CAS-076

Human Herpesvirus-6 in Cerebrospinal Fluid: Innocent Bystander or True Pathogen?

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Summary

- Detection of Human Herpesvirus 6 (HHV-6) in cerebrospinal fluid can signal active infection, viral reactivation, or latent DNA.
- Using the QIAstat-Dx ME Panel, four HHV-6–positive cases were identified across different age and immune groups. Two infants showed mild, self-limiting illness and recovered fully. In contrast, two adults with co-infections—pneumococcal meningoencephalitis and advanced HIV—had severe neurological disease and died.
- Hence, HHV-6 positivity interpretation must consider immune status, co-pathogens, and viral load ratio between CSF and blood. Careful clinical and imaging correlation is essential to distinguish true HHV-6 encephalitis from incidental or reactivated infection.

Introduction

Human Herpesvirus 6 (HHV-6) is a member of *Roseolovirus* genus under *Betaherpesvirinae* subfamily. Detection in cerebrospinal fluid raises diagnostic and therapeutic challenge as it can be either primary infection or viral latency. We report a case series highlighting HHV-6 related CNS involvement across different age group and immune status detected using automated multiplex panel – Qiastat ME panel.

Case 1 is a 3-month-old infant presented with persistent vomiting, gastroenteritis, hypovolemic shock and suspected seizure at home. Initial peripheral blood and CSF culture was negative. Subsequent CSF detected HHV-6. The infant improved with supportive care and empirical antibiotics, and was discharged well with a working diagnosis of septic shock and suspected inborn error of metabolism (IEM), pending further investigation.

Case 2 involves a 6-month-old male infant with complex febrile seizure. CSF multiplex PCR revealed HHV-6, while at the same time nasopharyngeal swab was also positive for rhinovirus/enterovirus. The child responded to anticonvulsants and a short course of antibiotics, and was discharged well.

Case 3 describes a previously healthy 30-year-old Myanmar man presenting with acute meningoencephalitis, requiring intubation and intensive care. CSF multiplex PCR detected both *Streptococcus pneumoniae* and HHV-6. Despite empirical treatment including ceftriaxone and acyclovir, the patient developed multi-organ failure and succumbed to hypoxic-ischemic encephalopathy after 8 days.

Case 4 reports on a 32-year-old male with newly diagnosed HIV and hepatitis B co-infection who developed progressive neurologic symptoms, disseminated tuberculosis, and neurotoxoplasmosis. HHV-6 was detected in the CSF during a deterioration phase. Despite broad antimicrobial and supportive therapy, the patient died after prolonged hospitalization due to AIDS-related complications.
Table 1 outlines the comparison between the cases.

Table 1. Comparison of cases

Parameter	Case 1	Case 2	Case 3	Case 4
Total white count (x10^9/L)	23.53 Neutrophils: 68.9%, Lymphocytes:15.5 %, Monocytes: 15.5%	6.8 (Neutrophils: 62.1%, Lymphocytes: 28.9%, Monocytes: 8.5%)	30.2 (Neutrophils: 84.9%, Lymphocytes:6.6%, Monocytes: 8.0%)	3.0 (Neutrophils: 70.6%, Lymphocytes: 22.0%, Monocytes: 4.7 %)
C-Reactive Protein (mg/dl)	Not available	1.39	28.36	Multiple blood taking with range of 1.5 to 8.6
CSF glucose (mmol/L) (normal 2.2-3.9)	5.8	3.9	<0.28	2.83
CSF protein (mg/L) (normal 150-400)	0.62	0.23	32356	1071
CSF polymorphonuclear cells (cells/mm3)	20	0	Blood stained	0
CSF lymphocytes (cells/mm3)	0	0	0	0
CSF multiplex PCR HHV-6 CT value	33.0	37.7	18.2	37.7
Other alternative diagnosis	Inborn error of metabolism	Rhinovirus/ enterovirus (CT value 35.0)	Streptococcus Pneumonia (CT value 15.9)	HIV, Disseminated tuberculosis, neurotoxoplasmosis
Treatment directed towards HHV-6	No	No	No (Treated with ceftriaxone for streptococcal meningitis)	Yes Ganciclovir (later stopped due to leukopenia)
Course of disease	Recovered well	Recovered well	Passed away	Passed away

Discussion

Primary infection of HHV-6 commonly cause acute febrile illness in children up to 3 years old with rarely neurologic symptom (Agut 2011) and majority recovered completely without specific antiviral given(Berzero et al. 2021), as demonstrated in case 1 & case 2. Diagnosis of HHV-6 as primary pathogen in adults is challenging as nearly all individual are already exposed to the virus by adulthood. The presence of HHV-6 in cerebrospinal fluid may also indicate chromosomally integrated HHV-6 (ciHHV-6) seen in about 1% of general population (Agut et al. 2015). Both HHV-6A and HHV-6B can undergo chromosomal integration but primary infections are associated exclusively with HHV-6B (Ward et al. 2007). Most HHV-6 encephalitis cases reported are among the immunocompromised population due to reactivation (Webb et al. 2024). Apart from this, immunomodulation during HHV-6 reactivation may boost activity of immune system leading to enhancement of certain disease (Agut et al. 2015) as seen in Case 3 and 4. MRI findings usually will show symmetrical hyperintense signal in the limbic system specifically the mesial temporal lobes, hippocampus and amygdala (Marcelis et al. 2022) however these findings are not seen in Case 3 and 4. One helpful tool in differentiating HHV-6 encephalitis from HHV-6 bystander is the ratio of HHV-6 viral load in CSF compared to the viral load in the blood. CSF/blood replication ration of >1 suggest HHV-6 encephalitis (Berzero et al. 2021). Unfortunately, whole blood PCR was not tested in all cases.

Conclusion

Human Herpesvirus-6 (HHV-6) infection affects people at different age of life. However, the severity of infection is less in primary infection especially in children as compared to infection in adults especially in the presence of co-infection. Therefore, establishing a correlation between HHV-6 detection in the CSF and the patient's overall clinical presentation is crucial. A comprehensive evaluation of the full clinical picture, including the patient's level of immunosuppression, clinical symptoms, laboratory results, and imaging findings is therefore important.

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