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Human Herpesvirus 6 Encephalitis in Immunocompetent and Immunocompromised Hosts

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Abstract

Objective

The aim of this study was to analyze the clinical, radiologic, and biological features associated with human herpesvirus 6 (HHV-6) encephalitis in immunocompetent and immunocompromised hosts to establish which clinical settings should prompt HHV-6 testing.

Methods

We performed a retrospective research in the virology database of Fondazione IRCCS Policlinico San Matteo (Pavia, Italy) for all patients who tested positive for HHV-6 DNA in the CSF and/or in blood from January 2008 to September 2018 and separately assessed the number of patients meeting the criteria for HHV-6 encephalitis in the group of immunocompetent and immunocompromised hosts.

Results

Of the 926 patients tested for HHV-6 during the period of interest, 45 met the study criteria. Among immunocompetent hosts (n = 17), HHV-6 encephalitis was diagnosed to 4 infants or children presenting with seizures or mild encephalopathy during primary HHV-6 infection (CSF/blood replication ratio <<1 in all cases). Among immunocompromised hosts (n = 28), HHV-6 encephalitis was diagnosed to 7 adolescents/adults with hematologic conditions presenting with altered mental status (7/7), seizures (3/7), vigilance impairment (3/7), behavioral changes (2/7), hyponatremia (2/7), and anterograde amnesia (1/7). Initial brain MRI was altered only in 2 patients, but 6 of the 7 had a CSF/blood replication ratio >1.

Conclusions

The detection of a CSF/blood replication ratio >1 represented a specific feature of immunocompromised patients with HHV-6 encephalitis and could be of special help to establish a diagnosis of HHV-6 encephalitis in hematopoietic stem cell transplant recipients lacking radiologic evidence of limbic involvement.

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Glossary

ciHHV-6 = chromosomally integrated HHV-6; **HHV-6** = human herpesvirus 6; **HSCT** = hematopoietic stem cell transplantation.

Human herpesvirus 6 (HHV-6) is a ubiquitous herpesvirus that commonly infects children younger than 3 years.[1] Primary infection sometimes causes exanthema subitum, a common exanthematic disease among infants that may be accompanied by neurologic manifestations such as febrile seizures and encephalitis.[2–4]

The ability of HHV-6 to cause encephalitis in older children and adults remains debated. Although, indeed, the literature reports some cases of HHV-6 encephalitis in immunocompetent adults, in those cases, the detection of HHV-6 DNA in the CSF more likely reflects chromosomal integration rather than active CNS infection.[5] About 1% of healthy individuals harbor in fact sequences of HHV-6 DNA integrated in their genome,[6] highlighting the need to be extremely careful in the interpretation of the results of PCR testing.

Similarly to other herpesviruses, HHV-6 is able to establish lifelong latency in the host following primary infection and reactivate in the event of immune suppression.[1] HHV-6 reactivation is especially common following hematopoietic stem cell transplantation (HSCT), resulting in delayed engraftment,[7] fever, rash, hepatitis, pneumonitis, and encephalitis.[1] HHV-6 encephalitis is typical of the early posttransplantation period and has been classically described as a limbic encephalitis.[8] Nonetheless, some reports suggest that the spectrum of neurologic manifestations associated with HHV-6 in HSCT recipients might be much broader.[9]

The lack of clarity on the phenotypes associated with HHV-6 encephalitis in immunocompetent and immunocompromised individuals has hampered to reach a consensus on the criteria that should guide HHV-6 testing and interpretation in immunocompetent and immunocompromised hosts, with a high risk of misdiagnosis and a waste of economic resources. In this study, we analyzed a large cohort of patients who tested positive for HHV-6 in the CSF and/or in blood with the aim to define the phenotypes associated with HHV-6 encephalitis in immunocompetent and immunocompromised individuals and pinpoint which clinical settings should prompt HHV-6 testing.

Methods

We performed a retrospective research in the virology database of Fondazione IRCCS Policlinico San Matteo (Pavia, Italy) for all patients tested for HHV-6 DNA in the CSF using standard PCR assays from January 2008 to September 2018. The medical records from all patients who tested positive for HHV-6 DNA in the CSF and/or in whole blood during the period of interest were reviewed by a trained team of physicians. Patients with insufficient clinical information, patients without neurologic symptoms or tested more than 15 days after neurologic symptom onset were excluded from the study. We separately assessed the number of patients meeting the criteria for febrile seizures/encephalitis in the context of primary HHV-6 infection[2] and for HHV-6 encephalitis due to viral reactivation[10] (table 1) in the group of immunocompetent and immunocompromised hosts. Hair follicle testing was performed in all patients who tested positive for HHV-6 DNA in whole blood and CSF and who had viral loads in blood exceeding 10^6 copies/mL.[11] Patients who tested positive for HHV-6 DNA on hair follicles were considered as having chromosomally integrated HHV-6 (ciHHV-6).[11]

Standard Protocol Approvals, Registrations, and Patient Consents

Ethic approval was obtained from local institutional review boards.

