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BRIEF REPORT

Long-term Outcomes of Patients With Human Herpesvirus 6 Encephalitis

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Human herpesviruses 6 (HHV-6) A and B cause encephalitis in patients with hematologic malignancies, especially those undergoing allogeneic hematopoietic stem cell transplantation. In this cohort of 10 patients, persistent neurologic deficits associated with moderate to severe bilateral hippocampal atrophy were characteristic long-term findings, despite prolonged antiviral treatment.

Keywords. bone marrow transplant; human herpes virus 6 encephalitis; viral encephalitis.

Human herpesviruses 6 (HHV-6) A and B are ubiquitous betaherpes viruses, often acquired early in life as a transient febrile illness [1]. Once acquired, the virus assumes latency in the lymphocytes and salivary glands and can reactivate in immunocompromised individuals [1]. HHV-6 reactivation occurs in 35% to 46% of all hematopoietic stem cell transplant (HSCT) recipients [2–6]. Rates of reactivation are up to 90% in those with umbilical cord blood (UCB) transplant, with a median time to reactivation of 20 to 29 days [2–6].

Several disease processes have been associated with HHV-6 reactivation in HSCT recipients, including interstitial pneumonitis and febrile syndrome with rash. HHV-6-associated encephalitis, however, remains the most well-recognized illness, with devastating clinical presentation [3, 7, 8]. Data on the long-term outcomes of patients with HHV-6 encephalitis are limited. To assess the clinical and diagnostic characteristics and long-term outcomes of patients with HHV-6 encephalitis, we performed a retrospective review of all patients with a diagnosis of HHV-6 encephalitis at our center.

METHODS

We retrospectively searched and collected data for all patients with allogeneic HSCT, leukemia, or lymphoma who were positive for HHV-6 and were seen at the Mayo Clinic, Rochester, Minnesota, between 2011 and 2017. Patients were identified by searching the Advanced Cohort Explorer (ACE), which is our institutional search engine for medical records. Patient data reviewed included clinical findings; laboratory, microbiologic, and radiologic data; and medications. Patients with HHV-6 encephalitis were identified on the basis of clinical symptoms and positive findings of HHV-6 in cerebrospinal fluid (CSF) or plasma by polymerase chain reaction (PCR), with or without radiologic evidence of HHV-6 encephalitis. Patients were categorized on the basis of predefined criteria as having *definite* HHV-6 encephalitis (clinical, radiologic, and CSF PCR evidence), *probable* HHV-6 encephalitis (clinical and radiologic evidence only), and *possible* HHV-6 encephalitis (microbiologic evidence with atypical clinical disease without radiologic evidence).

Qualitative detection of HHV-6 was performed by Mayo Medical Laboratories (Rochester, MN) using a laboratory-developed assay [9]. Viral nucleic acids were extracted with the MagNA Pure 1.0 or 2.0 System (Roche Life Science) and detected by PCR. The PCR primers targeted the immediate early gene of HHV-6 and generated a 195-bp amplicon, which was detected by fluorescence resonance energy transfer probes using the LightCycler 2.0 System (Roche Diagnostics).

HHV-6 quantitative testing was performed using real-time PCR by either ARUP Laboratories (Salt Lake City, UT) or Quest Diagnostics (Minneapolis, MN). Descriptive statistics were used to summarize the data.

RESULTS

Ten patients with leukemia (n = 5), lymphoma (n = 2), and other hematologic cancers (n = 3) met the criteria for definite (n = 8), probable (n = 1), and possible (n = 1) HHV-6 encephalitis (Table 1). All except 1 were allogeneic HSCT recipients (3 UCB and 6 matched unrelated donors). There were a total of 531 patients who underwent allogeneic HSCT, including 42 who had UCB transplant, during the study period. Nine allogeneic HSCT patients met the study inclusion criteria. Thus, the incidence of HHV-6 encephalitis among all allogeneic HSCT recipients during the study period was 1.7% overall (9/531) and 7.1% (3/42) among those with UCB transplant. Among the 9 HSCT patients, the median time to onset of symptoms (interquartile range) was 23 (20.5–29.5) days after transplant. Individual patient findings are shown in Supplementary Table 1.

