Bulletin of the *Transilvania* University of Braşov
Series VI: Medical Sciences • Vol. 17 (66) No. 2 – 2024
https://doi.org/10.31926/but.ms.2024.66.17.2.2

HUMAN HERPESVIRUS 6 ENCEPHALITIS IN A PATIENT WITH A HISTORY OF PSYCHOTROPIC DRUG USE: A CASE REPORT

E.V. CIUDIN[1] G. BUTNARIU[1] M.E. COCUZ[1,2]

Abstract: *Human herpesvirus 6 (HHV-6) is a beta-herpesvirus typically associated with asymptomatic infections but can cause severe encephalitis, especially in immunocompromised individuals. This report details a case of HHV-6 encephalitis in an immunocompetent 35-year-old male with recent cocaine use. The patient initially presented with confusion and focal neurological deficits, with MRI showing bihemispheric demyelinating lesions. Acyclovir was initiated as empirical antiviral therapy, resulting in partial improvement. However, the patient was readmitted following discharge due to recurrent neurological symptoms, with MRI findings showing extensive, periventricular white matter lesions consistent with acute disseminated encephalomyelitis (ADEM) secondary to HHV-6. Given the atypical response to the treatment, this case highlights the need for further research on optimal antiviral therapies and the role of psychoactive substance use in neurological infections such as HHV-6 encephalitis.*

Keywords: *encephalitis, HHV-6, psychotropic drugs, cocaine.*

1. Introduction

Human herpesvirus 6 (HHV-6) is a prevalent beta-herpesvirus that encompasses two distinct variants: HHV-6A and HHV-6B. HHV-6 is genetically related to human cytomegalovirus (HCMV), exhibiting a wide cell tropism in vivo. Like other herpesviruses, induces a lifelong latent infection in humans. [1]

Many active HHV-6 infections—whether primary infections, reactivations, or exogenous reinfections—are asymptomatic. Primary infection with HHV-6 is associated with roseola infantum, also known as exanthem subitum, which is a common childhood illness. However, reactivation of HHV-6 in immunosuppressed individuals, particularly in AIDS patients and transplant recipients, can lead to severe complications, including organ rejection and death. [2]

The diagnosis of HHV-6 infection is conducted using both serological and direct methods. The most prominent

[1] Clinical Hospital of Pneumophthisiology and Infectious Diseases, Braşov
[2] Faculty of Medicine, *Transilvania* University of Braşov
* Corresponding author: E.V. Ciudin, vanda.ciudin@gmail.com

technique involves quantifying viral DNA in blood, other bodily fluids, and tissues through real-time PCR. [1]

Given that HHV-6 can lead to an active infection through three mechanisms—primary infection, reactivation of a latent acquired infection, or activation of inherited chromosomally integrated HHV-6 (iciHHV-6)—whole blood quantitative polymerase chain reaction (qPCR) serves as a valuable tool for differentiating among these mechanisms. [3]

The treatment strategies for active HHV-6 infections may include antiviral medications such as ganciclovir, foscarnet, and cidofovir; nevertheless, formal approval regarding their specific indications and administration guidelines is still awaited. [4]

2. Case Presentation

We present the case of a 35-year-old male with no known prior medical history, who was admitted to the Clinical Hospital of Pulmonology and Infectious Diseases in Brașov in May 2024. The patient initially sought care at the Clinical Hospital for Psychiatry and Neurology in Brașov, presenting with a sudden onset of confusion, disorientation, and fever. He reported a history of alcohol and cocaine use prior to admission. Neuroimaging via MRI revealed multiple bihemispheric demyelinating lesions, indicative of an inflammatory process. Analysis of cerebrospinal fluid (CSF) revealed a positive Pandy test, elevated albumin levels, and lymphocytosis. Considering the clinical presentation and laboratory findings, the patient was subsequently transferred to the Infectious Diseases department with a suspected diagnosis of acute viral encephalitis.

Upon admission, the patient presented with confusion, disorientation, and agitation, although he remained hemodynamically and respiratory stable. Laboratory tests revealed leukocytosis with neutrophilia, lymphopenia, and elevated lactate levels. Empirical therapy was promptly initiated, encompassing antiviral treatment with Acyclovir, antibiotics (Ceftriaxone and Vancomycin as empirical treatment for encephalitis, given the inability to initially exclude a bacterial etiology; antibiotic therapy was subsequently discontinued following negative CSF culture results), corticosteroids (Dexamethasone and Solumedrol), Mannitol, fluid and electrolyte replacement, and sedatives. Nine days following the initial lumbar puncture, a second lumbar puncture was conducted, which identified Human Herpesvirus 6 (HHV-6) using reverse transcription polymerase chain reaction (RT-PCR). Bacterial cultures from cerebrospinal fluid (CSF) and IgM and IgG serological tests for Borrelia burgdorferi were negative. The diagnosis was confirmed as acute viral encephalitis caused by HHV-6.

Upon the neurologist's recommendation, additional analyses were conducted in a private setting, including anti-thyroid peroxidase (anti-TPO) antibodies, anti-double-stranded DNA (anti-dsDNA) antibodies, antinuclear antibody (ANA) panel, anti-aquaporin-4 (anti-AQP4) antibodies - indicative of Devic's disease, anti-NMDA receptor antibodies - suggestive of autoimmune encephalitis, anti-myelin oligodendrocyte glycoprotein (anti-MOG) antibodies - associated with multiple sclerosis, anti-leucine-rich glioma-inactivated 1 (anti-LGI1) antibodies - indicative of

autoimmune encephalitis, and Borrelia-specific IgM and IgG antibodies in cerebrospinal fluid (CSF) were all tested, with negative results. Additionally, beta-2 microglobulin levels were within normal limits, as was Vitamin B12.