Statistical Analyses

Statistical analyses were performed using the software R, version 3.6.1. Descriptive statistics were used to summarize quantitative data. The distribution of categorical variables between groups was assessed using the Fisher test. The established threshold for statistical significance was $p = 0.05$.

Data Availability

Additional data can be made available on request to the authors.

Results

Of the 926 patients who had their CSF tested for HHV-6 DNA during the period of interest, 45 met the study criteria (figure e-1, links.lww.com/NXI/A384). Thirty patients were children/adolescents (aged <18 years) (30/45, 67%), and 15 were adults (aged ≥18 years) (15/45, 33%). Seventeen patients were immunocompetent (17/45, 38%) and 28 patients immunocompromised (28/45, 62%). The main clinical characteristics in the whole cohort (n = 45), in the group of immunocompetent (n = 17), and in the group of immunocompromised (n = 28) patients are reported in table e-1.

Immunocompetent Hosts

The median age in the group of immunocompetent patients was 2.7 years (range: 0.0–77.0 years). Fever and rash were present in 9 (9/17, 53%) and 3 (3/17, 18%) patients, respectively. Neurologic symptoms included altered mental status (6/17, 35%),

Table 1 Diagnostic Criteria Used for the Definition of Febrile Seizures or Encephalitis in the Context of Primary Human Herpesvirus 6 (HHV-6) Infection and for the Definition of HHV-6 Encephalitis Due to Viral Reactivation

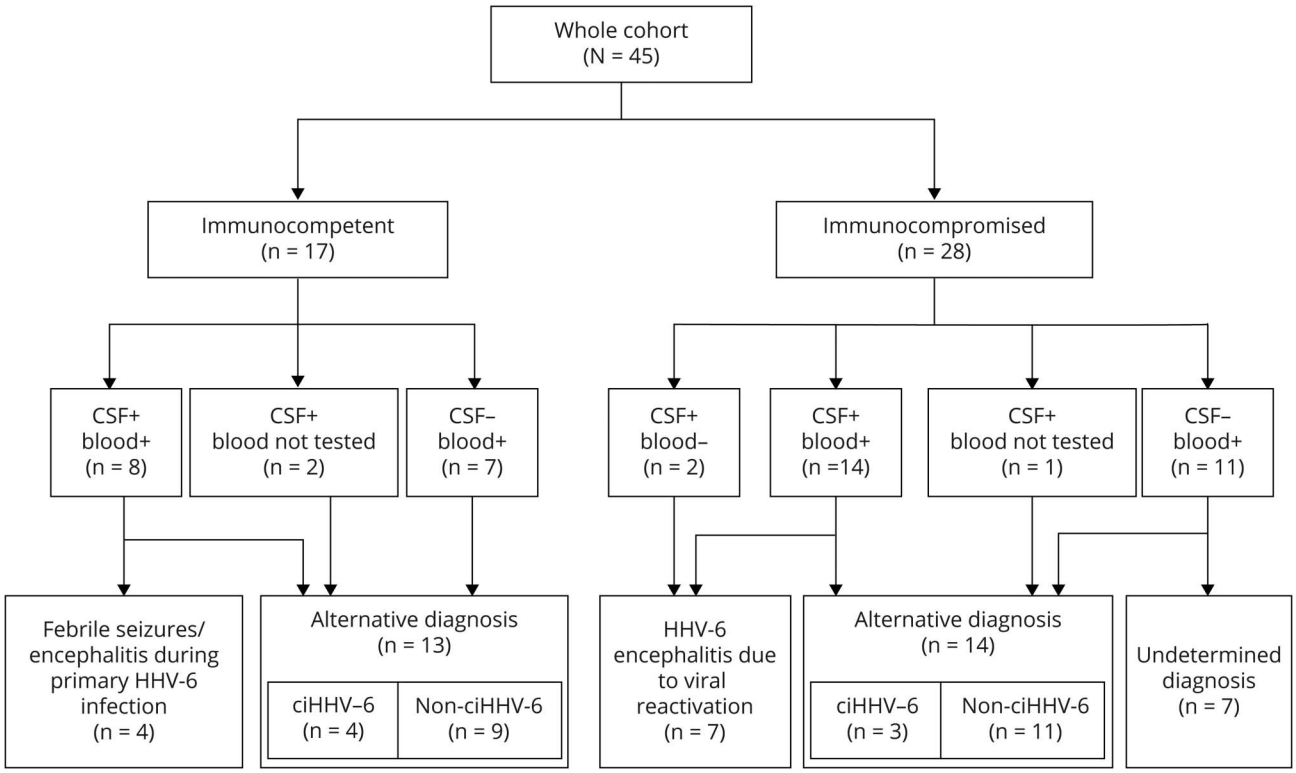
Febrile seizures or encephalitis during primary HHV-6 infection, modified from Ward et al., 2005[2]
(1) Children presenting with suspected encephalitis and/or severe illness with fever and convulsions
(2) HHV-6 DNA detection in blood not attributable to chromosomal integration
(3) Exclusion of alternative etiologies that could explain clinical symptoms or findings
HHV-6 encephalitis due to viral reactivation, from Bhanushali et al., 2013[10]
(1) Clinical symptoms of encephalitis (i.e., altered mental status and/or amnesia and/or seizures)
(2) Presence of HHV-6 in the CSF
(3) Exclusion of alternative etiologies that could explain clinical symptoms or findings

