Case Report

Seronegative herpes simplex virus (HSV) encephalitis causing temporal lobe epilepsy resulting in new-onset psychosis: a case report and literature review

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Background: Herpes simplex virus (HSV) encephalitis is the most common nonepidemic encephalitis and can result in temporal lobe necrosis. Inflammation of the temporal lobe can result in temporal lobe epilepsy which is known to cause psychiatric symptoms.

Case Description: We describe the case of a geriatric male patient who was admitted for new-onset visual hallucinations and other neuropsychiatric symptoms which began five days prior to admission. His lab work was unremarkable, and a computed tomography (CT) scan of the brain demonstrated small vessel ischemic disease. There was clinical suspicion for seizures, and electroencephalogram (EEG) monitoring showed focal seizure activity in the right hemisphere. He received a brain magnetic resonance imaging (MRI) which was suspicious for encephalitis. Various etiologies were considered, and he received an extensive workup including cerebrospinal fluid evaluation. Ultimately, he improved with empiric antiviral treatment added alongside multiple antiepileptic agents. The seizure control and resolution of symptoms with antiviral treatment, in addition to the findings of his central nervous system (CNS) workup, confirmed the presumptive diagnosis of HSV encephalitis.

Conclusions: Understanding the multifactorial causes of neuropsychiatric symptoms is important in determining an appropriate workup. The acute onset of specific symptoms in our patient increased suspicion for a structural neurological process. His initial presentation could largely be explained by the vascular dementia and epileptiform activity that were discovered during hospitalization. However, his refractory seizures were suggestive of another underlying etiology. The localization of his seizures and MRI findings were suggestive of HSV encephalitis despite negative HSV polymerase chain reaction (PCR). A patient may benefit from antiviral treatment when the clinical picture is consistent with HSV encephalitis even in the setting of negative serological studies. Clinicians should also be mindful of false negatives on serological tests.

Keywords: Case report; seronegative herpes simplex virus (seronegative HSV); encephalitis; temporal lobe epilepsy; psychosis

Received: 31 March 2024; Accepted: 04 July 2024; Published online: 02 September 2024.
doi: 10.21037/acr-24-69
View this article at: https://dx.doi.org/10.21037/acr-24-69

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Introduction

Temporal lobe encephalitis is inflammation of brain parenchyma, typically in the medial temporal lobe which can have infectious, metabolic, or paraneoplastic causes (1). Common infectious causes include HSV, human herpes virus (HHV-6), tuberculosis, varicella zoster, mucormycosis or other fungal infections (2). HSV encephalitis can present in HSV-1 or HSV-2, and is the most common nonepidemic encephalitis (3). The defining characteristic of HSV encephalitis is hemorrhagic necrosis of the temporal lobe (4). This can lead to temporal lobe epilepsy, which in turn can result in diverse psychiatric symptoms (5,6). We describe the case of a geriatric male patient who was admitted for new-onset neuropsychiatric symptoms due to temporal lobe epilepsy caused by underlying seronegative HSV encephalitis. We present this case in accordance with the CARE reporting checklist (available at https://acr.amegroups.com/article/view/10.21037/acr-24-69/rc).

Case presentation

A right-handed 74-year-old Caucasian male was admitted for new-onset visual hallucinations, confusion, delusions, nightmares, forgetfulness, and right unilateral orbital headaches for five days. He had also developed gait instability with recurrent falls over several months. He denied any auditory, tactile, or olfactory hallucinations. He had one prior psychiatric hospitalization decades ago for post-traumatic stress disorder (PTSD) after his military service. His PTSD symptoms had resolved decades prior. He had a history of paroxysmal atrial fibrillation status-post ablation on apixaban, multivessel coronary artery disease status-post coronary artery bypass graft, insulin-dependent diabetes mellitus, hypertension, hyperlipidemia, and stage 3 chronic kidney disease. Prior to onset of symptoms, he was independently able to ambulate, perform activities of daily living, and had intact fine motor control as he enjoyed woodworking.

He was otherwise asymptomatic, had normal vital signs, and did not appear acutely ill or in any type of distress. He denied using alcohol and/or any illicit drugs. He had no recent illnesses or travel. Vital signs remained stable throughout his hospital course.

