

The patient was placed on continuous EEG (cEEG) on HD2 (within 6 h of admission to our hospital) to assess for ongoing subclinical seizures, which initially showed only diffuse slowing with no focal features. An electrographic seizure with a right posterior temporal onset was captured on HD3, and cEEG interpretation was completed on HD4. Interictally, cEEG suggested dysfunction and increased seizure propensity from the right temporal region. Given these findings, HSV encephalitis was suspected. Empiric intravenous acyclovir was started, and levetiracetam was increased to 1.0 gram

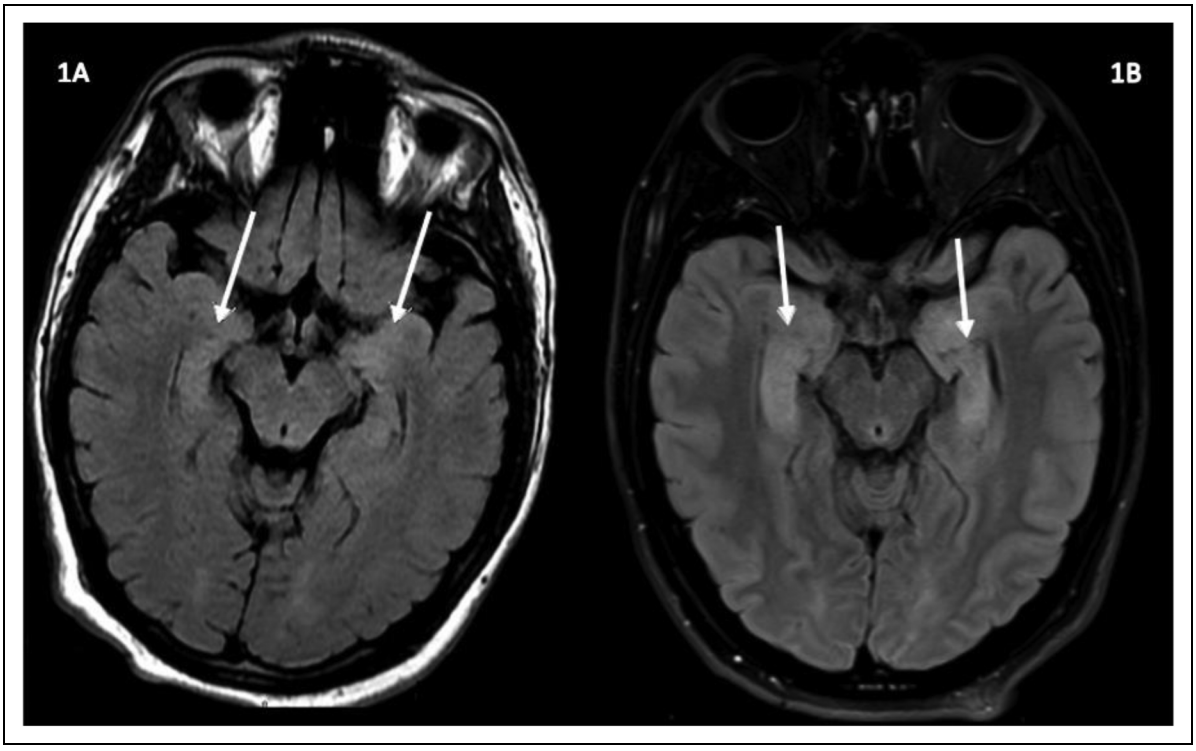

Figure 1. A: Axial T2 FLAIR from HD2. Increased FLAIR signal abnormality within the left greater than right temporal lobe. In the left temporal region abnormal signal extends into the left parahippocampal gyrus and medial aspect of the left thymus. Areas of abnormal signal indicated with arrows. B (Right): Axial T2 FLAIR from HD5. Mildly increased (compared to HD2) signal involving left greater than right medial temporal lobes and hippocampus bilaterally with areas of cytotoxic edema in the hippocampi. Areas of abnormal signal indicated with arrows.