seizures (3/17, 18%), and focal deficits (8/17, 47%). Eight patients tested positive for HHV-6 DNA in both CSF and blood (8/17, 47%), 2 patients tested positive in the CSF but were not tested in blood (2/17, 12%), and 7 patients tested positive only in blood (7/17, 41%). Regardless of HHV-6 positivity in the CSF, all immunocompetent individuals had a CSF/blood replication ratio <1. Final diagnosis was of febrile seizures/encephalitis in the context of primary HHV-6 infection in 4 patients (4/17, 24%) and other condition unrelated to HHV-6 in the remaining 13 cases (13/17, 76%) (figure 1).

Febrile Seizures/Encephalitis in the Context of Primary HHV-6 Infection

The main clinical and biological features in the 4 immunocompetent individuals meeting the diagnostic criteria for febrile seizures/encephalitis during primary HHV-6 infection are summarized in table 2. All 4 patients were infants or children younger than 2 years presenting with fever, with or without rash. Neurologic manifestations included seizures in 2 patients and irritability in other 2. All 4 patients tested positive for HHV-6 in both blood and

Figure 1 Flowchart Diagram Illustrating Final Diagnoses Depending on the Immunologic Status of the Host and the Compartment(s) of Viral Replication



ciHHV-6 = chromosomally integrated human herpesvirus 6.

Table 2 Clinical and Paraclinical Characteristics in the 4 Immunocompetent Infants Diagnosed With Febrile Seizures/Encephalitis in the Context of Primary HHV-6 Infection

Patient	Age, y	Sex	Systemic symptoms	Neurologic symptoms	HHV-6 copies/mL in the CSF	HHV-6 copies/mL in blood	CSF/blood replication ratio	Clinical evolution
1	0.9	F	Fever and rash	Seizures	14,060	495,540	0.03	Complete recovery
2	0.9	M	Fever	Irritability and behavioral changes	80	21,060	0.004	Complete recovery
3	1.8	M	Fever	Seizures	740	149,400	0.005	Complete recovery
4	0.1	F	Fever and rash	Irritability	40	4,750	0.008	Complete recovery

CSF, with a median viral load of 410 copies/mL in the CSF (range: 40–14,060 copies/mL) and 85,230 copies/mL in blood (range: 4,750–495,540 copies/mL), resulting in a CSF/blood replication ratio <<1 in all cases. CSF pleocytosis was present in 1 case of 3. A single patient underwent brain MRI (patient 1 in table 2), which showed normal findings. None of the patients received specific antiviral treatment. All of them recovered completely within a week from hospital admission.

Alternative Diagnoses

Alternative diagnoses in the 13 immunocompetent patients who did not meet the criteria for febrile seizures or encephalitis during primary HHV-6 infection included post/para-infectious neurologic syndromes (n = 6), MS (n = 1), aseptic meningitis (n = 1), *Listeria monocytogenes* meningoencephalitis (n = 1), febrile convulsions (n = 1), primary CNS lymphoma (n = 1), cranial mononeuritis (n = 1), and bacterial spondylodiscitis (n = 1).

In 4 patients, HHV-6 DNA detection in blood and CSF reflected chromosomal integration. Patients with ciHHV-6 had positive PCR results in both the CSF and blood, with viral loads in the order of magnitude of millions copies of HHV-6 DNA in blood (median: 6,630,575 copies/mL, range: 1,081,400–7,700,000 copies/mL) and thousands copies in the CSF (median: 6,640 copies/mL, range: 2,640–18,520 copies/mL). The median viral load in the 9 patients without ciHHV-6 was instead of 3,330 copies/mL in blood (range: 300–33,930) and 0 copies/mL in the CSF (range: 0–40). Individual patient data for patients in this group are reported in table e-2 (links.lww.com/NXI/A384).

