Human herpesvirus 6 meningitis in an adult

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ABSTRACT

Many cases of viral meningitis are idiopathic, but increased utilization of polymerase chain reaction testing has enabled physicians to better recognize rare causes of viral meningitis. This will likely continue to improve the rate of causative agent identification in seemingly idiopathic viral meningitis, including this case of human herpesvirus 6 (HHV-6) meningitis in an immunocompetent adult patient. More common viral etiologies need to be excluded before diagnosing HHV-6 meningitis, as this maximizes pretest probability and therefore increases validity of a positive result. By efficiently diagnosing HHV-6 meningitis, proper treatment protocols can be initiated earlier to reduce morbidity and mortality. Given the rarity of HHV-6 meningitis in immunocompetent adults, there are no established standard treatment guidelines; previous reported cases, as well as this case, suggest that either intravenous ganciclovir or intravenous foscarnet are the most reasonable first-line treatment options.

KEYWORDS HHV-6; infectious disease; meningitis; polymerase chain reaction; viral meningitis

Human herpesvirus 6 (HHV-6) often remains latent in the host after initial infection—a characteristic that HHV-6 shares with the rest of the herpesvirus family.¹ The virus itself is very common, with a global prevalence as determined by DNA testing around the world.¹ Given that the virus is so widespread, most individuals are infected with HHV-6 in childhood, but many are asymptomatic.² This article presents a rare case of HHV-6 meningitis in an adult.

CASE DESCRIPTION

A 62-year-old woman presented to the hospital with status epilepticus and altered mental status, including visual hallucinations and nuchal rigidity. An electroencephalogram showed significant abnormalities suggesting temporal lobe seizure activity, so she was started on antiepileptics, which resolved her seizures but led to a postictal coma. Magnetic resonance imaging and cardiac monitoring were unremarkable, so a lumbar puncture was obtained. The cerebrospinal fluid analysis revealed pleocytosis with normal glucose and protein levels. The polymerase chain reaction (PCR) was negative for numerous viral agents: cytomegalovirus, enterovirus, herpes simplex virus 1 and 2, human parechovirus, and varicella zoster virus. Despite high clinical suspicion for

herpes simplex virus 1 meningoencephalitis given temporal lobe seizure activity, the PCR only tested positive for HHV-6. The patient was therefore started on intravenous ganciclovir and gradually emerged from her coma. By day 4 of hospitalization, she was spontaneously opening her eyes and answering questions, but was still somnolent. After 14 days of ganciclovir, she had improved significantly and was recommended for discharge. The final assessment was HHV-6 meningitis, status epilepticus secondary to viral meningitis, postictal coma, and metabolic encephalopathy secondary to seizure disorder.

DISCUSSION

Primary infections of HHV-6 or reactivation of latent HHV-6 infections can infrequently lead to meningitis or meningoencephalitis, which have a poor prognosis. There have been very few cases reported of HHV-6 meningitis, but many of these cases have been fatal.¹ HHV-6 infections and reactivations are rare among adults due to the ubiquitous nature of the virus and the high rate of childhood infections; this is especially true for central nervous system involvement, making the diagnosis even less likely in this age group.¹ However, previous cases of HHV-6 meningitis have demonstrated clinical improvement upon administration of

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intravenous ganciclovir or valganciclovir,^{3,4} which guided treatment in this case.

Given the rarity of meningitis caused by HHV-6, it is certainly appropriate to question the validity of the tests for the virus. A study of HHV-6 diagnostic assays for active infection found that PCR detection of the viral DNA was 92% sensitive in the identification of primary infection compared to viral isolation.⁵ Furthermore, current guidelines for diagnosis of central nervous system involvement in HHV-6 infection call for positive viral identification in the cerebrospinal fluid and blood as well as IgM detection.¹

Another unique feature of the virus is that viral DNA of HHV-6 can be integrated into host chromosomal DNA and inherited through the germline.¹ In these individuals, the viral DNA would be present in all nucleated cells and bodily fluids.² While chromosomally integrated HHV-6 is certainly rare, occurring in only 1% of the population, it can complicate the diagnosis of HHV-6. It is important to note that PCR is reportedly unable to distinguish between active viral replication of DNA vs DNA that was already integrated into the host chromosome.⁵ While specific tests can differentiate between chromosomally integrated HHV-6 and true HHV-6 meningitis, these tests must be specifically obtained from specialty labs and are not routinely available at most hospitals.

Therefore, diagnosing HHV-6 meningitis requires clinicians to rely on test results in the context of the clinical picture. In this specific case, the test was performed twice and was positive both times for HHV-6 while being negative for any other viral etiologies. Furthermore, the patient had marked clinical improvement upon administration of ganciclovir, thus supporting the diagnosis of HHV-6 meningitis. Overall, the successful recognition and treatment of

HHV-6 meningitis requires exclusion of more common viral etiologies. In cases of viral meningitis in which the causative agent is unclear, it is important to keep rare causes such as HHV-6 in the differential. For physicians facing similar diagnostic challenges, the increased availability and utilization of PCR testing in the diagnosis of viral meningitis will certainly assist in recognizing rare etiologies such as HHV-6. Indeed, there will likely be additional cases of seemingly idiopathic viral meningitis that may now be attributed to previously known viral agents due to advances in PCR usage.

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1. Agut H, Bonnafous P, Gautheret-Dejean A. Laboratory and clinical aspects of human herpesvirus 6 infections. *Clin Microbiol Rev.* 2015; 28(2):313–335. doi:10.1128/CMR.00122-14.
2. Clark DA, Ward KN. Importance of chromosomally integrated HHV-6A and -6B in the diagnosis of active HHV-6 infection. *Herpes.* 2008;15(2):28–32.
3. Smith HZ, Paguia R, Horne J, et al. A case report of human herpesvirus-6 (HHV-6) meningitis masquerading as idiopathic intracranial hypertension in an immunocompetent patient. *Cureus.* 2019;11(5): e4636. doi:10.7759/cureus.4636.
4. Birnbaum T, Padovan CS, Sporer B, et al. Severe meningoencephalitis caused by human herpesvirus 6 type B in an immunocompetent woman treated with ganciclovir. *Clin Infect Dis.* 2005;15(40):887–889. doi:10.1086/427943.
5. Caserta MT, Hall CB, Schnabel K, et al. Diagnostic assays for active infection with human herpesvirus 6 (HHV-6). *Clin Diagn Virol.* 2010;48(1):55–57. doi:10.1016/j.jcv.2010.02.007.