Herpes virus type 6 encephalitis in an immunocompetent patient

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Abstract

Introduction: herpes virus type 6 (HHV-6) encephalitis is an infection mainly described in immunosuppressed patients. However, there are some reports of infections in immunocompetent patients.

Clinical case: a 28-year-old male patient with no significant medical history was admitted to the emergency room due to a one-week history of right-sided headache, associated with episodes of psychomotor agitation and disorientation. On the admitting exam he had no motor focalization signs or meningeal signs. Initial brain magnetic resonance imaging and magnetic resonance angiography indicated cortical hyperintensity in the frontal and right insular FLAIR sequences. His state of consciousness deteriorated progressively, and therefore a follow-up cranial computed tomography scan was done, showing acute hydrocephaly. A lumbar puncture had an opening pressure of 36 cm H_20, with an inflammatory cytology report showing low cerebrospinal fluid (CSF) glucose, lymphocytic pleocytosis, 9.5 ADA and a multiplex PCR positive for herpes type 6. Given these findings, with the suspicion of possible meningeal tuberculosis, four-drug treatment was started along with antiviral treatment with ganciclovir for 14 days, due to HHV-6 isolation.

Discussion: Our patient's clinical presentation was marked by behavioral changes, confusion and delirium, in the absence of immunosuppression. These symptoms are compatible with a viral encephalitis profile, which was also corroborated by a positive CSF PCR. However, the findings of acute hydrocephalus with severely low CSF glucose, which are not reported in the literature on herpes encephalitis, raise the suspicion of a differential diagnosis, such as concomitant meningeal TB infection. **(Acta Med Colomb 2025; 50. DOI: https://doi.org/10.36104/amc.2025.3802).**

Keywords: *encephalitis, herpes type 6, immunocompetent, infection*

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Introduction

Human herpesvirus-6 (HHV-6) is a virus in the genus Roseolovirus, in the subfamily Betaherpesvirinae (1). One percent of healthy people harbor DNA sequences of this virus integrated into their genomes. Human herpesvirus-6 may remain dormant for the rest of the host's life after the primary infection and reactivate in the event of immunosuppression (2).

The clinical characteristics of HHV-6 encephalitis include altered level of consciousness, personality and behavioral changes, and seizures (1). The presence of neurological signs and symptoms suggesting encephalitis along with positive CSF polymerase chain reaction (PCR) results with no other objective explanations for central nervous system (CNS) dysfunction constituted the commonly used criteria for diagnosing HHV-6 encephalitis (2, 3).

Magnetic resonance imaging and computed tomography (CT) provide useful information for evaluating CNS infection. Magnetic resonance imaging with gadolinium contrast is much more sensitive and is the neuroimaging test of choice in most cases. Acute encephalitic changes may include edema and abnormalities of the basal ganglia, cortex and grey and white matter junction.

Treatment is based on ganciclovir or valganciclovir (4, 5). For patients who debut while on hemato-oncology treatment, foscarnet is the drug of choice (1).

Human herpesvirus-6 encephalitis mainly occurs in patients with some type of immunocompromise, especially transplant patients. Below, we present the case of an immunocompetent patient with herpes 6 encephalitis.

Case presentation

A 28-year-old male patient with no known medical history was admitted to the emergency room with a one-week history of right-sided headache with nonspecific characteristics and variable intensity, associated with episodes of psychomotor agitation and disorientation.

In his assessment on admission to the neurology service, he was bradypsychic, with modulated motor behavior, no focal motor or sensory signs and no meningeal signs. It was classified as a red flag headache, and there-

fore a simple CT was performed, which was interpreted as normal. Due to the presence of psychoactive substances in his urine on admission, brain magnetic resonance imaging and arterial phase angiography was ordered, looking for possible signs of vasospasm. However, the study was technically limited by marked movement artifacts due to psychomotor agitation during the test. Nevertheless, there was notable cortical hyperintensity on frontal and right insular FLAIR (Figure 1). An electroencephalogram was done to rule out a seizure-based cause of the symptoms, with no abnormalities found.