Immunocompromised Hosts

The median age in the group of immunocompromised patients was 14.3 years (range: 2.0–88.6 years). The underlying condition of immune suppression was represented by a hematologic disorder in 27 of the 28 cases. Patients in this group had been heavily treated, having previously received high-dose chemotherapy (25/27, 93%), monoclonal antibodies (9/17, 53%), and hematopoietic stem cell transplantation (23/27, 85%). The remaining patient was a solid organ transplant recipient who was still receiving immune suppressants for the prevention of graft vs host disease. Fever was an accompanying feature in 4 cases (4/28, 14%) and rash in 2 (2/28, 7%). Neurologic symptoms included altered mental status (17/28, 61%), seizures (11/28, 39%), and focal deficits (5/28, 18%). Fourteen patients tested positive for HHV-6 DNA in both CSF and blood (14/28, 50%), 2 patients tested positive only in the CSF (2/28, 7%), 1 patient tested positive in the CSF but blood was not investigated (1/28, 4%), and 11 patients tested positive only in blood (11/28, 39%). Final diagnosis was of HHV-6 encephalitis due to viral reactivation in 7 patients (7/28, 25%), other condition unrelated to HHV-6 in 14 patients (14/28, 50%), and remained undetermined in 7 cases (7/28, 25%) (figure 1).

HHV-6 Encephalitis Due to Viral Reactivation

Table 3 summarizes the main clinical and paraclinical features in the 7 immunocompromised patients who met the criteria for HHV-6 encephalitis due to viral reactivation. Five patients were adults, and 2 were adolescents. All patients were affected with hematologic conditions, and 6 of the 7 had received allogeneic HSCT (median delay from HSCT to neurologic symptoms: +91 days, range: 20–630). A single patient had systemic symptoms including fever, pruritus, and rash (patient 7 in table 3).

All 7 patients presented with altered mental status, which was associated with seizures (3/7, 43%), vigilance impairment (3/7, 43%), behavioral changes (2/7, 29%), hyponatremia (2/7, 29%), anterograde amnesia (1/7, 14%), and/or dysautonomia (1/7, 14%). CSF pleocytosis was detected in only half of cases (2/4, 50%) (patients 1 and 3 in table 3). Initial brain MRI, performed from 2 to 4 days after symptom onset, was altered in only 2 patients of 6 (2/6, 33%) (patients 3 and 7 in table 3). However, a second brain MRI, performed a median of 2 weeks after the first, disclosed radiologic alterations compatible with HHV-6 encephalitis in 2 additional patients who initially had normal findings (figure 2).

HHV-6 replication was limited to the CSF in 2 patients, whereas the remaining 5 also tested positive in blood. The median viral load in the CSF was 49,200 copies/mL (range:

Table 3 Clinical and Paraclinical Characteristics in the 7 Immunocompromised Patients Diagnosed With HHV-6 Encephalitis

Patient	Age, y	Sex	Hematologic condition	Mab	HSCT (days from HSCT and symptom onset)	Neurologic symptoms	Brain MRI (days from symptom onset)	HHV-6 copies/mL in the CSF	HHV-6 copies/mL in blood	CSF/blood replication ratio	Clinical evolution
1	58.4	M	NHL	Yes	Yes (+24)	Confusion, anterograde amnesia, behavioral changes, and hyponatremia	Normal (+3 d) → altered (+16 d)	49,200	4,500	10.9	Death because of systemic complications
2	11.7	F	ALL	Yes	Yes (+79)	Confusion, seizures, hyponatremia, and dysautonomia	Normal (+2 d) → altered (+16 d)	6,959,200	174,900	39.8	Favorable
3	63.0	M	CLL	Yes	Yes (+103)	Stupor and confusion	Altered (+2 d)	40	0	∞	Favorable
4	21.2	M	ALL	Yes	Yes (+115)	Confusion and seizures	Not performed	560	300	1.9	Death for sepsis
5	88.6	M	Pancytopenia under investigation	No	No	Stupor, confusion, and myoclonus	Normal (+4 d)	3,080	0	∞	Death because of systemic complications
6	14.0	M	ALL	Yes	Yes (+630)	Confusion and seizures	Normal (+2 d)	96,000	4,230	22.7	Favorable
7	61.5	M	AML	No	Yes (+20)	Confusion, agitation, and stupor	Altered (+4 d)	212,960	378,900	0.56	Death because of general status degradation

Abbreviations: ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; CLL = chronic lymphatic leukemia; HHV-6 = human herpesvirus 6; HSCT = hematopoietic stem cell transplantation; Mab = monoclonal antibody; NHL = non-Hodgkin lymphoma.

40–6,959,200 copies/mL), and the median viral load in blood was 4,230 copies/mL (range: 0–378,900 copies/mL). The CSF/blood replication ratio was >1 in all patients except for the one showing systemic symptoms of HHV-6 infection (fever, rash, and pruritus), in whom HHV-6 viral load prevailed in blood.

All patients received IV ganciclovir, with or without associated foscarnet, except for a single patient who died before receiving antiviral treatment (patient 5 in table 3). A total of 4 patients died during the acute phase as a consequence of intervening systemic complications or general status deterioration (4/7, 57%). The remaining 3 patients survived the infection but experienced mild to moderate cognitive sequelae (3/7, 43%).