Clinical labs were ordered on the day of admission. Complete blood count (CBC), thyroid stimulating hormone (TSH), folate, B12, syphilis antibodies were within normal limits. Remarkable findings on comprehensive metabolic panel (CMP) were creatinine of 1.65 mg/dL and glomerular filtration rate (GFR) of 43 mL/min/1.73 m^2. Urinalysis showed glucose and protein in the urine. CT brain without contrast (*Figure 1*) was ordered on day 2 after he was monitored psychiatrically for 24 hours, and showed no evidence of acute intracranial abnormalities including hemorrhage or extra-axial fluids. Cerebral parenchyma showed age-appropriate global atrophy with symmetrical and proportionate sulcal and ventricular enlargement. There were patchy white matter hypodensities, indicative of small vessel ischemic changes. We interpreted these findings as being indicative of Binswanger's disease, a form of vascular dementia.

We started him on risperidone 0.25 mg daily to target his psychosis on day 2 after labs and computed tomography (CT) results were available. We were concerned for seizures given his symptoms of episodic disorientation, headaches, falls, and visual hallucinations. Risperidone was preferred as it is suspected to reduce the seizure thresholds less than other atypical antipsychotics (7,8). Although he was admitted for primarily psychiatric concerns, we wanted to rule out other contributory causes given the sudden onset of various neuropsychiatric symptoms. We pursued a comprehensive workup for diagnostic clarification. His normal vitals and lack of inflammatory or constitutional symptoms were less suggestive of an infectious process.

A magnetic resonance imaging (MRI) and electroencephalogram (EEG) were performed on day 3. MRI brain with contrast (*Figure 2*) showed abnormal

Highlight box

Key findings

- Empiric treatment for herpes simplex virus (HSV) encephalitis can reduce temporal lobe seizure frequency.

What is known and what is new?

- Temporal lobe epilepsy can result in psychiatric symptoms.
- Encephalitis from HSV can be seronegative and empiric treatment can provide clinical benefit for reduction in temporal lobe seizure frequency.

What is the implication, and what should change now?

- Temporal lobe epilepsy should be considered in new-onset neuropsychiatric symptoms. Unclear neuropsychiatric symptoms warrant an electroencephalogram (EEG) as nondominant-hemisphere seizures can present without observable seizures. Underlying etiology of HSV encephalitis should be considered and treated if seizures are refractory and the remainder of the work-up is inconclusive.

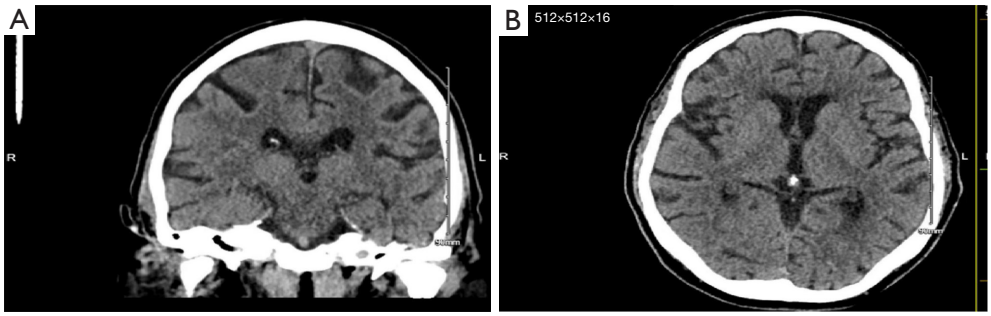

Figure 1 Coronal (A) and transverse (B) sections from CT brain without contrast. CT, computed tomography.

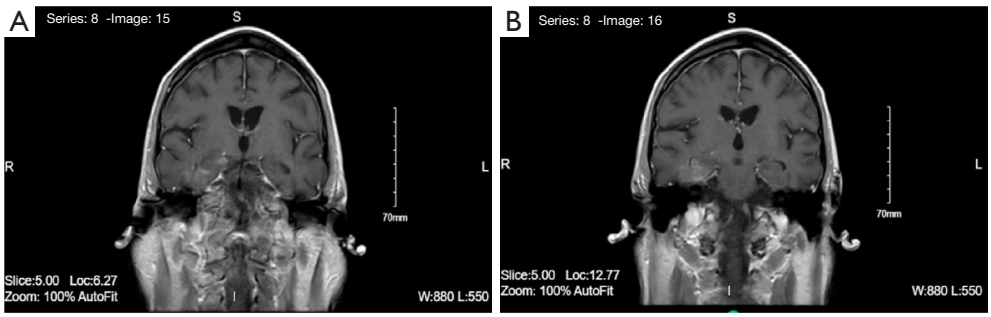

Figure 2 T2-weighted transverse sectional sequence of MRI brain with contrast demonstrating abnormal regional increased enhancement throughout the right medial temporal lobe as seen in cross-section 15 (A) and cross-section 16 (B). MRI, magnetic resonance imaging.