The patient demonstrated a slow yet consistent improvement in both clinical and laboratory parameters and was discharged at his request after 18 days of Acyclovir treatment.

Unfortunately, one week post-discharge, the patient was readmitted to the neurology department with deteriorating confusion, anarthria, and gait disturbances. Cerebral MRI revealed multiple lesions characterized by low signal on T1-weighted images, high signal on T2-weighted images and FLAIR sequences, and restricted diffusion. Most of these lesions demonstrated contrast enhancement and were located in the periventricular white matter of the bilateral frontal, parietal, temporal, and occipital lobes, as well as in the left internal capsule, with both isolated and confluent patterns. Based on clinical and paraclinical findings, the case was interpreted as acute disseminated encephalomyelitis (ADEM) of post-infectious etiology.

Under supportive therapy, corticosteroid treatment, five plasmapheresis sessions, antibiotics, probiotics, and prophylactic anticoagulation, the patient's condition improved, although behavioral disturbances persisted.

3. Discussion

This case is noteworthy due to its rare etiology, the favorable initial response to Acyclovir despite the absence of Ganciclovir, Cidofovir, or Foscarnet, and complicating factors related to psychotropic substance use.

The literature reports instances of acute viral encephalitis due to HHV-6 that have been effectively managed with Acyclovir. Nevertheless, Ganciclovir, Cidofovir, and Foscarnet continue to be the predominant antiviral agents utilized, despite the absence of a standardized treatment protocol. [5]

Cocaine is a potent psychotropic drug that significantly impacts both cardiovascular and central nervous system (CNS) functions. Chronic cocaine consumption can lead to dependence, frequently accompanied by severe psychiatric disorders and various behavioral issues. Extended use of this substance can result in psychomotor impairments, increased risk of suicide, loss of appetite, weight reduction, and cognitive decline. Given that cocaine causes significant hyperthermia and elevates serotonin turnover, it is plausible that this psychostimulant might trigger neurotoxic effects by altering the functionality of the blood-brain barrier. [6]

Consequently, in the differential diagnosis of this case of acute viral encephalitis associated with Human Herpesvirus 6, it is essential to consider other potential diagnoses such as cocaine-induced encephalopathy, as well as a less commonly recognized condition known as levamisole-induced encephalopathy. Levamisole is a medication that was formerly utilized for the treatment of parasitic infections, aphthous ulcers, rheumatological disorders, and colorectal cancer; however, it was withdrawn from use due to significant adverse effects. Furthermore, levamisole is frequently found as an adulterant in cocaine,

detected in as many as 86% of cocaine samples. The clinical manifestations associated with levamisole exposure may include encephalopathy, focal neurological deficits, fever, headache, and myalgias. Neuroimaging, particularly MRI, can reveal multiple hyperintense areas on T2-weighted and FLAIR sequences that are bilateral, asymmetric, and predominantly located in the periventricular regions, consistent with the findings observed in this clinical case. [7]

There remain many unanswered questions regarding HHV-6, which should encourage future research into the pathophysiology, diagnosis, and treatment of this ubiquitous human virus.

4. Conclusion

Viral encephalitis represents severe infections that are often difficult to diagnose etiologically and can manifest with a wide range of signs and symptoms. Encephalitis caused by HHV-6 can pose a diagnostic challenge, as it is typically associated with immunocompromised patients but can also occur in immunocompetent individuals, with severe and fatal cases reported in the literature. The use of psychotropic substances such as cocaine may delay the diagnosis and treatment of a neurological condition and serve as a risk factor for severe forms of the disease.

5. Acknowledgments

This case report was previously presented at the *National Congress of Infectious Diseases* held in Eforie Nord in October 10–12, 2024.

References

1. Agut H, Bonnafous P, Gautheret-Dejean A. Laboratory and clinical aspects of human herpesvirus 6 infections. *Clin Microbiol Rev*. 2015;28(2):313-35. doi: 10.1128/CMR.00122-14.
2. Campadelli-Fiume G, Mirandola P, Menotti L. Human Herpesvirus 6: An Emerging Pathogen. *Emerg Infect Dis*. 1999;5(3):353-66. doi: 10.3201/eid0503.
3. Ganea OA, Tilișcan C, Streinu-Cercel A, et al. Human Herpesvirus 6—A Rare Aetiologic Agent for CNS Infections in Immunocompetent Individuals or an Underestimation? *J Clin Med*. 2024;13(16):4660. doi: 10.3390/jcm13164660.
4. Webb G, Leong MYM, Bishop E, et al. Diagnostic dilemmas: A review of reported cases of human herpesvirus 6 encephalitis in immunocompetent adults. *Open Forum Infect Dis*. 2024;11(9). doi: 10.1093/ofid/ofae501.
5. Blackbourn L, Ahmad S, Yuan K, et al. Human Herpes Virus-6 (HHV-6) infectious encephalitis in an immunocompetent adult. *IDCases*. 2024;36. doi: 10.1016/j.idcr.2024.e01992.
6. Sharma HS, Muresanu D, Sharma A, et al. Cocaine-Induced Breakdown of the Blood–Brain Barrier and Neurotoxicity. *International Review of Neurobiology.* Vol. 88. Academic Press; 2009. p. 297-334. doi: 10.1016/S0074-7742(09)88011-2.
7. Sharma R. Levamisole-induced leukoencephalopathy. Reference article, Radiopaedia.org. Accessed 2024 Oct 4. doi: 10.53347/rID-183133