Alternative Diagnoses

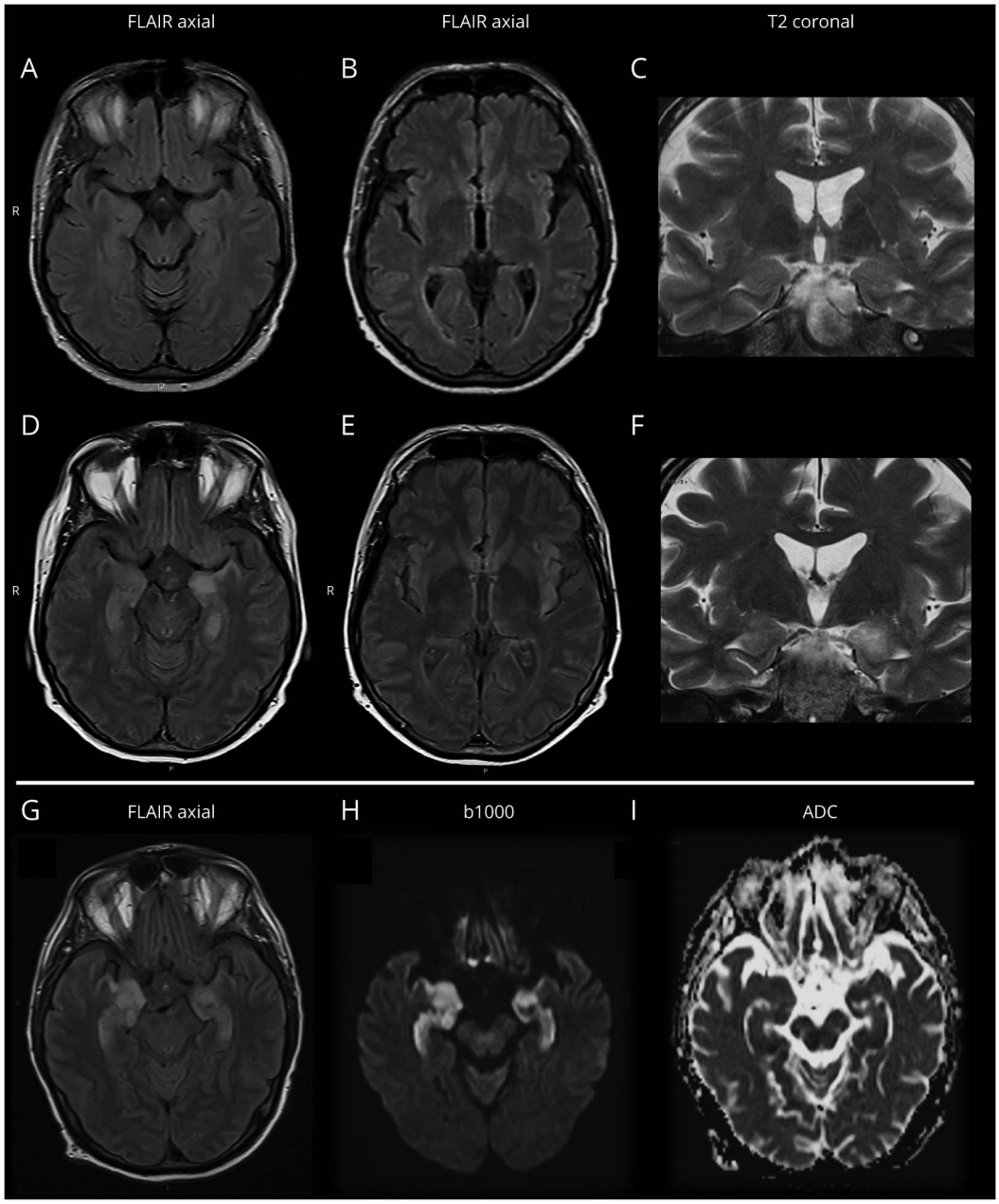
Fourteen immunocompromised patients received alternative diagnoses, including posterior reversible encephalopathy syndrome (n = 2), CNS localizations of their underlying hematologic malignancies (n = 4), cytomegalovirus infection (n = 2), metabolic encephalopathy (n = 2), ischemia (n = 2), inflammatory encephalomyelitis (n = 1) and migraine (n = 1). All patients in this group had HHV-6 viral loads largely prevailing in blood (CSF/blood replication ratio <1).

In 3 patients, HHV-6 DNA detection in blood and CSF reflected chromosomal integration. Patients with ciHHV-6 had viral loads in the order of magnitude of millions copies in blood (median: 572,220 copies/mL, range: 497,200–8,650,000 copies/mL) and thousands copies in the CSF (median: 53,240 copies/mL, range: 1,360–141,140 copies/mL). The median HHV-6 viral load in the 11 remaining patients was of 6,175 copies/mL in blood (range: 100–365,400 copies/mL) and 60 copies/mL in the CSF (range: 0–20,000 copies/mL).

