Human Herpes Virus 6 Encephalitis Presenting as Fatal Refractory Status Epilepticus: a Case Report and Systematic Review

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Abstract

Purpose: Encephalitis secondary to human herpesvirus 6 (HHV-6) infection is frequently encountered in immunocompromised patients; in contrast, HHV-6 encephalitis in immunocompetent patients is rare. There are only 3 reports of status epilepticus due to HHV-6 encephalitis in immunocompetent adults. In the present study, a case of refractory status epilepticus secondary to HHV-6 encephalitis was reported in an immunocompetent female.

Case Report: We report a case of a previously healthy 46-year-old female who presented with a one-week history of back pain, fever and generalized tonic-clonic seizures that progressed to status epilepticus. The video electroencephalography showed epileptiform discharges on both frontotemporal regions. Neuroimaging showed hyperintensities on the bilateral insula and temporal lobes. The cerebrospinal fluid showed elevated pressure and was positive for HHV-6. She was given ganciclovir and a total of eleven antiepileptic drugs. Despite these medications, she developed refractory status epilepticus and eventually succumbed due to multiple medical complications.

Conclusion: This case highlights HHV-6 encephalitis as an important diagnostic consideration in patients presenting with refractory status epilepticus, regardless of immune status.

Keywords: HHV-6 encephalitis; refractory status epilepticus; viral encephalitis

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INTRODUCTION

Human herpesvirus 6 (HHV-6) belong to the roseolovirus genus of the herpesvirus family and is the etiologic agent of roseola infantum. After initial viremia, the virus exhibits neurotropism and neuroinvasion, with predilection to astrocytes and oligodendroglial cells[(1)]. Reactivation of latent HHV-6 virus, particularly in immunocompromised patients, has been associated with the various neurologic disorders, including encephalitis.

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HHV-6 encephalitis can present with seizures due to glutamatergic excitotoxicity in the mesial temporal lobes[2]; however, there are only few documented cases of status epilepticus associated with HHV-6 encephalitis. We report a case of fatal refractory status epilepticus in HHV-6 encephalitis in an immunocompetent adult.

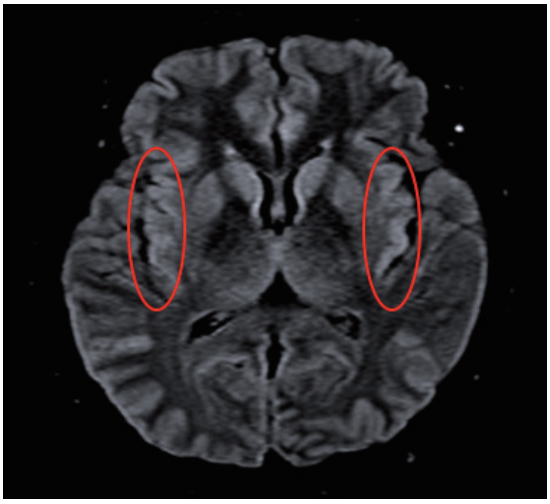

Figure 1. MRI of the brain showing areas of T2 fluid attenuated inversion recovery (T2 FLAIR) hyperintensities involving the bilateral insula and mesial temporal lobes.

CASE PRESENTATION

A previously healthy 46-year old female had a one-week history of increasing back pain, febrile episodes and generalized tonic-clonic seizures (GTCs). She was given intravenous (IV) diazepam and levetiracetam, then transferred to our hospital.

On examination at the emergency room, she was afebrile and hemodynamically stable. She had partial eye opening to tapping, unable to follow commands, symmetric withdrawal to pain and nuchal rigidity. The initial impression was a central nervous system infection, likely viral encephalitis. Levetiracetam was continued and IV valproic acid was added due to the persistence of altered sensorium, with strong consideration of subclinical seizures. She was started on IV acyclovir for empiric coverage of viral encephalitis.