regional increased enhancement throughout the right medial temporal lobe. The abnormal contrast enhancement was concerning for encephalitis but not definitive. An EEG was obtained during wakefulness and sleep, and found to be abnormal in wakefulness due to diffuse theta slowing and occasional delta activity. This was suggestive of mild-to-moderate nonspecific encephalopathy. Frequent right frontotemporal polymorphic delta slowing was indicative of underlying focal neuronal dysfunction. The patient also had four electrographic seizures which began with rhythmic right frontotemporal delta activity, evolved to increase in amplitude with embedded frontotemporal spikes, and spread to the whole right hemisphere. The seizures lasted 90–120 seconds. The patient did not display observable seizure activity which we suspected was because seizures were occurring in the nondominant brain hemisphere.

He was immediately admitted to the intensive care unit (ICU) for continuous EEG monitoring which showed ongoing focal seizure activity in the right hemisphere with frequency of 4–10 focal seizures per hour without any generalized events. He was treated with three antiepileptic agents: levetiracetam 1,500 mg twice daily, lacosamide 150 mg daily, and sodium valproate (Depakote) 250 mg every 6 hours.

At the same time, CT chest with contrast was ordered to rule out adrenal or paraneoplastic etiologies. Paraneoplastic autoantibody evaluation and serum *Cryptococcus* antigens were negative. Lumbar puncture results showed 11 milliliters of colorless, clear fluid with 2cmm cerebrospinal fluid (CSF) white blood cells (WBCs), and 1cmm elevated CSF red blood cells (RBCs). CSF neutrophils were elevated at 25%, suggestive of viral etiology. CSF lymphocytes were within normal limits at 75%, CSF glucose was elevated at 75 mg/dL, and CSF protein was elevated at 69 mg/dL. CSF culture showed no bacterial growth, WBCs, or organisms. CSF polymerase chain reaction (PCR) for herpes simplex virus (HSV) PCR (HSV-1 DNA and HSV-2 DNA), West Nile virus, Lyme disease, enterovirus, and *Cryptococcus* were negative. Venereal Disease Research Laboratory (VDRL) test for neurosyphilis was non-reactive. Anti-N-methyl-D-aspartate (NMDA) receptor was ordered to rule out NMDA encephalitis, and glutamic acid decarboxylase 65-kilodalton (GAD-65) was ordered as it is a biomarker for CNS autoimmune conditions including both encephalitis and

epilepsy (9). Both were negative.

He continued to have seizures after 24 hours which raised suspicion for encephalitis. We determined that treatment for suspected HSV encephalitis would be warranted for reduction in seizure frequency and the patient was started empirically on intravenous (IV) acyclovir. HSV was considered the cause of encephalitis despite negative PCR results due to temporal lobe findings on MRI, localization of seizure activity on EEG, and the negative results for the remainder of lab tests. IV acyclovir was renally dosed at 10 mg/kg every 8 hours. Continuous EEG readings following antiviral treatment showed no electrographic seizures for 24 hours. A timeline of patient's symptom presentation and resulting interventions is portrayed in *Figure 3*.

The patient remained alert and oriented and did not display signs of infection or clinical seizures. He continued to display improvement in mentation with empiric antiviral treatment and control of seizures. His hallucinations resolved. He was discharged from the ICU on day 7 and admitted to acute inpatient rehabilitation to address his functional decline and deconditioning.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was provided by the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

This case highlights the importance of HSV encephalitis as a potential diagnosis in an elderly patient with new-onset seizures and psychosis, despite negative serological studies. Interestingly, our patient had no prior history of herpes that he was aware of. The clinical picture and neuroradiographic findings were nonetheless indicative of HSV encephalitis. This was further reaffirmed with his drastic improvement with IV acyclovir. His right-sided headaches were attributable to right temporal seizures and imaging findings. We incidentally also found evidence of cerebrovascular disease which likely contributed to part of his presentation. It is also worth noting that his seizures were in the presumed non-dominant hemisphere given his right-handedness. This likely spared his language centers and could explain why his seizures were not clinically noticeable. The episodes of falling and intermittent confusion could have also been due to focal epileptic episodes.