Undetermined Diagnoses

Seven immunocompromised patients remained without a definite etiologic diagnosis despite a comprehensive work-up that included an extensive research for infectious, neoplastic, metabolic, vascular, and autoimmune etiologies. The clinical and paraclinical characteristics of these 7 patients are summarized in table 4. Four patients were children, and 3 were adults. All patients had an underlying hematologic disorder, 6 of the 7 having received allogeneic HSCT. All patients tested

Figure 2 MRI Findings in 2 HSCT Transplant Recipients Developing HHV-6 Encephalitis



Panels A–F (patient 1 in table 4): on initial brain MRI, performed 3 days after symptom onset, no abnormal findings were detected on axial FLAIR (panels A and B) and coronal T2-weighted (panel C) images, though in the presence of motion artifacts. At control MRI, performed 16 days after symptom onset, a quite marked hyperintensity was evident at the level of the left temporo-mesial region, with swelling of the amygdala and the ipsilateral insular cortex on axial FLAIR (panels D and E) and coronal T2-weighted (panel F) images. No diffusivity restriction or gadolinium enhancement was evident (not shown). Panels G–I (patient 7 in table 4): brain MRI performed 4 days after neurologic symptom onset showed bilateral hyperintensity of temporo-mesial structures, prevalent on the right side, on axial FLAIR images (panel G), with a correspondent b1000 hypersignal (panel H) and some areas of true low ADC signal (panel I) but predominant T2 shine through effect. FLAIR = fluid-attenuated inversion recovery; HHV-6 = human herpesvirus 6; HSCT = hematopoietic stem cell transplantation.

positive for HHV-6 only in blood (median: 9,180 copies/mL, range: 400–126,000 copies/mL). Two patients with stupor or seizures arising in a context of fever were diagnosed with systemic HHV-6 reactivation, for which they received IV ganciclovir that led to full recovery (patients 1 and 2 in table 4). Four patients presenting with seizures, encephalopathy, or cerebellar dysfunction had no accompanying fever or rash and spontaneously recovered within few days without specific treatment (patients 3–6 in table 4). The remaining patient (patient 7 in table 4) presented with confusion and anterograde amnesia 1 month after completing HSCT. She had extensive MRI alterations involving temporo-mesial structures and the mammillary bodies of the hypothalamus. HHV-6 viral load was positive in blood (126,000 copies/mL) but undetectable in the CSF. In the inability to distinguish between Wernicke encephalopathy and HHV-6 infection, the

Table 4 Clinical and Paraclinical Characteristics in the 7 Immunocompromised Patients With HHV-6 Replication Limited to Blood and No Definite Cause Identified for Their Neurologic Symptoms

Patient	Age, y	Sex	Hematologic condition	HSCT (days from HSCT and symptom onset)	Systemic symptoms	Neurologic symptoms	Brain MRI (days from symptom onset to MRI)	HHV-6 copies/mL in the CSF	HHV-6 copies/mL in blood	Antiviral treatment	Clinical evolution
1	8.3	F	Lymphoma	Yes (−2)	Fever	Seizures	Not performed	0	9,180	Yes	Complete recovery
2	11.3	M	ALL	No	Fever and rash	Stupor and involuntary movements	Normal (+1 d)	0	400	Yes	Complete recovery
3	2	M	Sickle cell disease	Yes (+24)	None	Seizures	Not performed	0	12,240	No	Complete recovery
4	9.4	M	ALL	Yes (+283)	None	Cerebellar syndrome	Normal (+6 d)	0	4,590	No	Complete recovery
5	18	M	Chronic granulomatous disease	Yes (+66)	None	Seizures	Normal (+2 d)	0	23,760	No	Complete recovery
6	47.2	M	ALL	Yes (+1,256)	None	Epileptic encephalopathy	Normal (+14 d)	0	6,840	No	Complete recovery
7	50	F	Myelodysplastic syndrome	Yes (+38)	None	Confusion and anterograde amnesia	Altered (+1 d)	0	126,000	Yes	Death due to general status deterioration

Abbreviations: ALL = acute lymphoblastic leukemia; HHV-6 = human herpesvirus 6; HSCT = hematopoietic stem cell transplantation.

patient received both vitamin B1 supplementation and IV foscarnet, but, unfortunately, she died few weeks later because of general status deterioration.

