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Case Report

Symptomatic central nervous system tuberculosis and human herpesvirus-6 coinfection with associated hydrocephalus managed with endoscopic third ventriculostomy: A case report and review of human herpesvirus-6 neuropathology

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ABSTRACT

Background: Human herpesvirus 6 (HHV-6) is a double-stranded DNA virus well established in the clinical literature to cause the near-universal childhood infection roseola infantum (exanthema subitum/sixth disease). Primary HHV-6 infection has been reported to cause meningoencephalitis in pediatric patients, although generally in the immunocompromised.

Case Description: The authors treated an immunocompetent 18-month-old female who transferred to our institution for a higher level of care given concerns for meningitis in the setting of decreased level of arousal (Glasgow Coma Scale 12), and bradycardia 9 days after the onset of nasal congestion, fatigue, and repeated bouts of emesis. Outside hospital cerebrospinal fluid (CSF) studies were notable for hypoglycorrhachia, elevated protein, elevated nucleated cells with a mononuclear predominance, and a meningitis polymerase chain reaction panel that was positive only for HHV-6. Brain magnetic resonance imaging with and without contrast revealed a basal cistern predominant leptomeningeal enhancement pattern as well as moderate ventriculomegaly with associated periventricular edema concerning acute communicating hydrocephalus. Considering the CSF studies, neuroimaging, and recent travel history to Mexico, central nervous system (CNS) tuberculosis (TB) was the leading suspicion, and antimicrobial therapy was initiated for this presumptive diagnosis with culture data only proving the TB suspicion correct after nearly 2 months in culture. Anti-viral therapy was initially not felt to be necessary as the HHV-6 was interpreted as incidental and not a cause of symptomatic meningitis in our immunocompetent host. The patient's hydrocephalus was treated with temporary CSF diversion followed by performance of an endoscopic third ventriculostomy. Despite appropriate hydrocephalus management, clinical improvement ultimately seemed to correlate with the initiation of antiviral therapy.

Conclusion: The authors present this case and review the literature on HHV-6-associated CNS infections with the goal of informing the neurosurgeon about this often clinically underestimated pathogen.

Keywords: Encephalitis, Endoscopic third ventriculostomy, Human herpesvirus 6, Meningitis, Tuberculosis

INTRODUCTION

Human herpesvirus-6 (HHV-6) is a ubiquitous linear double-stranded DNA virus responsible for causing the infection in early childhood known as roseola infantum (exanthem subitum/sixth disease). It is spread through the wet route, replicating in the salivary glands with likely spread to the central nervous system (CNS) through the olfactory pathway. It remains latent within lymphocytes, monocytes, bone marrow progenitor cells, and neurons.[22] The typical presenting symptom of primary infection is acute high fevers up to 40C/104F, lasting 3–5 days, followed by a characteristic non-pruritic, blanching, and maculopapular viral exanthem starting on the trunk with fever subsidence.[15] Two variants of HHV-6 have been described, A and B, with the HHV-6B variant responsible for nearly all infections in the United States, including associated cases of febrile seizures and encephalitis. The clinical significance of the A variant remains largely unknown.[2,6,27,30,55,60] Therefore, based on known epidemiology and association with disease, HHV-6 should be implied as HHV-6B unless otherwise stated. HHV-6 reaches a population seroprevalence of 80% by 2 years of age[8,36,59] and, like other *Herpesviridae,* is capable of CNS invasion, lifelong latency through host chromosome telomeric integration, and symptomatic reactivation.[12]

HHV-6 has been implicated in a variety of neurologic conditions following primary infection or reactivation, such as febrile seizure, encephalitis, multiple sclerosis, and mesial temporal lobe epilepsy (MTLE). The most notable CNS manifestation of HHV-6 infection is meningoencephalitis in immunocompromised hematopoietic stem cell transplant (HSCT) recipients through reactivation and is often pursued with laboratory investigation when these patients present with altered mental status or seizures.[12,16,87] The best described CNS complication is severe acute encephalitis, known to occur mainly in hematopoietic stem cell or bone marrow transplant recipients.[4,16] However, a variety of rare neurological manifestations of primary HHV-6 infection in immunocompetent children have been reported in the past two decades, including febrile seizure, meningitis, encephalitis, as well as distinct encephalitic syndromes such as acute encephalopathy with biphasic seizure and late reduced diffusion.[27,39,75] Within recent years, HHV-6 gene expression has been identified by *in situ* immunohistochemical staining of brains of patients with MTLE, neocortical epilepsy, acute necrotizing encephalitis, and Rasmussen encephalitis (RE).[26,49,81] We report a case of symptomatic HHV-6 meningoencephalitis in association with tuberculosis (TB) meningitis in a previously healthy immunocompetent 18-month-old female treated by endoscopic third ventriculostomy (ETV) for hydrocephalus followed by marked clinical improvement after initiation of antiviral treatment.

