Human Herpesvirus 6 (HHV-6) in the Cerebrospinal Fluid of a Newborn: Active Infection or Chromosomal Integration?

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Abstract

This article describes a case of congenital human herpesvirus-6 (HHV-6) infection in a five-day-old infant initially suspected of having meningoencephalitis. Despite positive detection of HHV-6 in cerebrospinal fluid, subsequent evaluation suggested vertical transmission of integrated virus rather than acute infection. High viral loads in cerebral spinal fluid, maternal blood, and neonatal blood supported this hypothesis. Normal neurodevelopmental evaluations during the first year of life further supported the suspicion of integrated HHV-6. This case highlights the importance of differentiating active HHV-6 infection from integrated virus and advocates whole blood quantitative PCR testing to avoid unnecessary antiviral treatment in immunocompetent infants.

Introduction

Human Herpes Virus-6 (HHV-6) is a member of the Herpesviridae family. It usually causes an asymptomatic infection or a benign childhood disease named "roseola" in young children. Serious infections more commonly affect immunocompromised patients (1). After primary infection it remains latent and may reactivate later. But the HHV-6 complete genome can also be integrated into a human chromosome in somatic cells or even in germline cells (2).

Congenital HHV-6 infection can result from transplacental transmission during a primary infection or a reinfection or more commonly from vertical transmission of inherited chromosomally integrated HHV-6 (iciHHV-6) (3-5). iciHHV-6 carriers have at least one copy of the HHV-6 genome in every nucleated cell and can therefore transmit it in a mendelian way (6). The prevalence of iciHHV-6 is 0.2 to 2.5% in the general population (3, 4).

With the increased use of multiplex molecular diagnostic panels, HHV-6 can be more easily identified in cerebrospinal fluid (CSF). Understanding the clinical significance of this finding is essential to avoid unnecessary investigations or treatments.

We report a case of congenital HHV-6 infection in a newborn admitted with a suspected meningoencephalitis.

Case report

A five-day-old male newborn was admitted to our neonatal intensive care unit (NICU) for fever (maximum temperature, 38.4°C) and irritability. His heart and respiratory rates were 137 and 30 bpm respectively, his saturation was 96%, and his blood pressure was 96/70 mmHg. He had a bulging fontanel and a mottled skin. The rest of the clinical examination was unremarkable.

Pregnancy was uneventful except for an episode of *Chlamydia trachomatis* infection at 12 weeks of gestation, which was successfully treated with azithromycin. The infant was born vaginally at 38 weeks of gestational age. He had an Apgar score of 9/10/10. There were no signs of chorioamnionitis or risk factors for early onset sepsis (no maternal GBS colonization, clear amniotic fluid and rupture of membranes 4 hours prior to delivery).

On admission, he had a full sepsis workup and broad intravenous antibiotic therapy (amoxicillin, amikacin, cefotaxime). Blood tests showed a normal white blood cell count (10,530 cells/mm³; 51.2% neutrophils) and no C-reactive protein (CRP) elevation (0.6 mg/L - normal value < 5 mg/L). Cerebrospinal fluid (CSF) analysis showed a slightly elevated protein concentration (1.63 g/L; normal value <1 g/L) and white blood cell count (29 cells/mm³; normal value for age is 20-22 cells/mm³) but the lumbar puncture was traumatic (131 red blood cells/mm³). CSF glucose level was 28.3 mg/dL but concomitant glycemia was unknown. CSF multiplex polymerase chain reaction (PCR) assay (BioFire FilmArray Meningitis/Encephalitis panel) performed on CSF was positive for HHV-6 only.

Blood and CSF cultures were negative at 48 hours. Treatment with intravenous ganciclovir (6 mg/kg q12h) was started on day 5 of life due to persistent irritability and lack of a clear explanation. Antibiotics were discontinued on day 7 of life.

A brain ultrasound and a brain magnetic resonance imaging on day 10 of life showed a grade II left lateral ventricular and intraventricular sub-ependymal hemorrhage. However, the correlation between such images, our patient's irritability, and the HHV-6 encephalitis and/or iciHHV-6 remains inconclusive. There were no other central nervous system abnormalities. An electroencephalogram on day 10 of life and auditory, visual and somatosensory evoked potentials on day 12 of life were normal. The added value of such evoked potentials is debatable. However, the daily clinical evolution of this patient was a concern, and we tend to lower the threshold for such assessment in all our patients with neurological signs. The patient recovered rapidly and remained afebrile after admission to the NICU. Intravenous ganciclovir was switched to oral valganciclovir (15 mg/kg q12h) on day 10 of life. The patient was discharged on day 13 and the treatment was discontinued after 3 weeks.