Discussion

In this study, we reviewed all patients tested for HHV-6 in the CSF at Fondazione IRCCS Policlinico San Matteo during a period of 10 years. Of the 926 patients tested during this period, only 43 tested positive for HHV-6 in the CSF (43/926, 4.6%), and a much lower number received a diagnosis of febrile seizures/encephalitis during primary HHV-6 infection (3/926, 0.4%) or a diagnosis of HHV-6 encephalitis due to viral reactivation (7/926, 0.8%). These proportions confirm that there is ample room for improvement when it comes to choosing which patients to test. Chromosomal integration was detected in nearly 1% of patients tested (7/926, 0.8%), a proportion similar to the one reported in the literature for the general population.[6]

The strong point of this study was the systematic review of all data concerning viral replication in both CSF and blood, analysis that had never been performed systematically in large cohorts of immunocompetent and immunocompromised hosts and that allowed to confirm the value of the CSF/blood replication ratio for the diagnosis of HHV-6 encephalitis in immunocompromised patients. On the other hand, this study has limitations that are inherent to its retrospective design: clinical presentation and evolution were reconstructed a posteriori from medical records, and data on viral coreplications were interpreted case by case in the light of the immune competence of the host and of individual clinical/paraclinical features. As this distinction is not routinely performed at our laboratory (and could not be performed for the present study due to the exhaustion of most biological samples), in our report, we did not distinguish between HHV-6A and HHV-6B. Although HHV-6A and HHV-6B are now considered as separate species, only HHV-6B has been consistently associated with disease in humans.[6] Based on known epidemiology and association with disease, we would thus expect all cases of febrile seizures/encephalitis during primary infection and all cases of encephalitis due to viral reactivation to be related to HHV-6B and cases of chromosomal integration to be distributed between HHV-6B and HHV-6A.[6]

In immunocompetent patients, the diagnosis of HHV-6 encephalitis was limited to 4 infants younger than 2 years presenting with seizures[2,3] or irritability in the context of a symptomatic primary HHV-6 infection. All 5 infants tested positive for HHV-6 in blood and CSF, with viral loads in blood largely exceeding the viral load in the CSF. Based on the observation that HHV-6 viral loads in the CSF of children developing febrile convulsions or encephalopathy during primary infection are generally low and transient,[6,12] some authors have hypothesized that neurologic symptoms might result from the indirect effects of cytokine release rather than from direct viral CNS infection.[6,13,14] Such pathogenetic mechanism would be consistent with the benign course generally observed in these cases, at least in Caucasian infants.[2,6]

The observation that, in immunocompetent individuals, HHV-6 encephalitis is limited to primary infection[6,15] suggests that testing for HHV-6 should be limited to infants younger than 3 years developing seizures[2,3] or encephalopathy[4] in a febrile context. All diagnostic tests performed outside these constraints not only represent a waste of economic resources but expose to a high risk of misdiagnosis: presenting high viral loads in both blood and CSF, adult immunocompetent patients with ciHHV-6 might in fact be wrongly diagnosed with HHV-6 encephalitis, delaying diagnosis and treatment for their actual condition. Viral loads in the order of thousands copies in the CSF and millions copies in blood should immediately raise a suspicion of ciHHV-6 and prompt confirmative hair follicle testing.[11]

Differently from immunocompetent hosts, immunocompromised subjects are at risk of developing HHV-6 encephalitis through a mechanism of viral reactivation.[6] HSCT and, especially, the early posttransplantation period is known to be a fertile ground for HHV-6 reactivation.[16–18] HHV-6 encephalitis was diagnosed to 7 immunocompromised adolescents or adults in our series having hematologic disorders and a history of allogenic HSCT. In most cases, clinical presentation was dominated by confusion and seizures, whereas more distinctive signs and symptoms such as anterograde amnesia and hyponatremia were present in only a minority of cases.[10] Although important to exclude alternative causes of neurologic deterioration, brain MRI showed typical limbic alterations in only two-thirds of cases and, at times, only when performed several days after symptom onset.[10] These observations suggest that all HSCT recipients presenting with altered mental status, seizures, or vigilance impairment should have their CSF tested for HHV-6, even in the absence of radiologic correlates of limbic involvement. Testing should then be followed by a cautious interpretation of results. Being prone to periodical HHV-6 reactivations, HSCT recipients may have HHV-6 DNA detected in their blood, or even in their CSF, without it being the cause of neurologic symptoms.[19] In this setting, the CSF/blood replication could be a precious tool to guide the clinician in the interpretation of the results of PCR testing. With the exception of a single patient who had systemic symptoms of infection, all immunocompromised patients diagnosed with HHV-6 encephalitis in our series had a CSF/blood replication ratio >1, feature that was exclusive of patients in this group. The CSF/blood replication ratio could thus represent a specific feature to distinguish immunocompromised patients with HHV-6 encephalitis from the remaining immunocompromised patients in whom HHV-6 detection in the CSF represented an incidental finding or reflected chromosomal integration. Being a hallmark of HHV-6 encephalitis in the immunocompromised, the detection of a CSF/blood replication ratio >1 could strengthen the certitude of diagnosis in patients lacking typical clinical and radiologic features or having low viral loads in the CSF, avoiding any delay in the administration of antiviral treatment. Although the role of the CSF/blood replication ratio is not been emphasized in most reports and guidelines, our data strengthen its value for the diagnosis of HHV-6 encephalitis in the immunocompromised so that, in our view, it could be considered a supportive criterion in atypical cases.