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Table 1. Clinical Characteristics and Outcomes of 10 Patients With HHV-6 Encephalitis

Variable	Value[a] (n = 10)
Men	6 (60%)
Age, y	52.5 (39.3–58.3)
HSCT	9 (90%)
Allogeneic, matched, unrelated donor PSCT	6
UCB transplant	3
Day of symptom presentation post-transplant	23 (20.5–29.5)
Time to diagnosis, d	4.5
Prediagnosis or concomitant conditions	9 (100%) (n = 9)
GVHD	5
Engraftment	4
CMV reactivation	2
Symptom presentation	
Confusion	9 (90%)
Amnesia	6 (60%)
Fever	5 (50%)
Rash	5 (50%)[b]
Headache	2 (20%)
Seizure	2 (20%)
Absolute lymphocyte count at presentation, $\times 10^9$/L	0.385 (0.128–0.822)[c]
Absolute neutrophil count at presentation, $\times 10^9$/L	2.301 (0.339–5.975)[d]
Positive plasma HHV-6 PCR	8 (80%)
Positive CSF HHV-6 PCR	9 (90%)[e]
CSF analysis	(n = 9)
TNC >5 cells/μL	5 (56%)
Protein >35 mg/dL	8 (89%)
MRI findings at presentation	
Bilateral mesial temporal lobe T2 signal	5 (50%)
Bilateral increased T2 hippocampal signal	4 (40%)
Normal	1 (10%)
EEG findings	(n = 6)
Nonspecific slow-wave changes	5 (83%)
Right temporal electrographic seizure	1 (17%)
Antiviral therapy	
Ganciclovir	10 (100%)
Foscarnet	2 (20%)
Duration of therapy, d	27.5 (21–39.5)
Follow-up MRI findings	(n = 6)
Residual deficit	6 (100%)
Hippocampal atrophy	3 (50%)
Improvement	1 (17%)
No change	2 (33%)
Death	5 (50%)[f]

Abbreviations: CMV, cytomegalovirus; CSF, cerebrospinal fluid; EEG, electroencephalography; GVHD, graft-vs-host disease; HHV-6, human herpesvirus 6; HSCT, hematopoietic stem cell transplant; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PSCT, peripheral stem cell transplant; TNC, total nucleated cells; UCB, umbilical cord blood.

[a]Values are No. of patients (%) or median (interquartile range).

[b]Skin biopsy showed GVHD in all 5 cases.

[c]Reference range, 1.0–3.0 × 10^9/L.

[d]Reference range, 1.70–7.00 × 10^9/L.

[e]CSF testing was not performed for 1 probable case because of severe thrombocytopenia, but the patient had HHV viremia and compatible clinical and radiographic findings.

[f]None directly due to HHV-6 encephalitis.

Definite HHV-6 Encephalitis

Among the 8 patients with definite HHV-6 encephalitis, all had compatible clinical symptoms and were positive for HHV-6 in the CSF by PCR. The symptoms included confusion (n = 7, 88%), maculopapular rash (n = 5, 62%), retrograde amnesia (n = 4, 50%), fever (n = 4, 50%), and generalized tonic-clonic seizures (n = 2, 25%). CSF analysis was performed in all 8 cases, which showed mild pleocytosis (white blood cell count, 5–22 × 10^9/L) in 6 and increased protein levels and positive qualitative HHV-6 PCR results in all. Quantitative HHV-6 CSF PCR was performed in only 2 cases, showing 34 120 and 79 200 copies/mL. Qualitative plasma HHV-6 PCR was positive in 6 patients; quantitative PCR analysis was performed in 5 of these patients, with results ranging from <500 to 792 000 copies/mL. Plasma HHV-6 PCR was negative in 2 cases despite having positive CSF PCR results. Brain magnetic resonance imaging (MRI) findings were normal in 1 case (Supplementary Table 1). The most common abnormality on MRI was increased T2 signal in the bilateral hippocampus (n = 4, 50%) and mesial temporal lobe (n = 3, 38%). All patients received induction dosing of intravenous ganciclovir for a median duration (range) of 27 (10–41) days. Maintenance therapy with valganciclovir was given in only 3 cases, which ranged from 10 to 77 days.

Follow-up MRI was performed at 4 to 40 weeks in 5 patients, which showed moderate to severe bilateral hippocampal atrophy in 3 cases. All 3 of these patients had residual neurologic deficits, including residual expressive aphasia or persistent memory deficits at 6-month follow-up. Another patient had persistent memory deficits and dysphagia despite improvement in findings on MRI at 4 weeks. In the fifth patient, MRI results at the time of diagnosis and follow-up were normal despite having recurrent headaches and confusion.

Follow-up clinical data were available for all 8 patients, with a median follow-up duration (range) of 20 months (10 days to 5.6 years); of these, 5 had residual neurologic deficits, which included anterograde amnesia, expressive aphasia, recurrent headaches, intermittent confusion, and persistent memory deficits. Four patients eventually died, but no deaths were due to HHV-6 encephalitis. In 3 of these cases, the management was transitioned to comfort care because of complications of graft-vs-host disease and bone marrow transplant; 1 patient died of massive gastrointestinal tract bleeding.

Probable HHV-6 Encephalitis

One patient with UCB transplant for underlying acute myeloid leukemia was identified as having probable HHV-6 encephalitis; clinical symptoms and imaging findings were consistent with HHV-6 encephalitis, and plasma HHV-6 PCR results were positive. CSF analysis was not performed because of severe thrombocytopenia. Clinical symptoms included amnesia and confusion. MRI showed enhancement in the basal ganglia and parasagittal right frontal lobe. The patient was treated with ganciclovir but died 2 months after diagnosis of multiorgan failure in the setting of a fungal pneumonia.