In light of the persistent headache with behavioral changes, a cerebrospinal fluid test was considered but had to be postponed due to an episode of agitation and a history of a bullet lodged in the spine with an unknown location. It was therefore planned to be performed by interventional radiology. On his third day of hospitalization, the patient's neurological status deteriorated further with visual and auditory hallucinations, greater psychomotor agitation, disorientation, insomnia, tachycardia and dysthermia. Given the findings on the first magnetic resonance imaging and his clinical progression, empirical coverage with acyclovir was started. During observation on the hospital floor, and despite empirical treatment, the patient continued to complain of severe headache and agitation despite antipsychotic therapy, requiring four-point restraints. In view of the sluggish clinical progress and inability to perform brain magnetic resonance imaging with sedation, a plain follow-up CT was done, which showed acute communicating hydrocephalus (Figure 2). He then underwent emergency ventriculostomy and was transferred to the intensive care unit (ICU) under deep sedation for neuroprotection.

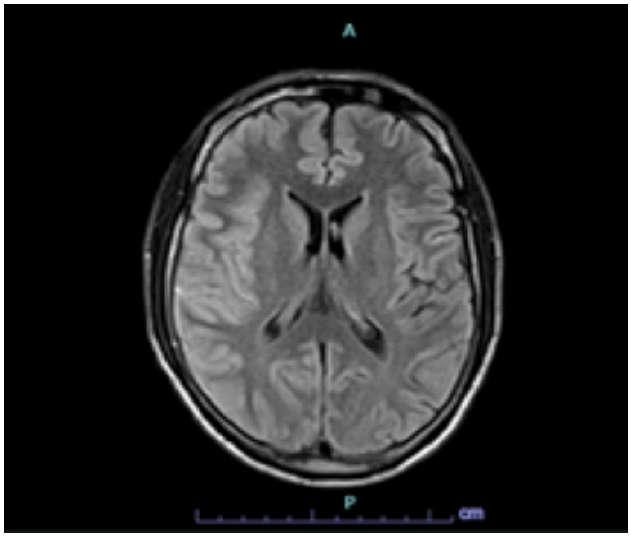

Figure 1. *Brain MRI with findings suggestive of right frontal-parietal cortical edema.*

Lumbar puncture was achieved that same day, with an opening pressure of 36 cm H_2O, inflammatory cytochemistry with markedly low cerebrospinal fluid (CSF) glucose levels, lymphocytic pleocytosis, an ADA of 9.5 and HHV-6 positive multiplex PCR.

Given the findings of acute hydrocephalus with markedly low CSF glucose levels and an ADA at the upper limit of normal, the potential diagnosis of meningeal tuberculosis was considered, for which dexamethasone therapy and empirical four-drug treatment were started. With herpesvirus-6 isolation, acyclovir treatment was changed to induction phase ganciclovir at a dose of 5 mg/kg every 12 hours for 14 days.

