

Spectrum of Neurological Manifestations of HHV-6 Encephalitis in Immunocompetent Children – A Retrospective Study at a Tertiary Care Center in South India

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Abstract

Background: Human Herpes Virus 6 (HHV6) can cause severe neurological manifestations in immunocompromised individuals. However, there is sparse data regarding this in immunocompetent children. **Objective:** To describe the spectrum of neurological manifestations of HHV 6 infection and outcome in immunocompetent children admitted with suspected meningoencephalitis from January 2017 to December 2023. **Methodology:** We retrospectively analysed the electronic medical records of children admitted for suspected meningoencephalitis in a tertiary care Pediatric Neurology centre in South India. The children whose cerebrospinal fluid (CSF) was found to be positive for HHV6 DNA in film array meningoencephalitis (FA-ME) panel were included. **Results:** 204 /416 children with suspected meningoencephalitis were included in the study. HHV 6 was detected in 12 children. The median age was 19 months (Range – 6 months to 16 years). 4 (33%) of them were classified as febrile status. 5 (42%) children had meningoencephalitis, and one had aseptic meningitis. One child each had features of probable acute demyelinating encephalo myelitis (ADEM) and anti NMDA receptor encephalitis. 9 (75%) children had uneventful clinical recovery, one child died, one child with probable ADEM had extrapyramidal signs at discharge, which improved completely at one year follow up and the baby with autoimmune encephalitis had significant neurological deficits. **Conclusion:** HHV 6 can cause significant neurological problems, with significant morbidity and mortality in immunocompetent children also.

Keywords: HHV-6 encephalitis, immunocompetent children, FA-ME panel

Introduction

Human herpes virus 6 (HHV-6) infection most commonly causes a benign illness known as exanthem subitum in children less than 3 years of age and is usually characterized by fever and rash occurring on the sixth day of illness. The viral infection is ubiquitous in nature, and serological evidence of exposure is present in nearly 100% of population in older children and adults.^[1] HHV-6 can remain latent after primary infection in the peripheral blood mononuclear cells and salivary glands, which act as its reservoir.^[1]

HHV-6 is a neurotropic virus and is known to cause severe neurological disease, especially in immunocompromised individuals. The neurological manifestations of HHV-6 in immunocompetent children are, nevertheless, rare and may include febrile seizures including complex febrile seizures status epilepticus HHV-6 encephalitis and distinct encephalitis syndromes such as HHV-6 encephalopathy with cluster of convulsions in eruptive stage, acute necrotizing encephalopathy of childhood, hemorrhagic shock and encephalopathy syndrome, and acute encephalopathy with biphasic seizure and late reduced diffusion.^[2-4] HHV-6 infection has also been associated with autoimmune encephalitis (anti-Gamma Amino Butyric Acid (GABA-A) receptor and N-methyl D- Aspartate (NMDA) receptor) and Rasmussen encephalitis.^[5] HHV-6 encephalitis can also have long-term neurological sequelae such as temporal lobe epilepsy, motor impairments, and ataxia.^[6-8]

Literature on the varied neurological manifestations, clinic-radiological patterns, and outcomes seen in HHV-6 encephalitis in immunocompetent children is scarce worldwide. This study aims to describe the spectrum of neurological manifestations of HHV-6 infection with its radiological features.

Methods

A retrospective study was conducted at a single tertiary care center in South India from January 2017 to December 2023. The study was approved by the institutional ethical committee with the approval number KIMS/IHEC/ APPROVAL/12/2023/01.