CASE DESCRIPTION

An 18-month-old female born at term by spontaneous vaginal delivery without significant past medical history was transferred to the pediatric intensive care unit of a large academic hospital for management of suspected meningitis and presented to us with a decreased level of arousal (Glasgow Coma Scale 12) and mild bradycardia. Before transfer, the patient had a 9-day history of nasal congestion, fatigue, and repeated bouts of emesis. Outside hospital cerebrospinal fluid (CSF) studies were notable for *hypoglycorrhachia*, elevated protein, elevated nucleated cells with a mononuclear predominance, and a FilmArray® meningitis/encephalitis (FA-ME) panel (BioFire Diagnostics, Salt Lake City, UT) that was positive only for HHV-6. An electroencephalogram performed on the day of admission to our institution showed moderate generalized slowing without evidence of electrographic seizures. Brain magnetic resonance imaging (MRI) with and without contrast demonstrated leptomeningeal enhancement, particularly in the basal cisterns, raising suspicion for TB meningitis, particularly in light of a travel history to Mexico and the outside hospital CSF studies [Figure 1]. Given the high clinical suspicion of TB meningitis and the severity of presenting symptoms, the patient was started on RIPE (Rifampin, Isoniazid, Pyrazinamide, Ethambutol) therapy and high-dose dexamethasone. Antiviral therapy was initially not felt to be necessary as the HHV-6 was interpreted as incidental and not a cause of symptomatic meningitis in our immunocompetent host. During the first several days of the patient's admission, her encephalopathy waxed and waned, with brief periods of increased interactivity noted on several occasions. However, given progressive ventriculomegaly on serial brain MRI, placement of an external ventricular drain (EVD) was recommended and performed without complication on hospital day 3.

With the EVD in place, intracranial pressures (ICPs) were maintained in a range of 2–15 mmHg. Eleven days after EVD placement, an EVD clamp trial was performed, and although the patient did not mount elevated ICPs or have a significant change in her still waxing/waning level of arousal, a follow-up brain MRI revealed ventricular enlargement in the setting of the EVD being clamped. Given this, EVD replacement was recommended for ease of ongoing serial CSF sampling and to allow for the consideration of initiating intrathecal antibiotics. An ETV was also performed with this trip to the operating room, given the patient's high risk for developing chronic post-infectious hydrocephalus, favorable anatomy for ventriculostomy os creation, and ongoing need for intensive care with the EVD in place.

When entering the third ventricle during performance of the ETV, small beige-colored raised nodules measuring up to 1 mm in diameter were observed lining the walls of the third ventricle [Figure 2]. Similar nodular lesions were found

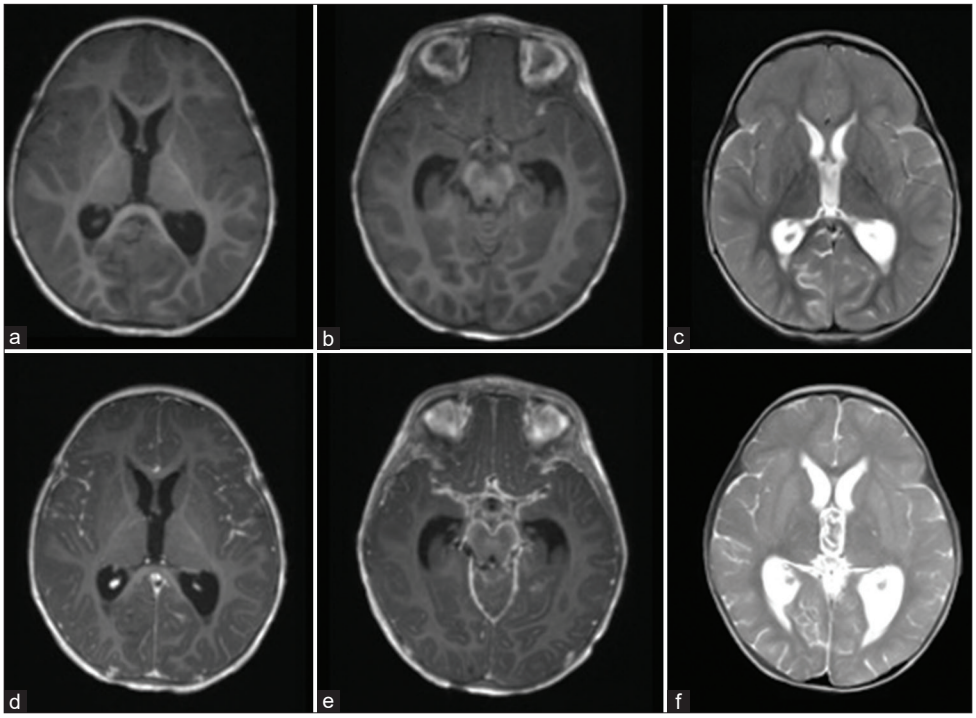

Figure 1: (a) Axial T1 precontrast image at the level of the Foramen of Monro. (b) Axial T1 precontrast image at the level of the suprasellar cistern. (c) Axial T2 image at initial presentation. (d) Axial T1 postcontrast image at the level of the foramen of Monro. (e) Axial T1 post contrast image at the level of the suprasellar cistern demonstrating enhancing basal exudate. (f) Axial T2 image immediately before external ventricular drain insertion.