HSV encephalitis is noted to have a bimodal distribution with peaks in patients younger than age 20 and older than 50 years (3). HSV-1 is generally associated with HSV encephalitis in adult patients. This occurs when a latent virus from a previously infected ganglion spreads retrogradely through neurons into the brain (4). The leading theory for how infection reaches the CNS is through using the trigeminal or olfactory nerve as a pathway for the herpes infection to ascend to the temporal lobe (4). Infection typically begins unilaterally and can progress to the contralateral temporal lobe in the late stage of the disease. Diagnosis is usually made by brain MRI which is about 80% sensitive (10). Findings on CT, clinical findings of focal neurological deficits, or CSF changes might take longer to manifest (10). The gold standard for HSV diagnosis is through PCR (11). However, false negatives can occur early after disease onset, as HSV DNA may not yet be present in detectable amounts or the virus is not actively replicating at high levels (12). In severe HSV encephalitis, initial negative CSF HSV PCR was independently associated with worse neurologic outcome at hospital discharge (13). A brain biopsy can also make a definitive diagnosis but is rarely used.

Patients presenting with HSV-1 encephalitis typically have altered mental status for longer than 24 hours as well as other symptoms of brain inflammation, including seizures, headaches, fevers, and focal neurological deficits (14). Changes in cognition, behavior, and personality have also been noted, with symptoms such as confusion, hallucinations and delusions leading to misdiagnoses as primary psychiatric disorders (14). There are cases of middle-aged patients with manic symptoms and elderly patients being psychiatrically hospitalized for acute psychosis who were found to have HSV encephalitis (15,16). Presentation with prominent psychiatric symptoms has delayed neurological workup, accurate diagnosis, and appropriate treatment which has led to fatal consequences (17). HSV-1 encephalitis is associated with a very high mortality rate of 70% without treatment (18). Damage to the temporal lobes of the brain caused by HSV encephalitis can sometimes lead to temporal lobe epilepsy (TLE) weeks or months after the original infection (5).

TLE is the most common type of focal epilepsy (19). It can be classified into mesial TLE or neocortical TLE (19). Mesial TLE is more common, affects medial structures, and is associated with hippocampal sclerosis which can be seen on MRI (19,20). Neocortical epilepsy affects more