Electronic medical records of children with fever, seizures, and/or altered sensorium were reviewed, and those with

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HHV-6 detected in cerebrospinal fluid (CSF) by the BioFire Film Array Meningo-Encephalitis (FA-ME) panel (BioFire Diagnostics, Salt Lake City, UT, USA) were included in the study. FA-ME panel is an automated multiplex polymerase chain reaction (PCR) system with 94.2% sensitivity and 99.8% specificity, which identifies 14 different viral, bacterial, and fungal pathogens from CSF, including *Escherichia coli* K1, *Haemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Streptococcus agalactiae*, cytomegalovirus, enterovirus, herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), HHV-6, human parechovirus, varicella zoster virus, and *Cryptococcus neoformans*. The demographic profile, history, and clinical examination findings, along with the results of CSF study and neuroimaging features, treatment details, and outcome were noted from the electronic medical records. Autoimmune encephalitis panel and myelin oligodendrocyte/neuromyelitis spectrum optica antibodies were tested in relevant cases as per clinical discretion by the treating team. Children with prolonged febrile seizures (seizure duration of more than 30 min), without meningeal signs and acellular CSF were classified as febrile status. Those with meningeal signs and cellular CSF/leptomeningeal enhancement were classified as meningitis and meningoencephalitis, if there was altered sensorium, and/or parenchymal changes on neuroimaging in addition. The discharge outcome was obtained from the electronic medical records. The outcomes at 1 and 2 years post-discharge were obtained from the electronic medical records for children who were on regular follow up at the outpatient department. For children who were lost to follow-up in the outpatient department, the outcome was assessed by telephonic conversation with the parents. The minimum period of follow-up was 1 year.

Statistical analysis

The statistical analysis was done by using Statistical Package for the Social Sciences version 25.0 (IBM Corp, New York, NY, USA). Descriptive data was expressed as numbers (n) and percentages (%) for categorical data and mean/median values for continuous variables.

Results

There were 416 children with suspected meningoencephalitis during the study period. The FA-ME panel test was performed in 204 children; the test was not performed in others because of financial constraints. A causative organism was identified in 63 children (31%) and HHV-6 was detected in 12 [Figure 1], which included nine children reported in a previous study published by us on the utility of FA-ME panel. FA-ME panel tested negative for other etiological organisms for all the 12 children in whom HHV-6 was positive.

The clinical features, CSF study results, neuroimaging features, treatment given, and the outcome are summarized in Table 1. The age of children ranged from 6 months to 16 years, with a median age of 19 months. Eight (66%) children

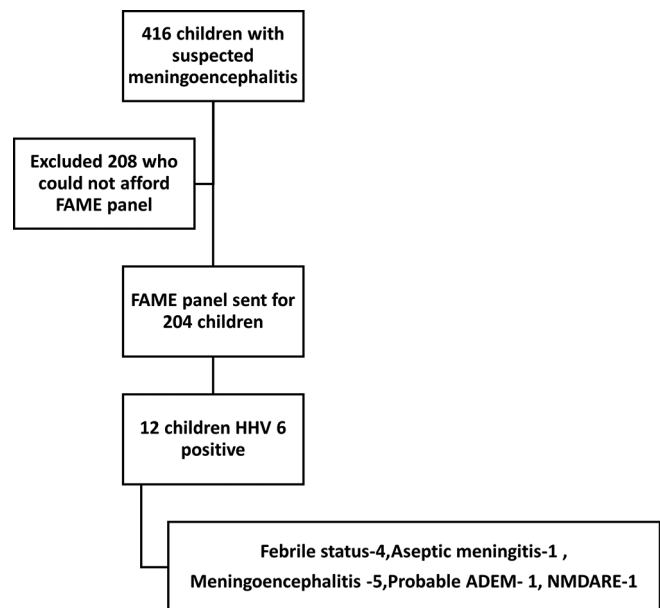


Figure 1: The study flow chart

belonged to the age group of less than 3 years, and three were infants. None of them developed exanthems in this cohort. Four (33%) were classified as febrile status. One 16-year-old boy presented as aseptic meningitis, with marked meningeal signs without altered sensorium and CSF pleocytosis (Case 1). Five (42%) children had meningoencephalitis. One child had normal cell counts but elevated protein levels with extrapyramidal symptoms and diffuse subcortical and basal ganglia involvement in magnetic resonance imaging (MRI) [Figure 2], suggesting meningoencephalitis/probable acute demyelinating encephalo myelitis (ADEM) (Case 6). A 1-year-old girl (Case 11) had the classical clinical features of anti-NMDA receptor encephalitis. She was treated with intravenous (IV) steroids, immunoglobulin, plasma exchange, rituximab, and cyclophosphamide. She received 14-day course of ganciclovir in addition. MRI abnormalities were noted in 6/7 children with meningoencephalitis [as detailed in Table 1].