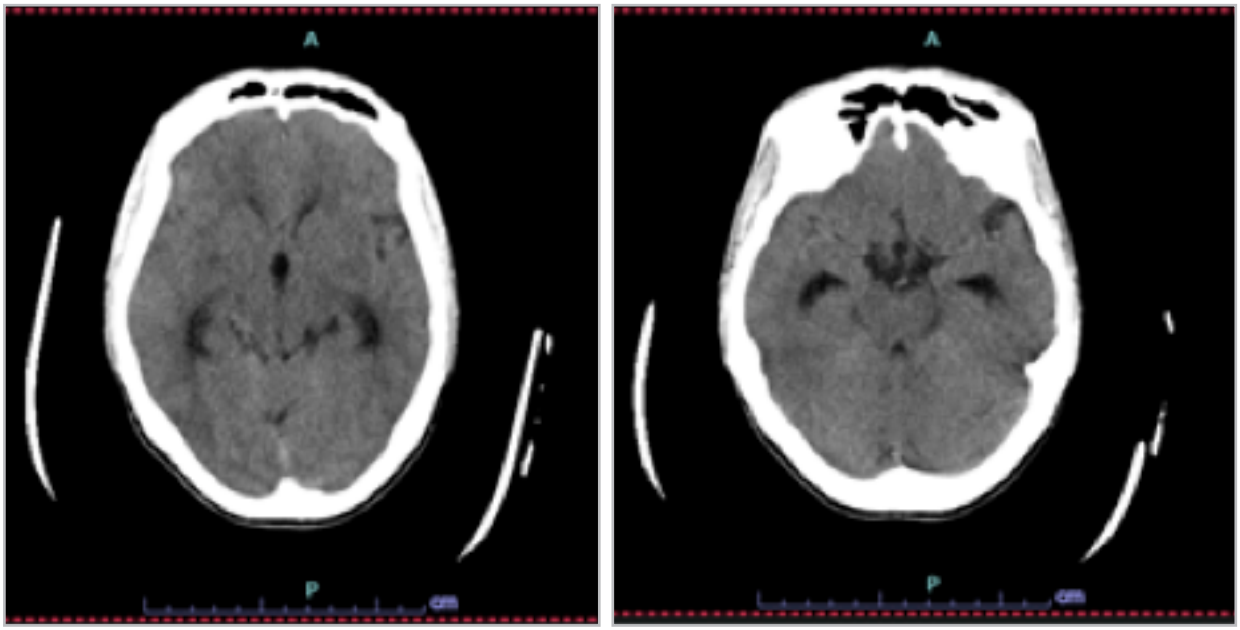

Figure 2. *A plain cranial CT suggestive of hydrocephalus: increased size of the lateral horn of the lateral ventricles, as well as enlargement of the third ventricle.*

After withdrawing sedation, ophthalmoparesis and right brachial-crural paralysis were found. Follow-up neuroimaging showed left pontine hypodensity, which was interpreted as a vasculitic infarction. Twelve days after a ventriculostomy, and with normal intracranial pressure, the neurosurgery service removed the external shunt, which was sent for culture and reported Pseudomonas aeruginosa on the catheter tip.

After 14 days of ganciclovir treatment, he underwent another CSF study showing an opening pressure of 22 cm H_2O, persistent pleocytosis, improved CSF glucose levels compared to the first study and a persistently positive PCR for herpesvirus-6, with an ADA of 10.4. Four-drug treatment was maintained, and the ganciclovir treatment was extended to 21 days, along with meropenem antibiotic coverage.

Seventy-two hours later another lumbar puncture was performed to complement the CSF studies, with a negative non-tuberculous PCR.

After completing the 21 days of ganciclovir treatment (induction phase), the patient showed clinical improvement. A follow-up lumbar puncture was done to confirm CSF sterilization after completing treatment; however, the PCR was once again positive for herpesvirus-6. The infectious disease and neurology services made the joint decision to begin a new 21-day cycle of ganciclovir treatment and take a serum IgG herpesvirus-6 viral load, which was held up by administrative problems.

Studies were also ordered to assess immunodeficiency, including HIV 1 and 2 antibody tests, which were non-reactive, as well as a negative viral load. In addition, flow cytometry was done to analyze the T-lymphocytes, finding 45.42% CD4 and 29.22% CD8. The CD4/CD8 ratio was 1.55, which is considered to be within the normal limits for adults.

During his hospital stay, he developed hospital-acquired pneumonia, and he was discharged to home care.

Two months later he was seen as an outpatient, with a complaint of infrequent episodic vascular-type headaches, improved dysexecutive syndrome and persistent right brachial-crural paralysis, requiring wheelchair assistance.

Discussion

Human herpesvirus-6 is one of the eight members of the *Herpesviridae family, whose main characteristic is their ability to remain dormant in their hosts throughout life and reactivate during periods of relative immunosuppression* (6); it is part of the genus Roseolovirus of the subfamily Betaherpesvirinae (1). There are two closely related variants: HHV-6A, which has not been etiologically linked to any disease, and HHV-6B, which is responsible for exanthema subitum in children (7).

