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Human Herpesvirus 6 (HHV-6) Associated Childhood Encephalitis and Fatal Outcome: A Laboratory Perspective

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Abstract

Background: *Human herpesvirus 6 (HHV-6), particularly HHV-6B, is an underrecognized cause of pediatric encephalitis and acute encephalopathy. In tropical settings, diagnostic evaluation is often focused on endemic viral etiologies, which may delay consideration of HHV-6 in cases of unexplained neurological deterioration.*

Methods: *Postmortem blood and cerebrospinal fluid (CSF) samples from a male child in Sri Lanka were received by the National Virology Reference Laboratory for virological investigation with the history of sudden onset fever and as with encephalitis. Initial testing targeted common endemic and neurotropic viral pathogens, including dengue virus, Japanese encephalitis virus, SARS-CoV-2, influenza viruses, enteroviruses, and herpes simplex virus (HSV). Subsequent molecular testing for HHV-6 was performed using a commercial real-time typing PCR assay capable of differentiating HHV-6A and HHV-6B.*

Results: *All initial investigations for common viral etiologies were negative. Postmortem findings demonstrated massive cerebral edema. HHV-6B DNA was detected by real-time typing PCR.*

Conclusion: *The detection of HHV-6B DNA in association with severe cerebral edema supports a probable role of HHV-6B in the fatal encephalopathic illness. This scenario highlights the importance of incorporating molecular testing for HHV-6 in the diagnostic evaluation of unexplained pediatric encephalitis and rapid neurological deterioration, particularly in tropical regions where attention is often directed toward endemic viral causes.*

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Introduction

Human herpesvirus-6 (HHV-6) is a ubiquitous double-stranded DNA virus belonging to the Betaherpesvirinae subfamily, with two distinct variants: HHV-6A and HHV-6B. Primary infection occurs predominantly in early childhood, with over 90% of children infected by the age of 2–3 years, making it one of the most common causes of febrile illness in infants [1]. Transmission of this virus occurs primarily through saliva and close interpersonal contact, particularly via asymptomatic adults or caregivers shedding the virus, while less common routes include blood transfusion, organ transplantation, and congenital infection [1,2]. The virus is most frequently associated with roseola infantum, a typically self-limiting illness characterized by high fever followed by a transient rash. Despite its generally benign course, HHV-6 demonstrates neurotropic properties, with the ability to invade the central nervous system (CNS), establish latency, and persist in brain tissue [2].

Although most infections are mild, HHV-6, particularly HHV-6B, has increasingly been recognized as a cause of severe neurological complications, including febrile seizures, encephalitis, and acute encephalopathy. CNS involvement may occur during primary infection, with reported cases showing diffuse cerebral inflammation, demyelination, and cerebral edema, occasionally leading to fatal outcomes [3,4]. Recent reviews have highlighted that HHV-6 contributes significantly to pediatric emergency visits for febrile illness and is an underrecognized etiological agent in encephalitis syndromes, particularly when routine pathogens are not identified [5,6].

In tropical regions such as Sri Lanka, acute febrile illness with neurological deterioration is commonly attributed to endemic infections such as dengue, Japanese encephalitis, herpes simplex virus (HSV), and varicella-zoster virus (VZV). This epidemiological bias may delay consideration of less common viral causes. However, emerging evidence indicates that HHV-6-associated encephalitis can present with rapid clinical progression, severe cerebral edema, and sudden death, even in previously healthy children **[7,8]**. Such hyperacute presentations pose significant diagnostic challenges, particularly in resource-limited settings where advanced molecular testing is not routinely performed.

Therefore, recognizing HHV-6 as a potential cause of fulminant pediatric encephalopathy is essential, especially in cases with negative routine viral investigations and unexplained rapid deterioration.

Methods

In May 2026, postmortem blood samples and cerebrospinal fluid (CSF) samples from a male child were received at the National Virology Reference Laboratory, Sri Lanka, for virological investigation. The child had presented to a tertiary care teaching hospital with a one-day history of fever with encephalitis and death on admission. Postmortem findings demonstrated severe cerebral edema.

Given the endemic infectious disease profile in Sri Lanka, initial laboratory investigations targeted common viral causes of acute encephalitis. Dengue NS1 antigen testing and RNA detection in CSF, Japanese encephalitis virus IgM in CSF, and molecular assays for SARS-CoV-2, influenza viruses, enteroviruses, and herpes simplex virus (HSV) were performed.

Subsequently, molecular testing for human herpesvirus 6 (HHV-6) was performed using a commercial real-time typing polymerase chain reaction (PCR) assay with an established sensitivity of 95–100% and specificity of 98-100%, and which is capable of differentiating HHV-6A from HHV-6B.

Results

All initial investigations for common viral etiologies of encephalitis, including dengue virus, Japanese encephalitis virus, SARS-CoV-2, influenza viruses, enteroviruses, and HSV, were negative.

The real-time typing HHV-6 PCR assay detected HHV-6 DNA, specifically identifying the HHV-6B subtype. The detection of HHV-6B DNA, together with postmortem findings of severe cerebral edema, supported a probable association between HHV-6B infection and the observed fatal encephalopathic illness.

Discussion

This study describes a fatal outcome of human herpesvirus 6B (HHV-6B) associated encephalopathy in a child. Differentiation between HHV-6A and HHV-6B is clinically important, as HHV-6B is more strongly associated with primary childhood infection and severe neurological disease, whereas the pathogenic role of HHV-6A remains less clearly defined [2]. Although HHV-6 infection is nearly universal in early childhood and usually self-limiting, evidence indicates that it can, in rare cases, cause severe and rapidly progressive central nervous system (CNS) disease even in immunocompetent individuals [2].

