Title: Cerebellitis as a Rare Manifestation of HSV Encephalitis: A Case Report

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Highlights

- A rare presentation of HSV encephalitis is cerebellitis.
- This case demonstrates the importance of maintaining a broad differential diagnosis when evaluating other etiologies that may mimic ischemic stroke.
- The use of adjunctive steroids in conjunction with acyclovir in the treatment of HSV encephalitis remains a subject of ongoing investigation.

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ABSTRACT.

Background: Herpes Simplex Virus (HSV) is a common cause of encephalitis. A feared complication of HSV encephalitis is hemorrhage and necrosis of the brain parenchyma most commonly in the temporal lobe(s). Less common sites of focal necrosis include the insula and inferior frontal lobes. A rare presentation of HSV encephalitis is cerebellitis.

Case: A 74-year-old female presented with a 1-month history of progressive balance difficulty and dizziness. The neurological exam showed truncal ataxia and scanning dysarthria. Serum labs were largely unremarkable, except for elevated sedimentation rate (ESR). Brain MRI revealed diffuse cerebellar swelling and T2 signal changes, with left medial enhancement. Cerebrospinal fluid (CSF) analysis showed elevated red blood cells (WBCs 5, RBCs 438, protein 54.7, glucose 64) and was positive for HSV-1 PCR. The CSF autoimmune encephalopathy panel was negative. She was treated with acyclovir 10 mg/kg every 8 hours for 14 days and IV methylprednisolone 1000 mg daily for 5 days, followed by an oral prednisone taper. Clinical improvement in ataxia and dizziness was observed soon after treatment began, with decreased cerebellar edema and enhancement on repeat MRI. After discharge, the patient was lost to follow-up, and long-term neurological status remains unknown.

Conclusions: Recognition of atypical HSV encephalitis is crucial as encephalitis has a broad differential and CSF HSV PCR is a widely available and highly specific test. Rapid administration of acyclovir is the current standard of care. Addition of pulse dose methylprednisolone may also impart symptomatic and radiographic benefit.

Key Words: Herpes Simplex Encephalitis, Herpes Encephalitis, Herpetic Encephalitis, Herpes Simplex Virus 1, Cerebellar Ataxia.

INTRODUCTION.

Encephalitis is defined as inflammation of the brain parenchyma and represents a significant cause of neurological morbidity and mortality worldwide. It often presents with a prodromal phase characterized by fever, lethargy, and headache. This is followed by more severe manifestations such as mental status changes, seizures, and non-focal neurological deficits. Among the various infectious agents, Herpes Simplex Virus type 1 (HSV-1) is recognized as the most prevalent cause of sporadic encephalitis in developed countries [2].

HSV-1 is a double-stranded DNA virus belonging to the Herpesviridae family, which comprises eight distinct pathogens. These pathogens include Herpes Simplex Virus type 2 (HSV-2), Varicella-Zoster virus (VZV), Cytomegalovirus (CMV), Epstein-Barr virus (EBV), and Human Herpesvirus 6, 7 and 8. HSV-1 has a predilection for the central nervous system. The virus typically resides dormant in the trigeminal ganglia as a latent infection and can become reactivated, leading to encephalitis. Primary infections account for only 30% of HSV-1 encephalitis cases [1]. A feared complication of HSV-1 encephalitis is the development of hemorrhage and necrosis in the temporal and frontal lobes, resulting in significant long-term neurological sequelae [2]. Isolated inflammation of the cerebellar parenchyma, cerebellitis, due to HSV-1 encephalitis is extremely rare in both the pediatric [11] and adult population [3] [4]. The objective of this case report is to describe a rare instance of HSV-1-induced cerebellitis in an immunocompetent adult. This case highlights the importance of considering HSV-1 in the differential diagnosis of cerebellar inflammation, and addresses the ongoing clinical debate regarding the use glucocorticoids in HSV encephalitis treatment.

THE CASE

Patient Background

A 74-year-old female with a past medical history significant for diabetes mellitus, hyperlipidemia, hypertension, hypothyroidism, and atrial fibrillation, presented with a one-month history of progressively worsening balance difficulty and dizziness. She denied excessive alcohol consumption and reported no history of Human Immunodeficiency Virus (HIV) infection or immunosuppressive therapy.