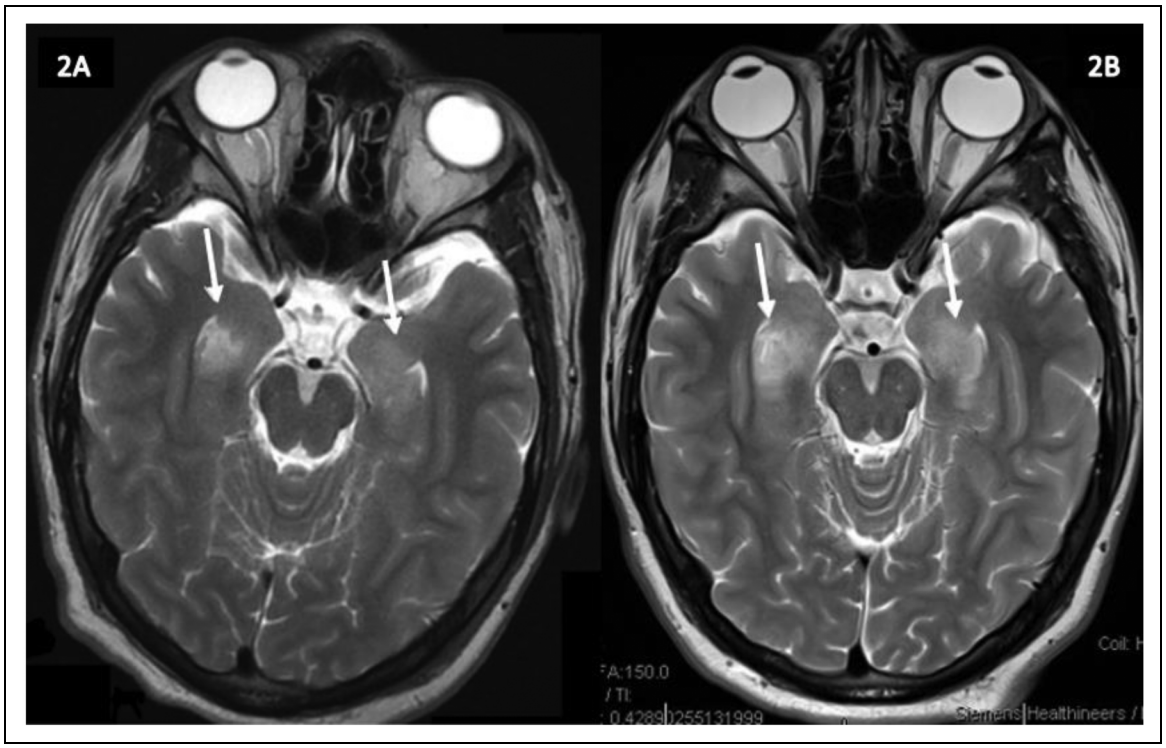

Figure 2. A (Left): Axial T2 propeller from HD2. Axial T2 imaging from HD2 demonstrating signal abnormalities with more extensive signal changes on the left versus right, demonstrated by white arrows. B (Right): Axial T2-weighted image from HD5. Axial T2 imaging from HD5 demonstrated enhanced signal bilaterally, worse on right side versus left, demonstrated by white arrows.

twice daily. cEEG was discontinued after 24 h of seizure-free recordings.

On HD5, the patient continued to exhibit severe encephalopathy, prompting a repeat MRI, this time with and without contrast. Imaging again demonstrated mildly increased abnormal T2 FLAIR signal involving bilateral medial temporal lobes and bilateral hippocampi (Figure 1B). Areas of cytotoxic edema in the hippocampi were again noted (Figures 1B and 2B). Suspected microhemorrhages (more extensive on right vs left) were appreciated on susceptibility weighted imaging (SWI) (Figure 3). There was no abnormal enhancement. The radiologist's differential included HSV encephalitis or autoimmune encephalitis. Ongoing seizure activity was excluded by cEEG.

Lumbar puncture (LP) was performed on HD5 (acyclovir treatment day 3). The CSF sample was without xanthochromia and showed a white cell count of 78 (differential with 5% neutrophils, 69% lymphocytes, and 26% monocytes), with a total nucleated cell count of 1/mm^3 and 181 red cells. Glucose and protein were 69 mg/dL and 34 mg/dL, respectively. A meningitis/encephalitis polymerase chain reaction (PCR) panel including cytomegalovirus (HCMV), enterovirus, varicella zoster virus, HHV-6, HSV-1/2, and human parechovirus was normal. Separate HSV type 1 and type 2 testing was performed by PCR and was negative. HSV IgG and IgM from this CSF sample were also negative, though these results were not available until HD13. The Mayo Clinic CSF and serum autoimmune encephalitis panels were negative. UCSF CSF metagenomics assay was sent.

Continued encephalopathy prompted repeat LP on HD8. The CSF had xanthochromia. This CSF sample had a white cell count of 51 (differential with 8% neutrophils, 80% lymphocytes, and 12% monocytes), with a total nucleated cell count of 7/mm^3 and 883 red cells. Glucose and protein were 71 mg/dL and 56 mg/dL, respectively. Repeat HSV-1/2 PCRs were negative.