HHV-6 is a neurotropic double-stranded DNA virus capable of establishing latency in the CNS and reactivating under certain conditions. Its neuropathogenesis is multifactorial, involving direct neuronal infection, immune-mediated injury, cytokine dysregulation, and blood–brain barrier disruption, which may lead to cerebral edema and encephalopathy [1]. The clinical spectrum ranges from mild febrile illness and seizures to severe encephalitis, including rare cases of acute necrotizing encephalopathy with high mortality [3,5].

Although uncommon, fulminant HHV-6 associated encephalitis with massive cerebral edema and fatal outcomes has been reported in previously healthy children, highlighting its potential for aggressive disease Regional evidence from South Asia also supports variability in disease severity and outcomes, including severe neurological complications in immunocompetent children with emerging data suggesting possible immune-mediated mechanisms contributing to complications [4,8,9,10].

In this study, common endemic causes of encephalitis in Sri Lanka, including dengue and Japanese encephalitis, were excluded through laboratory testing. Detection of HHV-6B DNA by typing PCR, together with autopsy findings of severe cerebral edema, supports a likely association between HHV-6B infection and the observed fatal neurological deterioration.

A diagnostic challenge in HHV-6 infection is distinguishing active disease from chromosomally integrated HHV-6 (ciHHV-6), which may cause persistent viral DNA detection without clinical illness. However, in the context of fulminant encephalopathy with compatible pathological findings and exclusion of alternative causes, the detection of HHV-6B is more consistent with true pathogenic infection rather than incidental viral presence.

Overall, this report supports growing evidence that HHV-6B should be considered an underrecognized but potentially fatal cause of pediatric encephalitis, particularly in cases of acute unexplained neurological deterioration with negative routine viral investigations [11,5,12,13].

Conclusion

These findings highlight the importance of considering HHV-6B in unexplained pediatric encephalitis and demonstrates the value of molecular diagnostics in identifying uncommon viral etiologies.

Author Contribution

HBCH contributed to manuscript drafting and editing. BS contributed to manuscript reviewing and editing. UKIUS contributed to laboratory testing. JIA contributed to conceptualization, overall supervision, data analysis, interpretation of findings and critical revision of the manuscript. All authors read and approved the final manuscript.

Ethical Statement

No patient-identifying information has been included in this report, and anonymity has been maintained throughout.

Conflict of Interest

The authors declare no conflict of interest.

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References

1. Dockrell DH (2003) Human Herpesvirus 6: Molecular Biology and Clinical Features. Journal of medical microbiology 52: 5-18.
2. Pellett PE, Ablashi DV, Ambros PF (2021) Human Herpesvirus 6: Biology, Clinical Features, and Diagnosis. Clinical Microbiology Reviews 34: e00131-20.
3. AlQasim E, Alawfi A, Hamad A, Alghamdi F,

Albaradi BA (2023) Human Herpesvirus-6 Encephalitis Associated with Acute Necrotizing Encephalopathy in an Immunocompetent Child: A Case Report and Literature Review. Cureus 15: e39897.

4. Yao K, Honarmand S, Espinosa A, Akhyani N, Glaser C, et.al (2009) Detection of Human Herpesvirus-6 in Cerebrospinal Fluid of Patients with Encephalitis. Annals of neurology 65: 257-267.
5. Chencheri N, Dirawi M, Tahir S, Shekhy J, Abuhammour W (2021) The Spectrum of Neurological Manifestations of Human Herpesvirus 6 Infection in Children. Cureus 13: e17183.
6. HHV-6 Foundation (2023) Review Summarizes the Substantial Disease Burden of Primary Hhv-6b Infection in Children. https://hhv-6foundation.org/encephalitis-encephalopathy.
7. Petersen CH, Nielsen H, Andersen PH (2025) Three-Day Fever-Associated Encephalitis with Rapid Deterioration: A Case Report. Ugeskrift for Laeger 187 https://doi.org/10.10.61409/v04250292.
8. Thomas DT, Devadathan K, Baby G, Kunju MP, Joji P (2025) Spectrum of Neurological Manifestations of HHV-6 Encephalitis in Immunocompetent Children - A Retrospective Study at a Tertiary Care Center in South India. Annals of Indian Academy of Neurology 28: 400-405.
9. Gagadam S, Foy V (2025) Systematic Review of HHV-6 and Febrile Seizures: Should the ER include it in the Viral Panel? Journal of Clinical Virology Plus 5: 100233.
10. Khalid A, Singh S, Khalid R, Payne M (2026) HHV-6 Encephalitis in an Immunocompetent Child: A Steroid-Responsive Case Complicated by Cerebral Venous Sinus Thrombosis. Sage open pediatrics 13: 30502225261421713 https://doi.org/10.1177/30502225261421713.
11. Victoria NC, Phan TL, Agarwal KA (2020) A Systematic Review of Sodium Disorders in Human Herpesvirus 6 Encephalitis. Biology of Blood and Marrow Transplantation 26: 1034-1039.
12. Webb G (2024). Diagnostic Dilemmas: Human Herpesvirus 6 Encephalitis in Immunocompetent Adults. Open Forum Infectious Diseases 11: ofae501.
13. Stathis CJ, Zhu H, Carlin K, Phan TL, Toomey D, et al (2024) A Systematic Review and Meta-Analysis of Human Herpesvirus 6 and Mortality after Hematopoietic Cell Transplant. Bone Marrow Transplantation https://doi.org/10.1038/s41409-024-02398-w.

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