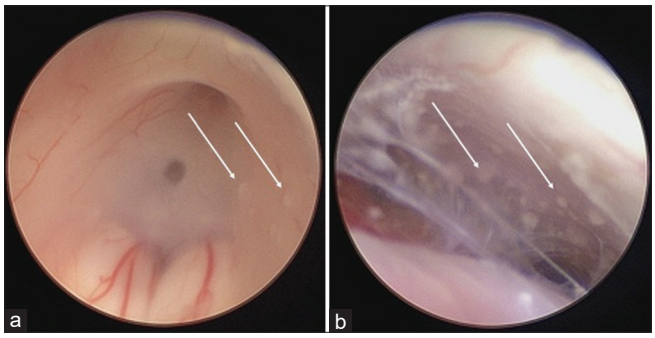

Figure 2: Endoscopic views of the (a) third ventricular floor with created stoma. (b) Prepontine cistern with basilar artery visualized at the bottom of the image. Arrows pointing to tubercles studding the (a) pre-mammillary area (b) prepontine cistern amidst thickened arachnoid membranes.

interspersed among the thickened arachnoid membranes within the prepontine cistern following the creation of an os in the tuber cinereum. In spite of thickened prepontine cistern arachnoid membranes, the "naked" basilar artery was visualized amidst an adhesive basilar meningeal exudate during the procedure.

While the nodular lesions observed intraoperatively were very likely mycobacterial tubercles, the possibility that these lesions represented collections of HHV-6-infected perivascular lymphocytes and microglia/macrophages, previously reported to produce macroscopically visible subependymal nodules[82] could not be ruled out. This prompted reconsideration by the surgical team of whether the previously discovered HHV-6 antigen by the FA-ME panel could be confidently declared clinically inconsequential. In consultation with the infectious disease team, this consideration resulted in the decision to initiate treatment with ganciclovir, in addition to ongoing RIPE therapy, immediately after surgery.

An EVD clamp trial performed 1 week after placement of the second EVD was not associated with elevations in ICP, changes in ventricular size, or clinical status. The second EVD was removed 8 days after placement. The patient was downgraded to a lower level of care, where steady improvements in mental status were noted. She was subsequently discharged to a pediatric rehabilitation facility 20 days after EVD removal and remained there for 12 days. Three days after discharge from rehab, CSF cultures drawn initially from the first EVD returned positive for *Mycobacterium tuberculosis* (MTB) complex, nearly 2 months after these cultures had initially been drawn.

The patient subsequently developed symptomatic secondary adrenal insufficiency (AI) following initial corticosteroid

taper and was referred to pediatric endocrinology for an extended prednisone weaned with a resolution of symptoms. This patient received >2 months of RIPE therapy and had confirmed sensitivities of MTB which showed no resistance. Infectious disease specialists placed the patient on a regimen of isoniazid and rifampin for the next 10 months. At the most recent clinical follow-up, our now 2-year-old patient is continuing to develop well, headache free, fully ambulatory, and speaking in full sentences.

DISCUSSION

Rationale for treatment strategy

Our patient required surgical intervention to definitively manage her hydrocephalus, which at the time of surgical intervention was presumed to be a consequence of her strongly suspected but not yet confirmed tuberculous meningitis with hydrocephalus (TBMH). While the placement of a ventriculoperitoneal shunt (VPS) was certainly considered, we ultimately decided to perform an ETV for several reasons. First, there was a desire for ongoing CSF sampling and escalation of care to include the use of intrathecal antibiotics, so access to the ventricular system with an EVD catheter was preferred. Second, the patient's anatomy (generous prepontine cistern and large foramen of Monro) was favorable for the performance of a low-risk ETV. Finally, the literature regarding ETV success rates in the setting of TBMH is favorable and has been suggested as first-line therapy for CSF diversion.[40] A study by Husain *et al*.[40] showed that 19/28 (68%) of patients with TBMH benefitted from ETV placement, with satisfactory outcomes in 14 (50%) (defined by no further surgical treatment required, persistent improvement in symptoms of raised ICP along with radiological improvement at 3 month follow-up examination), and acceptable in 5 (18%) (defined as temporary clinicoradiological improvement, but requiring external shunt for definitive management; however, further surgery was simplified or the patient was diagnosed primarily by endoscopy). A meta-analysis of eight studies by Legaspi *et al*.[44] found among 174 subjects with TBMH, ETV performance had a pooled success rate of 59%, defined as (1) no need for further CSF diversion surgery, (2) resolution of symptoms of increased ICP or clinical improvement, or (3) decrease or stability in ventricular size on postoperative imaging, while maintaining a technical failure rate of 5% (similar to failure rates observed for other etiologies)[52] and complication rate of 15%. CSF diversion surgery for TBMH seems to provide good outcomes (resulting in excellent function to mild/moderate disability) in about 55–63% of patients.[63] The best prognostic factor is intact sensorium before surgery, and the largest risk is neurovascular injury during ETV performance due to poor visualization within the thickened opaque third ventricular floor, particularly in the acute phase of the disease.[33,63]