Laboratory investigations revealed normal values (NV) for white blood cell count (8520, neutrophils=73% lymphocytes=27%), procalcitonin (<0.05), electrolytes (Na=142 mEq/ml, K=3.6 mEq/ml), creatinine (0.58 mg/dL), liver function and arterial blood gases. A cranial magnetic resonance imaging (MRI) with contrast revealed signal hyperintensities on bilateral insula and mesial temporal lobes on T2-fluid attenuated inversion recovery (FLAIR) (Figure 1A). Lumbar puncture was performed with note of elevated opening pressure (27 cms. H20). CSF analysis showed 8 white blood cells, all lymphocytes with normal protein, glucose and CSF:serum glucose ratio. The CSF was tested with the FilmArray Meningitis/Encephalitis (ME) panel (BioFire, Salt Lake City, UT, USA) multiplex polymerase chain reaction-based assay, which detected human herpesvirus 6 (HHV-6). The panel was negative for the following bacteria: Escherichia coli K1, Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitides, Streptococcus agalactaiae and Streptococcus pneumonia; viruses: Cytomegalovirus, Enterovirus, Herpes simplex virus 1, Herpes simplex virus 2, Human parechovirus and varicella zoster virus; and yeast: Cryptococcus neoformans/ gatti.

Acyclovir was shifted to IV ganciclovir (250 mg every 12 hours, 5mg/kg) on the second hospital day, nine days after symptom onset. Meanwhile, blood and endotracheal cultures were negative for bacteria or viruses.

A 2-hour video electroencephalography (vEEG) showed numerous epileptiform discharges on both frontotemporal regions (Figure 2). Levetiracetam (3 grams/day) and valproic acid (1.5 grams/day) were continued and midazolam infusion (2 mg/kg/h) was added for seizure control. Despite these anti-epileptic medications (AEDs), there was increasing frequency of seizures. Subsequently, a referral to epilepsy specialist was done and additional AEDs were introduced for seizure control: lacosamide (100 mg/day), perampanel (12 mg/day), phenytoin (300 mg/day), pregabalin (600 mg/day), topiramate (800 mg/day), clonazepam (3 mg/day), phenobarbital (180 mg/day). Ketamine infusion (3 mg/kg/hr) was subsequently started. IV dexamethasone (20 mg/day) was initiated for seizure control. Valproic acid levels by immunoassay done on the 4th, 8th, and 13th day of administration showed a corrected result of 90 mcg/ml, 108 mcg/ml, and 80.8 mcg/ml respectively (NV: 50-100 mcg/ml). Phenyotin levels by enzyme immunoassay done on the 2nd and 7th day of