IV ganciclovir was given for three children. Oral valganciclovir was given for one child with HHV-6 meningitis. IV acyclovir was continued in three children with encephalitis symptoms for variable duration (7–10 days), as they showed good recovery. Five children were not treated with antivirals.

Nine (75%) children had uneventful clinical recovery. One child died due to malignant brain edema (Case 7). The girl with subcortical and basal ganglia involvement in MRI had spasticity and dystonia of left upper and lower limbs at discharge (Case 6); she became completely normal at follow-up at 1 year. The baby with NMDA receptor encephalitis had severe sequelae despite immunotherapy (Case 11). She had attained head control and started rolling over at 1-year follow-up. One 2-year-old child with febrile status developed afebrile seizures after 2 years (Case 4).

Table 1: Clinical characteristics and outcome of children with HHV6 infection

Age	CSF pleocytosis	CSF protein (mg/dl)	CSF glucose (mg/dl)	Seizures	Headache/ vomiting	Altered sensorium	Clinical signs	MRI	Final diagnosis	Treatment	Discharge outcome	Follow-up outcome
9 months	576, L-71%	42.5	59.3	Yes	Yes	Yes	No	Normal	HHV-6 meningoencephalitis	Acyclovir (10 days)	No seizures, normal behavior and cognition	No seizures, normal behavior and cognition
16 years	50, L-100%	48.2	72.9	No	Yes	No	Meningeal signs	Not done	HHV-6 meningitis	Acyclovir (7 days)	No seizures, normal behavior and cognition	No seizures, normal behavior and cognition
6 months	8, L-75%	13.4	63	Yes	No	No	No	Not done	Febrile status	Supportive	No seizures, normal behavior and cognition	No seizures, normal behavior and cognition
2 years, 2 months	0	38.5	58	Yes	No	Yes	No	Not done	Febrile status	Supportive	No seizures, normal behavior and cognition	Afebrile seizures at 2-year follow-up
7 years	210, N-84%	34.8	87	No	Yes	Yes	Meningeal signs	Meningeal enhancement	Meningoencephalitis	Supportive	No seizures, normal behavior and cognition	No seizures, normal behavior and cognition
3 years	3, L-100%	12.5	62	No	Yes	Yes	Meningeal signs. Pyramidal tract signs. Choreoathetoid movements	FLAIR-hyperintense lesions in bilateral basal ganglia, thalamus, and subcortex	Probable ADEM	Acyclovir × 3 days, then ganciclovir (14 days) IVIG, pulse steroids	Tracheostomized, left UL spasticity, and dystonia at discharge. Prolonged hospital stay	Complete recovery. No neurological deficits, normal cognition (at 1-year follow-up)
1 year 2 months	14, L-100%	44.6	30.3	Yes	Yes	Yes	Raised ICT	Right MCA and ACA infarct. Fulminant cerebral edema on repeat CT	Meningoencephalitis with vasculitis, fulminant cerebral edema	Acyclovir changed to ganciclovir (1 day)	Death	-
1 year	5, L-60%	16.1	52.8	Yes	No	No	No	Normal	Febrile status	Supportive	No seizures, normal behavior and cognition	No seizures, normal behavior and cognition
10 months	5, L-100%	12.9	57.8	Yes	No	Yes	No	Not done	Febrile status	Supportive	No seizures, normal behavior and cognition	No seizures, normal behavior and cognition
10 years	31, L-90%	15	50	Yes	No	Yes	Meningeal signs	Limbic encephalitis	Meningoencephalitis	Acyclovir (10 days)	No seizures, normal behavior and cognition	No seizures, normal behavior and cognition
1 year	8, L-100%	18.8	75	Yes	No	Yes		Subtle cortical hyperintensities	Autoimmune encephalitis (NMDA positive)	Ganciclovir IVIG Pulse steroids PLEX	Regression of all milestones, severe dyskinesia	Attained head control and started rolling over. No rolling over. No dyskinesia (at 1-year follow-up)
9 years	56, L-100%	46	64	No	Yes	No	Meningeal signs	Normal	Meningoencephalitis	Valganciclovir (10 days)	No seizures, normal cognition	No seizures, normal cognition