ETV has also been found to have a significant advantage in good outcomes when compared with VPS (41–77% vs. 25–68%, respectively) in a systematic review of eight studies encompassing 603 patients, with good outcome defined either clinically or radiologically: Clinically as a resolution of signs and symptoms of increased ICP and radiologically as a reduction in dilatation of the ventricular system and resolution of periventricular ooze ($P > 0.008$).[13] Multiple studies have suggested that ETV should be the first-line treatment for CSF diversion in pediatric patients with TBMH,[9,17] with the caveat being for higher Palur grade TBMH patients, direct VPS is a reasonable option due to technical difficulty of ETV in the acute phase of the disease, although shunt infection, blockade, and need for shunt revision is higher for TBMH patients compared with other causes of hydrocephalus.[13,72]

The macroscopically visible subependymal and cisternal nodules presented in this case initially prompted reconsideration of alternative causes for the patient's meningoencephalitis. On further review of the literature, including manuscripts with *in vivo* imaging of MTB-induced changes in the appearance of the cerebral ventricles and arachnoid membranes[42,85], the authors acknowledge that the nodules observed were very likely mycobacterial tubercles. However, our suspicion that the nodules observed might be related to HHV-6 seemed to prove useful as the initiation of anti-viral therapy correlated with rapid clinical improvement. Although TBMH is common in developing countries, neurosurgeons in non-endemic regions have limited experience with MTB-induced changes that can be observed by neuroendoscopy. Briefly, these findings are thickened membranes, particularly along the third ventricular floor, cisternal exudate (histopathologically composed of large mononuclear cells, including epithelioid cells, which may fuse to form Langhans' giant cells)[21], and studding of the ependymal surface with tubercles.[9,42] Husain *et al*.[40] biopsied septal tissue in patients with TBMH and found consistent histopathologic findings with MTB infection. It remains unclear whether these tubercles occur in the context of co-TB HHV-6 infection or TB alone, as evidence of HHV-6 infection has been found in the subependymal region. While it seems quite probable that the unique ventricular and arachnoid membrane nodules observed in our patient were a consequence of MTB, it remains unclear if these nodules were more prominent than is typical, given increased vascular permeability and inflammation resulting from HHV-6 coinfection. Unfortunately, detailed histopathological analysis of the nodules observed in our patient was not possible as we felt that the surgical risk associated with lesion biopsy could not be justified. Despite this, our patient's quite striking clinical improvement suggests that the case presented adds to the growing body of literature that reframes the neurotropic HHV-6 as having the potential to be of greater clinical importance in the immunocompetent host than previously appreciated.

HHV-6 background

HHV-6 was first described in 1986. It was originally named human B lymphotropic virus (HBLV) after a novel virus was isolated from peripheral blood lymphocyte cultures in six patients with acquired immunodeficiency syndrome or other lymphoproliferative disorders.[66] Further detailed molecular and morphological studies in susceptible cell lines demonstrated that the virus was T-cell tropic, and HBLV was renamed to HHV-6 in accordance with the virus's natural host and order of discovery following the 1976 International Committee for Taxonomy of Viruses.[3,51] HHV-6 is a ubiquitous virus, reaching a seroprevalence globally between 70% and 100%.[7,48] There are two variants of HHV-6, called A and B, designated officially as separate species under the International Committee on Taxonomy of Viruses.[2]

The *Herpesviridae* family is a diverse group of enveloped DNA viruses divided by sequence phylogeny into three groups: alpha, beta, and gamma. The alphaherpesvirinae subfamily is comprised of the herpes simplex virus (HSV)-1, HSV-2, and varicella-zoster viruses (VZVs), which infect epithelium causing vesicular lesions and are neurotropic, occasionally manifesting as encephalitis. VZV, well known for primary infection of chickenpox (varicella) in children and symptomatic reactivation as shingles (zoster) in immunocompromised and older adults, is the only alphaherpesvirus with an available vaccine. The gammaherpesvirinae subfamily includes Epstein-Barr virus and HHV-8, which are linked with cancers and are markedly lymphotropic. The betaherpesvirinae subfamily, comprised of human cytomegalovirus (CMV), HHV-7, and HHV-6, establishes latency within multiple cell types including bone marrow progenitor cells, lymphocytes, monocytes, and neurons.[22] HHV-6A, identified mostly in central and sub-Saharan Africa, has traditionally been considered an orphan virus, with primary infection not yet linked to any clinical entities, and remains under investigation.[10,11]