Most cases of HHV-6 encephalitis have been reported in immunodepressed and transplant (especially hematopoietic transplant) patients, as seen in a compilation of cases and cohort studies (8, 9).

The clinical presentation of acute disease is nonspecific and may manifest as a febrile syndrome, skin rashes, and hematological disorders with leukopenia and thrombocytopenia, especially in children (7). There may also be electrolyte disorders, like hyponatremia, due to inappropriate antidiuretic hormone secretion, or hypernatremia due to central diabetes insipidus; hypernatremia almost always precedes hyponatremia (10, 11).

Herpesvirus-6 encephalitis generally manifests with limbic system involvement, loss of short-term memory, confusion, disorientation, encephalopathy, delirium and neurocognitive impairment. Temporal lobe seizures are common, but focal neurological deficits are rare (10, 12).

In a systematic review, Erin Isaacson et al. described four cases of immunocompetent patients with a variety of nonspecific signs and symptoms like emotional lability, headache, photophobia or respiratory symptoms (13).

Our patient's clinical presentation was marked by behavioral changes, confusion and delirium. Acquired immunodeficiency was ruled out, and his CD4/CD8 ratio was greater than 1.

In immunocompromised patients, HHV-6 encephalitis tends to affect the mesial temporal lobe and may resemble herpes simplex virus (HSV) encephalitis. Noguchi et al. *conducted a comparative study of patients with HHV-6 and HSV to try to differentiate their imaging findings, as a determinant tool in deciding early empirical treatment. Four of the eight patients with HHV-6 had no relevant abnormalities on simple head CTs, compared to HSV patients, who showed parenchymal edema, hypodensity in the affected areas and abnormal gyral enhancement, with a significant difference* ($p<0.05$) (14). As far as brain magnetic resonance imaging (MRI) results, all patients had abnormalities in the hippocampus and amygdala, most of which were bilateral; compared to patients with HSV, who in addition to having changes in the hippocampus and amygdala, had abnormalities including insular, basal frontal, medial, parietal, occipital, deep grey matter and temporal lobe involvement, with a statistically significant difference ($p<0.01$) (14).

Contrast media enhancement was not common in patients with HHV-6, and parenchymal edema was also significantly greater in HSV than HHV-6 (14).

In our patient's case, specifically, the initial head CT was normal, and the brain MRI could not be fully interpreted due to movement artifacts, with the only relevant finding being right frontal-insular FLAIR hyperintensity. The patient later developed communicating hydrocephalus, which we did not find documented in the literature as related to HHV-6.

Yassin et al. analyzed the imaging findings of five patients with HHV-6 encephalitis who were immunosuppressed due to transplantation. Four patients had T2/FLAIR hyperintensity of the temporal lobe, bilaterally, two with restricted diffusion-weighted imaging (DWI). One patient had thalamic, hypothalamic, brainstem and basal ganglia involvement, and another had periventricular involvement

(1). These findings did not correlate with our case, either.

Isaacson et al. *reported four HHV-6 cases in immunocompetent adult patients, finding plain MRI abnormalities in only one case, with temporal lobe involvement (13).*

In our patient's case, despite a negative PCR and cultures for Mycobacterium tuberculosis, it is hard to emphatically rule out concomitant tuberculous meningitis along with HHV-6 encephalitis, in the context of acute hydrocephalus (a finding not described in the literature) and such low CSF glucose.

Three drugs have proven effective in treating HHV-6 infection: ganciclovir, foscarnet and cidofovir. Their mechanism of action is based on viral DNA polymerase inhibition, in a triphosphate form for ganciclovir and diphosphate form for foscarnet and cidofovir. The treatment strategies have been extrapolated from those used for cytomegalovirus (15).

The International Herpes Management Forum and American Society of Transplantation recommend beginning antiviral treatment for encephalitis, suggesting the use of intravenous ganciclovir and foscarnet (15).

Our patient completed 42 days of ganciclovir and is currently in the maintenance phase with four-drug treatment, with acceptable clinical progress and receiving comprehensive rehabilitation. Although CSF sterilization could not be verified, his clinical improvement suggests a positive response to treatment.

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