The etiological workup was completed with quantitative HHV-6 PCRs on day 7 of life (AltoStar HHV6 PCR kit). They revealed very high viral loads in CSF (106,000 copies/mL) and in maternal and neonatal whole blood samples (6,105,270 copies/mL and 4,021,580 copies/mL, respectively). This suggested an iciHHV-6 rather than an acute primary infection.

Follow-up during the first year of life was unremarkable. At 12 months of age, neurodevelopmental assessments (Amiel-Tison and Gosselin; Bailey Scales of Infant and Toddler Development-III) were normal.

Discussion

Herein we report a case of congenital HHV-6 infection in a 5-day-old infant initially suspected of meningoencephalitis. PCR performed on CSF and whole blood samples did not confirm this diagnosis but rather suggested a vertical transmission of integrated virus.

The multiplex PCR meningoencephalitis (M/E) panel can detect 6 bacteria, 7 viruses, and 1 yeast in CSF in about 1 hour and is therefore increasingly used (7). Interpretation of a positive result for HHV-6 should be made with caution, remembering that it could reflect acute infection, latency, reactivation, or asymptomatic chromosomal integration (5, 7). HHV-6 DNA can be recovered from CSF of iciHHV-6 carriers even though there is no viral replication. Indeed, every nucleated cell contains at least one copy of HHV-6 genome (normal CSF containing up to five nucleated cells/µL) (2). Viral load on whole blood can help distinguish an infection from integrated DNA (2). An HHV-6 viral load greater than 1 x 10^6 copies/mL on whole blood is described as strongly suggestive of an iciHHV-6 (1-4).In our case CSF quantitative HHV-6 PCR showed 106.000 copies/mL, which exceeds 1 viral copy/CSF leukocyte. Moreover, HHV-6 PCR on whole blood sample largely exceeded 1 x 106 copies/LI. HHV-6 PCR analysis of hair and nails could have provided a definitive answer but is not readily available. This test is not mandatory to confirm the diagnosis as quantitative whole blood PCR testing provides a high level of certainty regarding a case of iciHHV-6 (2, 5). The very high viral load in the maternal whole blood sample supports our suspicion of a vertical transmission from an iciHHV-6 carrier parent.

Previous studies have suggested that replicating virus could arise from integrated genome, leading to reactivation, particularly in immunocompromised patients (2, 6). In immunocompetent adults and young children, acute neurological symptoms ranging from seizures to fulminant brain edema have been associated with HHV-6 DNA in the CSF (1, 8). Yet, this should be interpreted with caution due to the unclear role of HHV-6 and the difficult distinction between primary infection and integration (1). Occurring in approximately 1% of births, congenital infection usually remains asymptomatic (4). However, adverse neurodevelopmental outcomes at 12 months of age have been reported in a prospective cohort study of 57 patients (9). Congenital HHV-6 infection was associated with lower Bayle Scale scores at 12 months of age (mean difference: 4.3 (95%CI: 0.4-8.1) compared to infants without congenital HHV-6 infection.

Given these conflicting data, the scarcity of guidelines and the immaturity of the neonatal immune response, we opted for an antiviral treatment with ganciclovir. HHV-6 is susceptible to ganciclovir, foscarnet, and cidofovir. Each of them has possible toxicities such as bone marrow suppression and renal insufficiency for the major ones. However, randomized control trials are lacking and data on efficacy are limited. As such, antiviral treatment is usually not recommended for immunocompetent patients (10). However, a neonate might be considered as an immunocompromised patient, justifying the initial therapeutic choice. No adverse effects have been observed in our patient.

Our understanding is that no definite conclusion can be drawn regarding the etiology of our patient's clinical manifestations. Our working hypothesis is that it is probably related to benign grade II subependymal hemorrhage without concurrent infection. However, as mentioned above, due to uncertainties regarding diagnostic, prognostic and therapeutic options in HHV-6 encephalitis, our multidisciplinary medical consensus was to continue the ganciclovir treatment as precautionary measure. The risk/benefit of such medication, including both long-term neurological development after HHV-6 exposure and antiviral side effects need further clarifications.

Conclusions

This case report highlights the need to further understand the clinical implications of iciHHV-6 and to improve the rapid differentiation between integrated virus and active primary infection. When HHV-6 is recovered from CSF, clinicians should consider the possibility of iciHHV-6, particularly in immunocompetent children without documented encephalitis. In challenging clinical situations, quantitative PCR should be performed on whole blood samples.

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