Possible HHV-6 Encephalitis

One patient who underwent allogeneic HSCT for multiple myeloma was identified as having possible HHV-6 encephalitis. Amnesia with confusion and retinitis developed on post-transplant day 429, at which time quantitative CSF and plasma analysis were positive for HHV-6. Despite clinical improvement, the HHV-6 load remained greater than 2×10^6 copies/mL, which suggested that this case was reactivated, chromosomally integrated HHV-6. MRI in this case showed dural thickening, with a follow-up MRI at 12 weeks showing no changes.

DISCUSSION

HHV-6 was first recognized as a cause of encephalitis after allogeneic HSCT in 1994 [10]. The incidence rate of HHV-6 encephalitis found in our patients is consistent with the incidence previously reported in the literature of up to 1.4% in all HSCTs and 10% in those with UCB transplant [11].

The classic presentation of HHV-6 encephalitis is post-transplant limbic encephalitis. In our patients, the predominant symptoms were confusion and amnesia. Two patients had generalized tonic-clonic seizures. Five patients also had rash, but biopsy findings in all these patients were consistent with GVHD.

Definitive diagnosis typically requires detection of HHV-6 DNA in the CSF with an accompanying clinical picture. CSF examination findings in our patients were either normal or showed increased protein levels and pleocytosis, which is consistent with the previously published literature [12]. CSF PCR was positive in 9 of 10 patients, and CSF analysis was not performed in 1 case.

In patients with a high clinical suspicion for HHV-6 encephalitis, negative plasma PCR results do not rule out diagnosis, as is evident in our case series. This is also supported by the fact that preemptive therapy may not prevent all cases of HHV-6; in some patients, encephalopathy may develop even before high-level viremia develops [13]. Positive results should be interpreted in the context of clinical presentation; especially in those with an extremely high viral load (>500 000), chromosomally integrated HHV-6 should be considered, such as in our case of possible HHV-6 encephalitis [14].

HHV-6 is unique among the *Herpesviridae* because of its ability to integrate into the human chromosome in the telomere region. In our 1 patient with possible HHV-6 encephalitis, the quantitative plasma PCR count was >2 million copies/mL, which strongly suggests chromosomally integrated HHV-6 DNA. Additional testing to rule out chromosomally integrated DNA was not performed, as a consensus statement has suggested that a HHV-6 viral load >1 million copies is consistent with chromosomally integrated HHV-6 DNA [14].

MRI typically shows hyperintensities in the amygdala and hippocampal region, which were also seen in half our patients [12, 15]. Follow-up MRI was performed in 6 patients, which showed hippocampal atrophy; this may explain the high rates of persistent neurologic deficits in patients with HHV-6 encephalitis. Persistent neurologic deficits, including residual expressive aphasia, intermittent mental status changes, and memory deficits, were noted in 6 of 8 patients for whom follow-up was available. This finding is also consistent with loss of neurons in the amygdala and hippocampus found on pathologic analysis [12, 16].

The antiviral agents with in vitro activity against HHV-6 include foscarnet, ganciclovir, and cidofovir. No randomized trials have examined their efficacy in this setting, but small studies have shown decreases in viremia and better neurologic response rates after treatment with either foscarnet or ganciclovir [17–19]. All of our patients received ganciclovir. In 1 patient with suspected HHV-6 retinitis, foscarnet was added to the ganciclovir, but prolonged retinal inflammation still developed. In another patient, ganciclovir was used for 9 weeks, followed by foscarnet for another 20 weeks, and no residual neurologic deficits were noted at the end of therapy.

Our study has several limitations, including a small sample size, lack of quantitative HHV-6 PCR for most patients, and absence of follow-up imaging in most of the patients.

CONCLUSIONS

This study highlights many challenges associated with diagnosis of HHV-6 encephalitis. Although reactivation is common, clinically significant disease in the form of encephalitis is rare. Screening for asymptomatic HSCT patients is generally not recommended, although this practice varies by institution. Given the lack of a standardized molecular assay and the unpredictable viral replication kinetics, our institutional protocol is to screen for HHV-6 reactivation only in the context of a clinically compatible syndrome. Interestingly, a negative HHV-6 plasma PCR result in the blood or plasma does not rule out the diagnosis, and CSF cell count may be normal in some patients. Our study further reports that patients with HHV-6 limbic encephalitis suffer, in the long term, persistent neurologic deficits; this could be explained by the radiologic findings of moderate to severe bilateral hippocampal atrophy on MRI. Follow-up imaging may be helpful in those with persistent neurologic deficits to determine prognosis.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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