CSF: cerebrospinal fluid, CT: computed tomography, FLAIR: fluid-attenuated inversion recovery, HHV-6: human herpes virus 6, MRI: magnetic resonance imaging, L: lymphocytes, N: neutrophils, IVIG: intravenous immunoglobulin, PLEX: plasma exchange, UL: Upper Limb

The clinico-radiological profiles of two children with HHV-6 meningoencephalitis are described in detail below.

Case 7: A previously healthy female child aged 1 year and 1 month was brought with complaints of fever and vomiting for 3 days with altered sensorium, somnolence, lethargy, and left focal seizures. At presentation, she had low Glasgow Coma Scale (GCS) of 9/15 with weakness and hypertonia of left upper and lower limbs and exaggerated deep tendon reflexes bilaterally and was intubated. MRI of the brain showed diffusion restriction involving the right frontal lobe, insula, and basal ganglia, suggestive of an acute infarct involving right Anterior Cerebral Artery (ACA) and Middle Cerebral Artery (MCA) territories [Figure 3a and b]. CSF study showed mild lymphocytic pleocytosis with CSF hypoglycorrhachia. Child was started on IV ganciclovir and pulse steroids. However, she deteriorated rapidly over the next 2 days and had refractory seizures with worsening of sensorium and features of raised intracranial tension (ICT). A repeat computed tomography of the head [Figure 3c] showed severely edematous right hemisphere with midline shift and mass effect on the brainstem. The baby deteriorated rapidly, despite antiedema measures, and succumbed to death.

Case 10: A 10-year-old previously healthy girl presented with complaints of one episode of seizure and altered behavior of 1 day duration associated with fever. On examination, her GCS

was 12/15. The neurological and systemic examination was otherwise normal. MRI of the brain showed hyperintensities in the left hippocampus and medial temporal lobe, suggesting limbic encephalitis [Figure 4]. Child improved within 72 h of hospitalization and recovered completely without any neurological deficits. She was started on IV acyclovir, which was continued for 10 days. She remained seizure free, and her memory and cognition remained normal on follow-up at 12 months.

Discussion

The wide spectrum of clinical and radiological manifestations of HHV-6 infection ranging from febrile seizures/status to severe neurological deficits and even death in immunocompetent children has been highlighted in our study. Immunocompromised individuals, especially post-hematopoietic transplant patients, are at a greatly elevated risk of HHV-6-associated encephalitis/encephalopathy. Recent studies have suggested that HHV-6 infection can cause severe neurological disease even in immunocompetent individuals, the diagnosis of which can be difficult because of the ubiquitous nature of the viral infection.^[9] HHV-6 primary infection typically occurs in children less than 3 years of age as exanthem subitum. Interestingly, none of the HHV-6-positive cases in this series had any exanthematous eruption. The absence of the rash does not rule out HHV-6 encephalitis and has been noted in one earlier study.^[10] HHV-6 encephalitis could be an independent severe form of infection, different from exanthem subitum, as many cases were described without any rash in previous studies^[9] and it has been observed in our study as well.

Among the 204 children with suspected meningoencephalitis, 12 children (5.88%) tested positive for HHV-6, which is comparable to previous studies where the incidence varied from 4.8% to 10%.^[11,12] Among them, four (33%) had febrile status. Higher occurrence of complex febrile seizures and febrile status has also been noted in previous studies on HHV-6 infection in children. The virus was found in CSF of 6% of children with febrile seizures without evidence of