The question on whether, in HSCT recipients, HHV-6 replication could be associated with neurologic symptoms, when limited to blood, remains debated. This was the case of few patients in our series, who developed otherwise unexplained neurologic symptoms in a context of systemic HHV-6 reactivation. An original study by Zerr et al.[9] has shown an association between early HHV-6 reactivation in blood following HSCT and the development of delirium and cognitive decline. Patients developing neurologic symptoms did not always have a detectable viral load in the CSF,[9] suggesting that the latter is either modest and/or transient, and thus difficult to detect, or it is not required to develop neurologic symptoms. Future studies will possibly clarify the nature of these neurologic manifestations and their causal relationship with HHV-6 reactivation, as well as the need for preemptive antiviral treatment.[20,21]

In conclusion, our study reinforces the evidence that (1) in immunocompetent hosts, CNS involvement from HHV-6 is limited to infants younger than 3 years presenting with primary infection; (2) HSCT recipients can develop HHV-6 encephalitis as a consequence of viral reactivation, although typical clinical imaging features of limbic encephalitis might be lacking, especially when brain MRI is performed shortly after symptoms onset; and (3) the CSF/blood replication ratio can be of great help to interpret the results of PCR testing and establish an accurate diagnosis of HHV-6 encephalitis in HSCT recipients.

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Appendix Authors

Name	Location	Contribution
Giulia Berzero, MD	IRCCS Mondino Foundation, Pavia, Italy	Study conception and design, clinical data collection, analysis and interpretation of the data, and manuscript drafting and revision for intellectual content
Giulia Campanini, MD	Fondazione IRCCS, Policlinico San Matteo, Pavia, Italy	Virologic data collection and interpretation, manuscript revision for intellectual content
Elisa Vegezzi, MD	IRCCS Mondino Foundation, Pavia, Italy	Clinical data collection, analysis and interpretation of the data, and manuscript revision for intellectual content

Appendix *(continued)*

Name	Location	Contribution
Matteo Paoletti, MD	IRCCS Mondino Foundation, Pavia, Italy	Radiologic data collection and interpretation and manuscript revision for intellectual content
Anna Pichiecchio, MD	IRCCS Mondino Foundation, Pavia, Italy	Radiologic data collection and interpretation and manuscript revision for intellectual content
Anna Maria Simoncelli, MD	Fondazione IRCCS, Policlinico San Matteo, Pavia, Italy	Radiologic data collection and interpretation and manuscript revision for intellectual content
Anna Amelia Colombo, MD	Fondazione IRCCS, Policlinico San Matteo, Pavia, Italy	Clinical data collection, analysis and interpretation of the data, and manuscript revision for intellectual content
Paolo Bernasconi, MD	Fondazione IRCCS, Policlinico San Matteo, Pavia, Italy	Clinical data collection, analysis and interpretation of the data, and manuscript revision for intellectual content
Oscar Borsani, MD	Fondazione IRCCS, Policlinico San Matteo, Pavia, Italy	Clinical data collection, analysis and interpretation of the data, and manuscript revision for intellectual content
Angela Di Matteo, MD	Fondazione IRCCS, Policlinico San Matteo, Pavia, Italy	Clinical data collection, analysis and interpretation of the data, and manuscript revision for intellectual content
Virginia Rossi, MD	Fondazione IRCCS, Policlinico San Matteo, Pavia, Italy	Clinical data collection, analysis and interpretation of the data, and manuscript revision for intellectual content
Thomas Foiadelli, MD	Fondazione IRCCS, Policlinico San Matteo, Pavia, Italy	Clinical data collection, analysis and interpretation of the data, and manuscript revision for intellectual content
Salvatore Savasta, MD	Fondazione IRCCS, Policlinico San Matteo, Pavia, Italy	Clinical data collection, analysis and interpretation of the data, and manuscript revision for intellectual content
Francesca Compagno, MD	Fondazione IRCCS, Policlinico San Matteo, Pavia, Italy	Clinical data collection, analysis and interpretation of the data, and manuscript revision for intellectual content
Marco Zecca, MD	Fondazione IRCCS, Policlinico San Matteo, Pavia, Italy	Clinical data collection, analysis and interpretation of the data, and manuscript revision for intellectual content
Fausto Baldanti, MD	Fondazione IRCCS, Policlinico San Matteo, Pavia, Italy	Virologic data collection and interpretation and manuscript revision for intellectual content

Appendix *(continued)*

Name	Location	Contribution
Enrico Marchioni, MD	IRCCS Mondino Foundation, Pavia, Italy	Study conception and design, clinical data collection, analysis and interpretation of the data, and manuscript revision for intellectual content

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