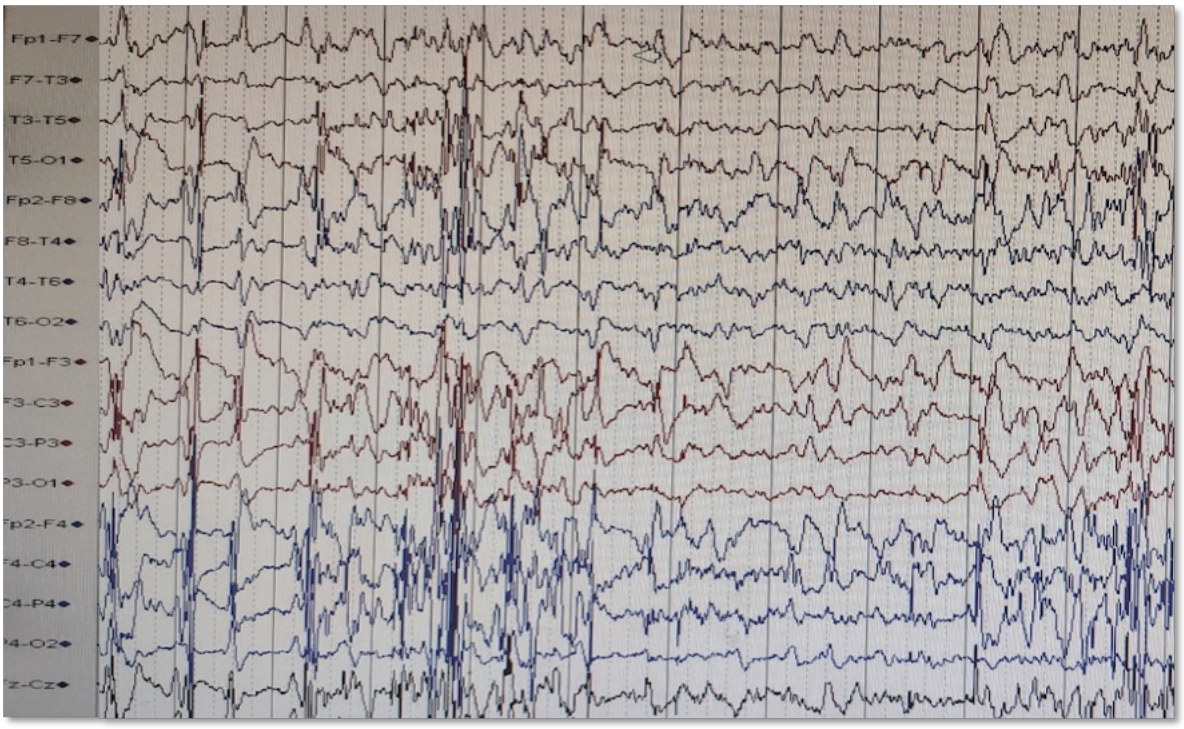

Figure 2. Multiple epileptiform discharges on the bilateral frontotemporal regions with generalized slowing of background activity.

administration was 12 mcg/ml and 15.88 mcg/ml (NV: 10-20 mcg/ml).

Despite multiple AEDs and intravenous anesthetics, there were still occasional episodes of focal and generalized motor seizures. A repeat vEEG still showed occasional epileptiform discharges on both frontotemporal regions. She eventually succumbed after a month due to multiple medical complications.

METHODS

We performed a systematic review in multiple databases (including PubMed, MEDLINE, Google Scholar) using the keywords "HHV-6 encephalitis", "status epilepticus" and "immunocompetent" from 1966 to September 30, 2019 to identify all case reports involving immunocompetent adult patients with human herpesvirus 6 encephalitis that presented with status epilepticus. This systematic review was performed in accordance with the Preferred Reporting Items for a Systematic Review and Meta-analysis. The demographic data, CSF analysis results, imaging findings, therapeutics (antimicrobials and AEDs) and outcomes were recorded.

RESULTS

A search of electronic databases yielded only 3 case reports on HHV-6 encephalitis with status epilepticus in immunocompetent adults (Figure 3)[3-5]. Two of the cases completely recovered, while one patient expired 3 3 weeks after symptom onset (Table 1). In comparison to the three reports, our patient was given the most number of AEDs and intravenous anesthetics (total of 11) in order to control the seizures.

DISCUSSION

HHV-6 can reactivate under conditions of immunosuppression, which can result to neurologic manifestations such as seizures and encephalitis[5]. However, these are rarely documented in immunocompetent patients[1]. Our patient has no known medical co-morbids,