HHV-6B is the major species circulating in the USA, Europe, and Japan with primary infection causing a benign and self-limited infantile infection called roseola infantum, also called *exanthema subitum* or *sixth disease.*[76] HHV-6 DNA is often detected *in vivo* in the saliva, as the salivary glands are the main reservoir and site of replication for the virus. Saliva is the presumed method of transmission between mother and child or between children 6 months and 2 years of age. Viral susceptibility increases during this period of life as maternally conferred HHV-6 antibodies wane by 4–6 months of age.[19,28,32,45,77] HHV-6 enters the cell by binding to CD46, a ubiquitous glycoprotein on the surface of nucleated cells also exploited by the measles virus.[76] Once inside the cell, the viral genome replicates in the host nucleus, induces hypomethylation of the short arm of chromosome 17, and integrates its entire genome into the host genome through break-induced replication repair in the telomeric region of 17p13.3, thus achieving latency and high viral loads in the blood.[18,76] The latent virus is then able to escape immune surveillance – a cardinal feature of all *Herpesviridae*.[73]

Chromosomally integrated HHV-6

When integrated into the host genome, the 162kb length of integrated DNA is termed inheritable chromosomally integrated HHV-6 (iciHHV-6), estimated to be prevalent in 40–70 million people worldwide.[34] iciHHV-6 is considered extremely rare and estimated to comprise about 1% of the cases that test positive for HHV-6 by polymerase chain reaction (PCR) of CSF samples.[62] Individuals with iciHHV-6 present a diagnostic challenge in differentiating active primary HHV-6 infection from reactivated HHV-6 when clinical suspicion for immunocompromise is high.[62] iciHHV-6 causes high titers in the millions of copies of DNA in whole blood samples due to 1 genomic copy present in every cell. iciHHV-6 was first proposed when HHV-6 DNA was found in peripheral blood mononuclear cells and hypothesized to integrate into the host genome randomly.[50] Because ici-HHV-6 is inherited through the germline in Mendelian fashion, at least 1 copy of the HHV-6 genome is thought to be present within every nucleated body cell with a 50% chance of passage to the child.[62,88] Interestingly, although the clinical spectrum of primary HHV-6A infection is poorly described, iciHHV-6A was linked with symptomatic disease in a Japanese child with X-linked SCID transmitted through the germline from the father.[18,29] This is consistent with evidence suggesting iciHHV-6A predominantly achieves latency within brain tissue, whereas iciHHV-6B was shown to have no such organ predominance.[43] Normally, ici-HHV6 causes higher detected loads of virus in both blood and CSF samples compared with active infection. This is because iciHHV-6+ subjects have vastly increased numbers of viral copies per million cells than individuals with active infection (1 million vs. 80), respectively. However, quantitative PCR (qPCR) of cell-free samples (plasma and CSF) cannot distinguish between chromosomal integration and active infection. Therefore, iciHHV-6 can be diagnosed through sampling whole blood with >5.5 log10 copies/mL, much higher than what would be expected with active primary infection, reflective of cell turnover, and can be confirmed with testing of hair follicles or nails.[62,88] More evidence is needed to evaluate whether patients with iciHHV-6 might reactivate to the point of needing antiviral intervention. In the case described at our hospital, there was low clinical suspicion of reactivated iciHHV-6B due to immunocompetent status, and no pathology has been previously well-described by iciHHV-6B reactivation.

Pathogenesis

In vitro PCR studies have demonstrated that HHV-6 can establish latency in neuroglial cell lines.[22,23] HHV-6 likely

spreads to the CNS through the olfactory route, with the highest frequency of HHV-6 DNA found in the olfactory ensheathing cells of the olfactory bulb/tract.[22,37] HHV-6 might enter the brain through the blood-brain barrier weakened by inflammatory pathologies.[74] Evidence suggests that HHV-6 infects vascular endothelium and adjacent lymphocytes and macrophages. A possible route of entry has been suggested by which HHV-6 passes from the fenestrated capillaries within the choroid plexus to the nearby specialized ependymal cells.[68] HHV-6 can infect the central nervous system as well as epithelial and endothelial cells using surface protein CD46 present on all nucleated cells.[5] This mechanism is supported by the finding of HHV-6 infected perivascular lymphocytes and microglia/macrophages by immunohistochemical staining of subependymal nodules in a patient with tuberous sclerosis who died suddenly (sudden unexpected death in epilepsy) in the setting of HHV-6 encephalitis.[82] In our patient's case, we hypothesize the proinflammatory state[20] caused by TBMH allowed HHV-6 to gain access to the CNS through increased vascular permeability making symptomatic HHV-6 encephalitis more likely.