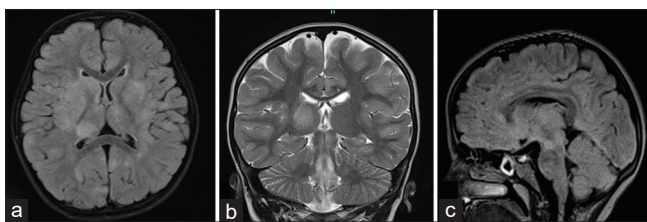


Figure 2: 3-year-old child with probable ADEM: MRI brain Axial T2 FLAIR (a), T2 coronal (b) and midsagittal T2 FLAIR (c) showing hyperintense signals in bilateral thalami, basal ganglia, brainstem, cortical and subcortical regions. ADEM: Acute demyelinating encephalo myelitis, MRI: Magnetic resonance imaging, FLAIR: Fluid-Attenuated Inversion Recovery

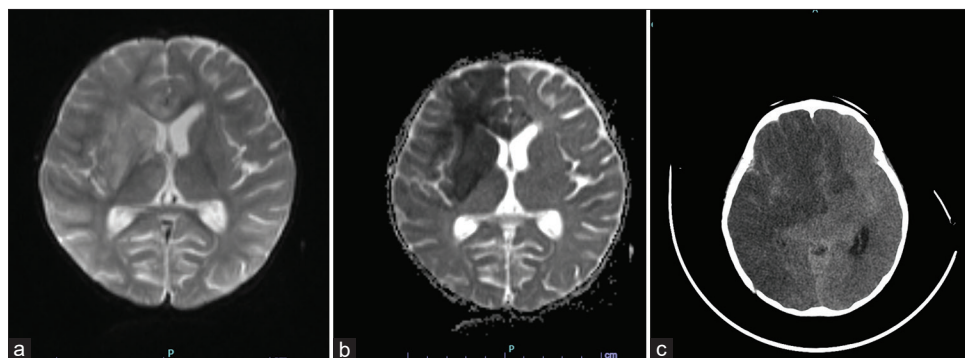


Figure 3: 1 year 1 month old child with severe HHV6 encephalitis. MRI brain axial DWI (a) and ADC (b) showing diffusion restriction over the right frontal, insula and right basal ganglia. (c) CT scan head done on day 4 showing severe brain edema over the right hemisphere causing midline shift and herniation of the brainstem. HHV6: Human herpes virus 6, MRI: Magnetic resonance imaging, DWI: Diffusion weighted imaging, ADC: Apparent diffusion coefficient, CT: Computed tomography

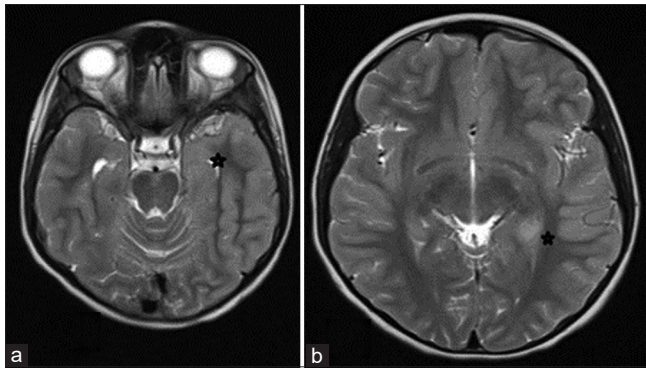


Figure 4: 10 year old child with limbic encephalitis: MRI brain T2 axial showing hyperintensities in left medial temporal lobe (a) and left Para hippocampal region and subcortical (b) regions. MRI: Magnetic resonance imaging

encephalitis.^[13] In the FEBSTAT study, 38% of children with febrile status had CSF viremia without pleocytosis.^[14] HHV-6 infection has also been associated with afebrile seizures in children older than 5 years of age.^[15] One child in our cohort developed afebrile seizures after 2 years. HHV-6 encephalitis has been implicated in the development of temporal lobe epilepsy following febrile status.^[16]

Autoimmune encephalitis associated with HHV-6 encephalitis has been reported recently, the possible mechanism being autoreactivity caused by antigenic exposure to HHV-6.^[17] In the series by Linnoila et al.,^[18] HHV-6 was identified in CSF of a 15-year-old girl with anti-N methyl D Aspartate Receptor (NMDAR) encephalitis. Anti-NMDA, anti-GABA-A receptor, and Rasmussen encephalitis have been reported following HHV-6 infections.^[19]