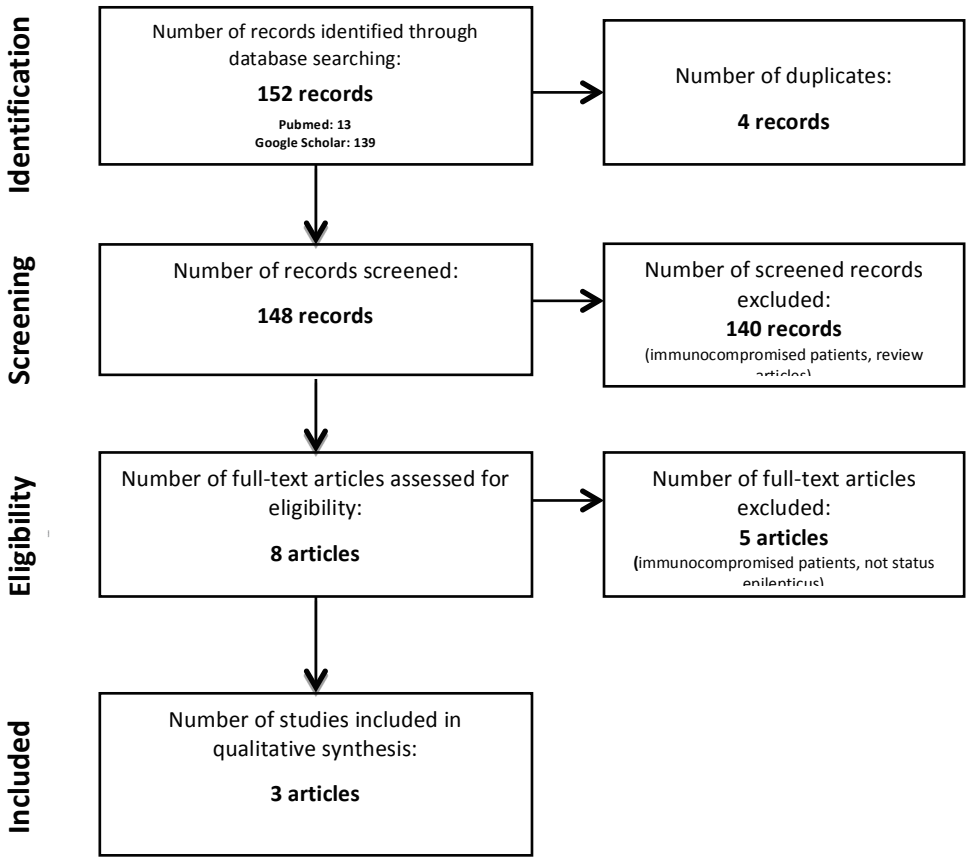

Figure 3. The PRISMA flow diagram for the systematic review.

immunosuppressive conditions, or intake of immunosuppressant medications.

Our patient developed super refractory status epilepticus despite being on 9 AEDs and 2 intravenous anesthetics, the most number of AEDs compared to other cases. Plasma levels of valproic acid and phenytoin were monitored and were found to have therapeutic levels in the blood.

The refractoriness may be attributed to several factors. The virus can establish latent infections which can be reactivated and disrupt astrocyte homeostasis, trigger immune reaction toward latent antigens and lower the seizure threshold[6-8]. There is downregulation of glutamate transporter EAAT2 expression, causing decreased glutamate uptake in infected astrocytes and increased glutamate levels, resulting to neuronal excitotoxicity, hippocampal injury, and epileptogenesis[9]. It can also evade host immune response by induction of CD4 lymphocyte depletion, down-regulation of CD3 expression and IL-2 and decreased generation of reactive oxygen species[5]. There is increased expression of pro-inflammatory mediators contributing to epileptogenesis and blood brain barrier damage[9,10]. Lastly, ganciclovir-resistance has been reported in previous studies[11,12].

The HHV-6 viral load in the serum and CSF was not determined and a repeat CSF analysis were not done in our patient. Also, additional CSF tests to investigate for possible paraneoplastic or autoimmune encephalitis were not performed due to financial constraints. The plasma concentrations of the other AEDs were also not done due to the unavailability of the test kits.

Nevertheless, our case highlights HHV-6 encephalitis as an important consideration in patients with status epilepticus, regardless of immune status. Early detection of HHV-6 and prompt treatment is essential, as HHV-6 encephalitis can be associated with poor outcome.

Table 1. Review of cases with HHV-6 encephalitis presenting with status epilepticus in immunocompetent individuals

Author	Age/ Sex	Seizure Presentation	CSF	Imaging	Treatment	Outcome
Troy, et al. (2008) [4]	34/ M	Status myoclonus	WBC: 127 Lymphocytes: 87% RBC: 3355 cells/μL Protein: 92mg/dL Glucose: 36mg/dL	Brain MRI Initial: Normal Day12: Small areas of restricted diffusion, bilateral cerebral hemisphere	acyclovir vancomycin ceftriaxone	Complete recovery
Persinger, et al. (2012) [3]	21/ M	Status epilepticus	Normal cell count Normal protein Normal glucose PCR: HHV-6	Bilateral hippocampal enhancement and hyperintense bi-hemispheric signals	ganciclovir cidofovir valproate phenytoin levetiracetam lorazepam midazolam	Expired
Shahani (2014) [2]	65/ F	Initial: confusion and muscle twitching and jerking in her upper extremity During admission: Status epilepticus	Normal cell count Normal protein Normal glucose	Brain MRI: Multifocal hyperintensities on the T2WI, FLAIR pulse image involving cortical grey matter of the right cingulate gyrus, right parietal, occipital and temporal regions	foscarnet, ganciclovir lorazepam, phenytoin, valproic acid phenobarbital midazolam	Seizure free after one year
Ocampo, et al. (2020)	46/ F	Generalized motor seizures progressing to refractory status epilepticus	WBC: 8, all lymphocytes Protein: 46.7 mg/dL Glucose: 55 mg/dL PCR: HHV-6	Brain MRI: hyperintensities on the bilateral insula and temporal lobes	ganciclovir cefipime levetiracetam valproic acid lacosamide phenytoin perampanel pregabalin topiramate phenobarbital clonazepam midazolam ketamine dexamethasone	Expired

HHV-6: human herpesvirus 6
CSF: cerebrospinal fluid
MRI: magnetic resonance imaging
WBC: white blood cell
RBC: red blood cell

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