On HD13, the patient returned to baseline and acyclovir was discontinued after 10 days. He was discharged with a diagnosis of presumed viral encephalitis. Following discharge, the UCSF metagenomics CSF assay resulted positive for HHV-7. Given this delayed result, HHV-7 antibody avidity testing was not completed; as such, we were unable to confirm primary infection versus reactivation of a prior CNS infection.

The patient was instructed to continue with 1.0 gram levetiracetam twice daily. He completed high school without accommodations and has remained seizure-free 6 months post discharge, though no follow up imaging studies are available.

Discussion

Upon initial presentation, we considered the possibility that our patient's symptoms were due to ongoing subclinical seizures (which were ultimately ruled out via cEEG) and postictal encephalopathy. At that time, it was thought that his seizure threshold was lowered in the setting of significant marijuana use and/or potential noncompliance with anti-seizure medication. As his symptoms persisted well beyond the usual 36-h

resolution period,[3] postictal encephalopathy became increasingly unlikely. Our differential then shifted towards a more probable case of HSV encephalitis, with autoimmune encephalitis being a less likely etiology. This shift was prompted by the cEEG data captured on HD3 (interpreted on HD4), which revealed right temporal lobe dysfunction. This finding led to the immediate commencement of empiric acyclovir treatment. Concern for HSV encephalitis gained further traction on HD5 when SWI revealed temporal lobe microhemorrhages, which were more pronounced on the right compared to the left. Despite initially negative CSF studies, suspicion for HSV encephalitis remained high given the patient's persistent encephalopathy, EEG findings, and concomitant hippocampal microhemorrhages without evidence of other common etiologies. In general, CSF PCR testing requires clinical correlation, as results may be negative within the first 72 h of illness, followed by subsequent positive testing.[4] It is possible that the initial CSF studies, which were performed on HD5 (acyclovir treatment day 3), were impacted by treatment. However, this is unlikely given PCR results are typically unaffected if LP is performed within 72 h of treatment initiation.[5] Concern for the significant morbidity and mortality associated with HSV encephalitis prompted continued empiric treatment and repeat LP on HD8 (acyclovir treatment day 6). The elevated red cell count of this CSF sample was attributed to a traumatic tap, and the results received during hospital admission were considered nondiagnostic. Upon the patient's return to baseline and subsequent discharge, the working diagnosis was unspecified viral encephalitis.

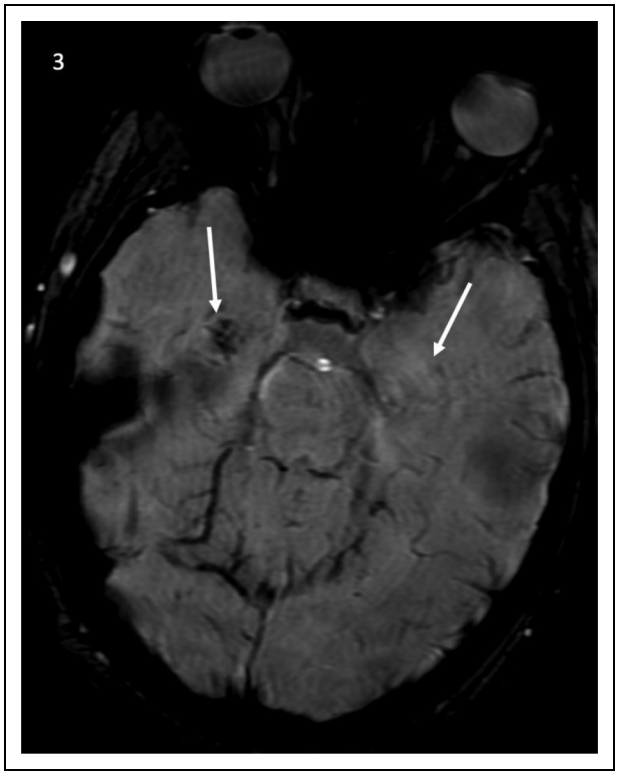

Figure 3. SWI from HD5. SWI from HD5 demonstrating microhemorrhages with more extensive hemorrhaging on the right versus left, demonstrated by white arrows. Comparatively, no microhemorrhages were appreciated on HD2 MRI SWAN (not shown).