Testing

The main blood compartment for HHV-6 is in nucleated cells. The only Food and Drug Administration approved multiplex PCR test for HHV-6 detection in the setting of acute encephalitis/meningitis is the BioFire® FilmArray® Meningitis/Encephalitis (BioFire Diagnostics) (FA-ME) panel.[35] However, the FA-ME panel does not distinguish between CSF samples reflecting primary infection, reactivated, or chromosomally integrated HHV-6. Immunocompetent adults who test positive for HHV-6 with high viral loads in CSF (thousands of copies) and blood (millions of copies) should not be diagnosed with HHV-6 encephalitis as this likely reflects iciHHV-6.[12] qPCR samples of CSF and whole blood may distinguish between active infection and reactivation from chromosomal integration if there is high clinical suspicion for immunosuppression.[62] Higher quantitative levels of HHV-6 DNA detected in plasma are associated with an increased risk of encephalitis, with >10,000 copies/mL in plasma found highly sensitive for HHV-6 encephalitis.[88] It has previously been suggested that testing for HHV-6 encephalitis in the immunocompetent by FA-ME should be limited to infants <3 years of age presenting with seizures and fever.[12] However, based on the case presented, the authors feel it reasonable to pursue HHV-6 testing in immunocompetent infants with fever and depressed levels of consciousness once other conditions have been ruled out or have failed to respond to medical intervention, even in the absence of confirmed seizures. Among immunocompromised hosts, the ratio of HHV-6 replication in CSF/blood >1 is helpful in making the diagnosis when imaging findings are lacking.[12]

Imaging findings

MRI is an indispensable tool in diagnosing HHV-6 encephalitis; however, early MRIs are frequently negative.[12] Thus, repeating MRI days to weeks after the onset of encephalopathy can be useful. The typical imaging findings of post-transplant acute limbic encephalitis (PALE) occurring in immunocompromised allogeneic HSCT patients are hyperintensity of bilateral medial temporal lobes on T2 fluid-attenuated inversion recovery and diffusion-weighted imaging.[70,86]

Clinical manifestations of HHV-6B infection

Most commonly, HHV-6B causes an acute febrile illness >40C in children <2–3 years of age. A subset of these patients will suffer a pink exanthem starting on the trunk and spreading to the face and neck with fever subsidence. HHV-6B accounts for approximately 10–20% of febrile seizures <2 years of age.

Immunocompromised hosts

Reactivation is the primary mechanism by which HHV-6B causes encephalitis in immunocompromised HSCT recipients and has been best described in patients who have undergone an umbilical cord blood transplant (UCBT).[22] UCBT is curative to several hematopoietic disorders in children, but due to late immune reconstitution, HHV-6B reactivates in 87–100% of recipients.[53] One systematic review and meta-analysis found that the prevalence of HHV-6 reactivation and HHV-6 encephalitis was significantly higher in patients receiving UCBT as the stem cell source than in patients receiving another stem cell source (72.0% vs. 37.4%, $P < 0.0001$; 8.3% vs. 0.50%, $P < 0.0001$, respectively).[69] While reactivation rates are particularly high following UCBT, HHV-6B is also the most frequently detected virus in the CNS (76%) of patients after all forms of HSCT, based on a large-scale study involving over 500 transplant centers.[12] Post-transplant acute limbic encephalitis (PALE) is potentially fatal and should prompt investigation with CSF HHV-6 qPCR, plasma qPCR, neuroimaging, and empiric treatment.[38,86] The acute limbic encephalitis described in HSCT patients is localized to the amygdala, hippocampus, and hypothalamus, causing anterograde amnesia, confusion, and epilepsy.[53] Santoro and Hemond[67] found that lower CSF viral loads were significantly associated with seizures ($\beta = -0.15$, 95% confidence interval [CI] −0.28, −0.02, $P = 0.028$) in a single institutional study of 11 pediatric PALE patients. This likely reflected primary infection rather than secondary reactivation; however, no assay was performed for definitive delineation.[67] The sequelae of PALE syndrome include lasting neurologic dysfunction and temporal lobe epilepsy (TLE). Seeley *et al*. described nine patients with PALE, 56% (5/9) of whom died, and 75% (3/4) of surviving patients

were severely cognitively impaired.[70] In a study of 197 Japanese patients undergoing various forms of HSCT, eight were diagnosed with post-transplant HHV-6 encephalitis by positive CSF PCR, with six demonstrating characteristic imaging findings of hyperintense lesions in the hippocampus with onset of encephalitis. Half of the patients (4/8) who developed post transplant HHV-6 encephalitis underwent UCBT, which was identified as the only risk factor.[65] After treatment with ganciclovir or foscarnet, four out of five living patients at minimum 1 year follow-up were unable to return to social or work life due to neuropsychological illness. The authors noted that MRI showed prominent hippocampal atrophy during the late phase of HHV-6 encephalitis, suggesting that some of the limbic effects of HHV-6 encephalitis can be irreversible , resulting in lasting neurocognitive impairments.[65] HHV-6 encephalitis in the immunocompromised is associated with a CSF/blood viral replication ratio > 1 whereas primary HHV-6 infection in an immunocompetent host is associated with a CSF/blood viral replication ratio << 1, even in patients presenting with seizures and/or mild encephalopathy.[12]