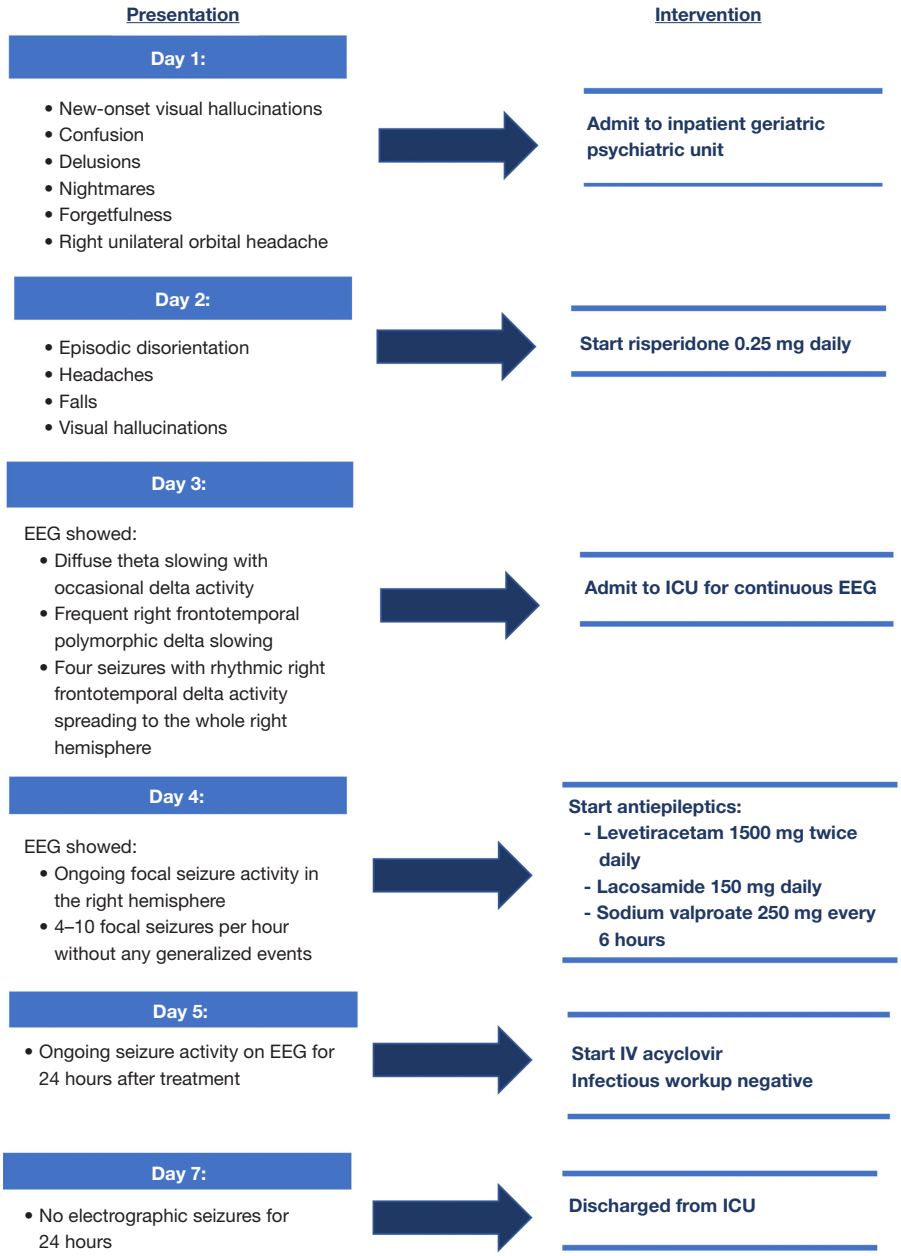

Figure 3 Timeline of patient's presentation and subsequent interventions. EEG, electroencephalogram; ICU, intensive care unit; IV, intravenous.

lateral structures (19). Although rare, TLE can progress to tonic-clonic seizures (21). TLE can present with psychosis, panic disorder, depression, bipolar disorder, and dissociative disorders (6). Psychosis from epilepsy typically includes paranoia, delusions, hallucinations, and can occur before, during, or after the seizure (22). Depressive disorders are the most prevalent psychiatric conditions found in patients with TLE (23). The presentation can vary based on the hemisphere impacted, with left sided TLE patients tending to exaggerate depressive symptoms and right sided TLE patients minimizing depressive symptoms (24). It is worth noting that mood and anxiety symptoms in epilepsy can be a result of neurophysiological changes from seizures, adverse effects from antiepileptic medications, or due to

psychosocial stressors from living with epilepsy (25). In about a quarter of patients, antiepileptic medications do not provide adequate symptom control and the definitive treatment is surgery (26).

Conclusions

The case highlights the importance of maintaining a broad differential in elderly patients presenting with psychiatric and neurological symptoms. It also serves as a reminder of false positives and negatives in serological studies. The interplay between our patient's pre-existing medical comorbidities, age-related functional decline, vascular dementia, seizures, and other neuroradiographic findings led to a situation of uncertain etiology. This further emphasized the importance of clinical judgment as using empiric treatment even when serological findings were negative ended up being both diagnostic of HSV and therapeutic for it.

Acknowledgments

Funding: The authors would like to acknowledge Riverside Medical Center GME for funding publication fees.

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://acr.amegroups.com/article/view/10.21037/acr-24-69/rc

Peer Review File: Available at https://acr.amegroups.com/article/view/10.21037/acr-24-69/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://acr.amegroups.com/article/view/10.21037/acr-24-69/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was provided by the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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doi: 10.21037/acr-24-69
Cite this article as: Khan S, Khadri S, Haque LA, Anderson M, Witkowska M. Seronegative herpes simplex virus (HSV) encephalitis causing temporal lobe epilepsy resulting in new-onset psychosis: a case report and literature review. AME Case Rep 2024;8:100.