Although HHV-6 has been established as a cause of encephalitis, the CNS sequelae of the closely related HHV-7 are largely unknown, particularly in immunocompetent patients. However, several case reports have linked HHV-7 to encephalitis in otherwise healthy individuals. One such case involved limbic encephalitis in a 35-year-old immunocompetent man found on MRI to have hyperintensities in the bilateral hippocampi and periventricular white matter. CSF showed HHV-7 DNA, elevated protein, and mononuclear pleocytosis; improvement was noted after treatment with methylprednisolone, IVIG, and acyclovir.[6] Another case of encephalitis and flaccid paralysis in a 19-year-old immunocompetent man was associated with findings of HHV-7 DNA in the patient's CSF but not serum, with antibody avidity tests confirming primary infection.[7] A 2019 case report describes a 20-year-old immunocompetent man with seizures and encephalitis initially found on MRI to have T2 hyperintensity with areas of restricted diffusion in the left cerebral cortex, as well as the right periventricular and deep white matter, with follow-up MRI showing persistent T2 hyperintensity on the anterior temporal poles bilaterally. CSF

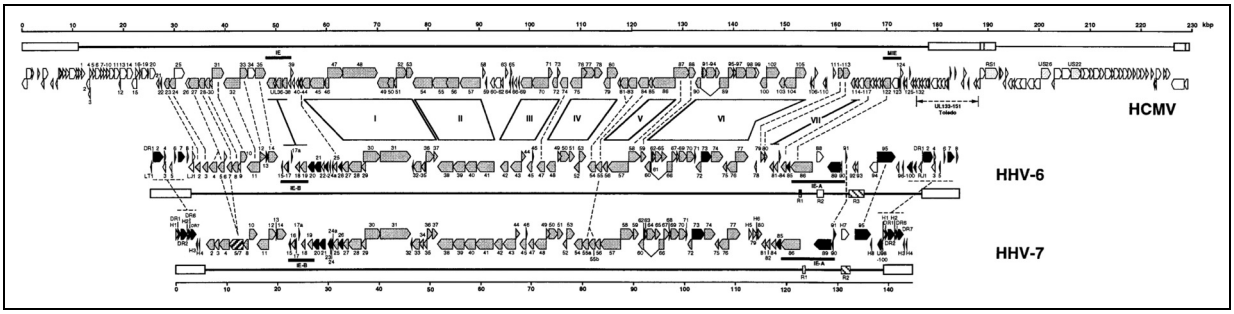

Figure 4. Alignment of the genomes of HCMV (AD169), HHV-6, and HHV-7.[10] Printed with permission from John Nicholas with the Johns Hopkins Department of Oncology. Alignment of these genomes shows homologous (shaded) and non-conserved (open) genes in these betaherpesviruses. Solid areas indicate genes conserved between HHV-6 and HHV-7 but not present in HCMV. The herpesvirus-conserved gene blocks (I to VII) are indicated.

examination was similar to that of our patient.[8] Further, a 2014 retrospective study found that HHV-7 primary infection in adolescents to be associated with serious neurologic disease, including encephalitis, meningitis, and Guillain-Barre syndrome; however, investigators noted that the presence of HHV-7 DNA in the CSF alone is insufficient in proving etiologic association, and that CSF PCR must be combined with serology to better establish the diagnosis.[9] Given these collective reports and the remarkable genomic similarity to HHV-6, it is reasonable to suspect a causal relationship between HHV-7 and CNS sequelae including encephalitis. (Figure 4)

To date, no specific treatment for HHV-7 encephalitis exists. Anecdotally, patients respond to acyclovir, though it is unclear if the improvement is due to treatment or self-limited disease. Notably, a 1998 study found HHV-7 to be resistant to acyclovir, penciclovir and ganciclovir in vitro; there are anecdotal reports of improvement with foscarnet, though no prospective studies on its efficacy are available.[11]

Conclusions

Given the remarkable structural similarity to HHV-6, an established cause of encephalitis, HHV-7 should be considered in the workup of suspected infectious encephalitis, particularly when testing for common etiologies is negative. Despite the ubiquitous nature of HHV-7, its CNS sequelae in immunocompetent patients are poorly described. Additional research is needed to establish the most effective diagnostic approach and treatment for HHV-7 encephalitis, though it seems clear that CSF PCR studies must be correlated with serology to establish HHV-7 as the etiology of encephalitis.

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Consent for Publication

Verbal informed consent was obtained from the patient for publication of this report.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics Approval and Consent to Participate

The study was exempt from review by the UCD School of Medicine's Internal Review Board.

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