Association of medically intractable epilepsy and HHV-6 in the immunocompetent

CNS involvement by HHV-6 in the immunocompetent host is limited to children <3 years of age with primary infection. Primary HHV-6 infection is generally considered a benign disease process. Roseola rarely needs intervention, although the high-grade fever may cause acute febrile seizures. Primary HHV-6B infection is associated with most cases of virus-associated febrile seizure, accounting for approximately one third of all first-time febrile seizures in children two years old and younger. Millichap and Millichap[56] reviewed 416 patients <3 years of age between 1995 and 2004 presenting with febrile seizures and reported that 101 (24%) had a primary HHV-6 infection. Furthermore, in 902 children under 3 years of age with primary HHV-6 infection and fever, 149 (16.5%) had a seizure.[56] Berzero *et al*. compared 17 immunocompetent and 25 immunocompromised patients who tested positive for HHV-6 DNA in CSF.[12] They found that 26% (4/17) of immunocompetent patients with primary HHV-6 infection were found to have HHV-6 encephalitis presenting as seizures/irritability, with all cases having a CSF/blood HHV-6 DNA ratio <1.[12]

There seems to be a clear association between HHV-6 infection and MTLE. Rasmussen was the first to suggest that viral encephalitis may be linked to the development of focal seizures after a histologic examination of cerebral tissue from three children with focal epilepsy and severe damage to one cerebral hemisphere.[64] Although HHV-6 is frequently detected in brain specimens without epilepsy, its frequency is higher in MTLE. A systematic review and meta-analysis of eight studies comprising 555 patients compared detected viral HHV-6 DNA from surgically resected hippocampal brain tissue in patients with MTLE versus controls with or without another epilepsy diagnosis (14 with epilepsy, 122 without epilepsy).[84] In that study, there was a positive association between MTLE and HHV-6 versus controls (Odds ratio = 2.016; 95% CI = 1.16–3.50). Furthermore, in the subgroup of MTLE patients with hippocampal sclerosis (HS), HHV-6 DNA was detected at significantly higher rates than the subgroup of MTLE without HS (22.1% vs. 11.8%, p<0.05).[84] Donati *et al*.[26] described the detection of HHV-6B in astrocytes of eight patients with medial TLE by PCR, confirmed with Western Blot analysis and immunohistochemistry. Fotheringham also detected HHV-6B through PCR in 15 brain sections from 24 patients with MTLE, localizing to glial fibrillary acidic protein positive glial cells.[31] They subsequently infected astrocyte cultures *in vitro* with HHV-6 and found a marked decrease in glutamate transporter EAAT-2 expression consistent with previous work demonstrating the relationship between glutamate transporter dysfunction and MTLE.[31] A Chinese study from 2011 found an association between MTLE and HHV-6 from surgically resected brain tissue and a possible association with the activation of transcription factor nuclear factor-kappa B (NF-κB). NF-κB expression was significantly increased in samples from MTLE patients who were positive for HHV-6B compared with HHV-6B-negative hippocampal samples ($P < 0.05$) and controls ($P < 0.05$)[47] Theodore *et al*. compared the incidence of HHV-6 from brain tissue of patients with drug resistant epilepsy found that HHV-6 was detected in the majority (29/54) of surgical resections in patients with mesial temporal lobe sclerosis (MTS) and were more likely to have HHV-6 detected in their surgical resections than patients with other pathologies (dysplasia, encephalitis, tumor, and vascular).[78]

Febrile seizure and febrile status epilepticus (FSE) have been observed in numerous studies to increase the risk for the development of MTLE. The association between higher HHV-6 DNA levels in a subset of MTLE patients with hippocampal sclerosis (HS) than MTLE patients without HS suggests a possibility that latent HHV-6 may contribute either primarily or through repeated neuroinflammatory insult to the development of MTLE, although no causal relationship has been established.[84] The establishment of latency, possible reactivation, and the induced glutamate uptake by HHV-6B-infected astrocytes makes this explanation plausible; however, it is unknown whether epilepsy itself may cause viral reactivation or the frequency by which FSE is related to subsequent development of HS and MTLE.[84]