Neurological sequelae following HHV-6 encephalitis are common and reported to be as high as 45%–50%.^[20] In our cohort, most of the children (66%) had good outcomes without any neurological deficits. Nonetheless, one child died due to acute infarct in the right MCA and ACA territory, fulminant cerebral edema, and brainstem herniation. HHV-6-related mortality in immunocompetent children is rather rare in literature.^[21] Miyahara et al.^[21] have described a 15-month-old baby who had a history of febrile seizure the previous day and was found dead at night. The autopsy showed severe brain edema and brainstem herniation, and CSF as well as brain tissue showed the presence of HHV-6B. Even though central nervous system (CNS) vasculitis has been described in varicella zoster, HSV-1 and -2, and Epstein–Barr virus encephalitis, we could not find any published reports of vasculitis due to HHV-6, even after extensive literature search.^[22]

The classical neuroradiological feature of HHV-6 encephalitis in immunocompromised individuals is limbic encephalitis with the involvement of mesial temporal lobes. Posttransplant acute limbic encephalitis, due to HHV6 infection, is a well described entity in solid organ recipients, who are immunosuppressed.^[23] Limbic encephalitis was observed in a 10-year-old previously healthy immunocompetent child in our study. Subcortical

restricted diffusion is an early radiological feature described in HHV-6 encephalitis within 24 h of onset of symptoms,^[24] which is not seen in any of our patients. Focal diffusion restriction suggestive of infarct, malignant brain edema with herniation, leptomeningeal enhancement, and subcortical and basal ganglia hyperintensities were other radiological features observed in our children.

Antiviral treatment is not necessary in children with HHV-6 infection presenting as febrile seizures/status. Ganciclovir/valganciclovir has good anti-HHV-6 activity and is recommended for treating HHV-6 encephalitis.^[25,26] Combining ganciclovir and foscarnet has been even shown to reduce sequelae in HHV-6 encephalitis associated with hematopoietic stem cell transplantation.^[27] In our study, three children with severe symptoms received ganciclovir (one died and one showed complete recovery) and one 9-year-old stable child with HHV-6 meningoencephalitis received oral valganciclovir, which resulted in a good outcome. Acyclovir/valacyclovir has been found to have poor anti-HHV-6 activity *in vivo* and has not been recommended as the first-line therapy in HHV-6 encephalitis.^[25] Pulse steroid therapy is often used as a treatment modality in encephalitis; it was reported to be associated with better outcomes and lesser neurological deficits in one study.^[26]

Another important consideration is the diagnosis of HHV-6 encephalitis in children with chromosomal integration of HHV-6 (ciHHV6). It is known to be present in approximately 1% of the population and occurs when HHV-6 genome gets integrated into the telomeric regions of host chromosomes of gametes, which can then be transmitted vertically to the offspring, resulting in HHV-6 integration into every cell genome.^[25] A very high viral load in CSF of patients with no clinical features of encephalitis and persistent high copy number over many months are suggestive of probable chromosomally integrated HHV-6. HHV-6 DNA testing in the fingernail or follicle can also confirm ciHHV6.^[28] We could not perform quantitative PCR in the serum and CSF for identifying chromosomally integrated HHV-6 due to technical reasons, which is an important limitation in this study. However, in the clinical setting of acute meningoencephalitis with CSF pleocytosis and imaging findings, a qualitative PCR positivity in CSF can help institute early treatment strategies such as IV antivirals and immunomodulation.

Conclusion

HHV-6 infection, even though commonly benign, can rarely be associated with life-threatening complications, even in immunocompetent children. CSF study with PCR testing and neuroimaging can aid the diagnosis in most cases. HHV-6 encephalitis is a diagnostic possibility in any child with acute CNS infection and has a variable prognosis with plausible treatment strategies.

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Conflicts of interest

There are no conflicts of interest.

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