MTS is the most frequently encountered drug-resistant TLE in neurosurgical practice, treated with anterior temporal lobectomy and the selective amygdalohippocampectomy

with excellent surgical outcomes relative to extra-temporal focus seizures.[58,61] A prospective multicenter study, the Consequences of Prolonged Febrile Seizures in Childhood (FEBSTAT), examined the relationship between prolonged childhood febrile seizures and the development of HS and epilepsy, particularly TLE, as well as the prevalence of HHV-6 and HHV-7 in febrile status epilepticus.[30] In FEBSTAT, 199 children between 1 month and 5 years of age recruited with febrile status epilepticus, HHV-6, or HHV-7 status could be determined in 169 (84.9%). HHV-6B viremia at baseline was found in 54 subjects (32.0%), including 38 with primary infection and 16 with reactivated infection.[30] In the 38 with primary HHV-6 infection, HHV-6 was concluded as the likely cause of FSE.[30] FSE was found to cause definite or equivocal hyperintense T2 hippocampal signal in 22 (11.5%) of children in the FEBSTAT study at follow-up.[71] HHV-6 infection is commonly associated with febrile status epilepticus, acute injury to Sommer's sector, and subsequent HS visible as hyperintense on T2 MRI.[46]

Although the primary mechanism for HHV-6 associated meningoencephalitis is reactivation from latency in immunocompromised patients, there have been at least 14 case reports demonstrating primary HHV-6 encephalitis in seronegative patients.[79] HHV-6 has been associated with several necrotizing brain lesions secondary to primary infection with roseola and should be distinguished from abscess and malignant brain tumor. For example, a 1-year-old infant was found to have acute bilateral striatal necrosis after showing typical signs of roseola.[57] In addition, an immunocompetent 5 years old with acute onset left-sided hemiparesis was found to have HHV-6 associated necrotizing encephalitis by PCR assay from a middle frontal gyrus biopsy and recovered 1 year later.[54]

HHV-6 has recently been implicated in the pathogenesis of RE. RE is a rare pediatric neurologic disorder characterized by hemispheric cortical inflammation with CD8+ T-cells, subsequent hemispheric atrophy, and drug-resistant epilepsy most often requiring cerebral hemispherectomy to alleviate seizures and cognitive deterioration.[80,83] Liu *et al.*[49] evaluated the expression of HHV-6 and EBV antigens in sections of cerebral tissue collected from patient with RE by IHC staining. They found HHV-6 antigens in 50% (15/30) individuals with RE compared with 0% from age-matched controls with cerebral trauma. They also found HHV-6 and EBV coexpression in 20% (6/30) of brains with RE, closely associated with a higher degree of cerebral atrophy. They also reported a case of a 4-year-old boy who developed RE after being diagnosed with an unspecified viral encephalitis. In this patient, EBV and HHV-6 were co-expressed in microtubule-associated protein 2 positive neurons and GFAP-positive astrocytes. The authors hypothesized that HHV-6 and EBV activate CD8 +T-cells, also detected in large amounts in the brain sample, leading to the development of cerebral atrophy.[49] This hypothesis is consistent with previous research demonstrating a CD8+ T-cell cytotoxic mechanism to neuronal loss in RE.[14] Both TLE and RE may result from HHV-6 infection however in contrast to TLE, which shows a stable balance between HHV-6 infection and innate immunity, brains with RE have been found to have increased CD8+ T-cell activation as evidenced by increased granzyme-b and lower innate antiviral immunity interferon-beta levels.[83]

Treatment strategies

The general treatment strategy for HHV-6 infection is based on antiherpetic guanosine analogs, given the virus' close relation to CMV. HHV-6 produces a homologous protein to CMV encoded UL97, a serine/threonine kinase pU69, which plays a similar role mechanistic role in activating ganciclovir, although at much lower levels *in vitro*.[24] *In vitro* studies have favored the use of ganciclovir and foscarnet for treating active HHV-6 infection. Foscarnet has shown both *in vivo* and *in vitro* activity against HHV-6 but is difficult to use in HSCT patients due to the risk of severe nephrotoxicity at therapeutic dosages.[25] Mycophenolate mofetil, a commonly used immunosuppressive agent to prevent graft versus host disease in HSCT, may contribute to the reactivation of latent HHV-6 infection and the development of severe encephalitis.[41] However, it has shown promise in potentiating the effects of ganciclovir in cell culture and animal models, and future research in humans is needed.[24]

CONCLUSION

HHV-6, the virus responsible for the near ubiquitous childhood illness roseola infantum, is a neurotropic virus that has long been recognized as a cause of clinically significant meningoencephalitis in the immunocompromised and has increasingly been linked to both acute neurologic symptoms of both MTLE and Rasmussen's encephalitis pathogenesis in the immunocompetent. The case presented illustrates that HHV-6 has the potential to cause symptomatic meningoencephalitis in the immunocompetent host and adds to the growing body of literature in support of this hypothesis. The literature review underscores the importance of increasing awareness of HHV-6 in the fields of pediatric neurosurgery, neurology, and infectious disease.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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