Clinical Examination

Upon presentation the patient was afebrile, and vital signs were stable. A comprehensive neurological examination revealed truncal ataxia and subtle scanning dysarthria, characterized by slurred and irregular speech. The exam also showed right eye ptosis which was reported to be chronic. Fundoscopic exam was normal. There was no evidence of nystagmus, dysmetria, motor or sensory deficits.

Laboratory Findings

Laboratory tests revealed serum studies, with the exemption of slight hypernatremia 146 mEq/L, within normal limits. There was an elevated erythrocyte sedimentation rate (ESR) of 88 mm/hr suggestive of an active inflammatory process. Vitamin levels, including thiamine (B1) and B12, were normal.

Imaging Studies

A CT scan of the brain showed multiple areas of mild hypoattenuation within bilateral cerebellar hemispheres, and an area of slightly higher density within the hypoattenuation of the left cerebellar hemisphere.

An MRI of the brain revealed diffuse swelling and T2 signal changes throughout the cerebellum, with associated left medial enhancement (**Figure 1).** These findings raised suspicion for an inflammatory process affecting the cerebellum, prompting further investigation with a lumbar puncture.

CSF Analysis

The CSF contained 5 white blood cells (WBC)/mm³, 438 red blood cells (RBC)/mm³, protein 54.7 mg/dL, and glucose 64 mmol/L. There was no evidence of pleocytosis, hyperproteinorrachia, or hypoglycorrhachia. The analysis revealed erythrocytosis, with an RBC count of 438. Although a traumatic tap was considered, this was deemed unlikely given the relatively consistent RBC count across multiple CSF samples. While erythrocytosis could suggest a hemorrhagic process, follow-up

MRIs demonstrated no signs of subarachnoid hemorrhage. In terms of inflammatory markers, the IgG index, IgG synthesis rate, and myelin basic protein levels were within normal limits, and no oligoclonal bands were detected. These findings reduced the likelihood of demyelinating conditions such as multiple sclerosis.

Autoimmune Panel

A Mayo ENC2 autoimmune panel of the CSF was negative, minimizing the likelihood that that the etiology of the cerebellitis was autoimmune.

Diagnosis

The CSF analysis demonstrated HSV-1 PCR positivity, confirming the diagnosis of HSV-1 cerebellitis.

Treatment

The patient was promptly initiated on antiviral therapy with acyclovir at a dose of 10 mg/kg every 8 hours for 14 days. They were also treated with intravenous methylprednisolone 1000 mg daily for 5 days which was followed by a tapering course of oral prednisone. The rationale of glucocorticoids being added to the treatment regimen was to reduce the likelihood of vasogenic edema demonstrated on imaging contributing to a long-term neurological deficit.

Outcome

Shortly after the initiation of treatment, the patient exhibited clinical improvement of ataxia, dizziness, and scanning dysarthria. A repeat MRI of the brain demonstrated decreased cerebellar edema and enhancement, indicating a positive therapeutic response **(Figure 2)**. Patient consented to the use of their case for publication. The patient was subsequently discharged to a rehabilitation facility. Unfortunately, numerous attempts to contact the patient for follow-up were unsuccessful, leaving their long-term neurological status unknown.

DISCUSSION.

The subacute onset of progressively worsening balance impairment with dizziness could have multiple localizations including a peripheral vestibulopathy, sensory ataxia or central spinocerebellar tract lesion. The combination of truncal ataxia, and subtle scanning dysarthria suggested the cerebellum or central spinocerebellar tract as the localization. Given the patient's history of diabetes mellitus, hyperlipidemia, hypertension, and atrial fibrillation—established risk factors for vascular disease and thromboembolism—ischemic cerebellar stroke was strongly considered as the primary diagnosis. Systemic symptoms such as fevers, chills, and weight loss, which could suggest an infectious or neoplastic etiology, were not present. The absence of papilledema on fundoscopic examination, and lack of a compressive lesion on initial CT scan excluded intracranial hypertension. Encephalitis initially was lower on the differential because the patient was afebrile, there was an absence of rapidly progressive mental status changes, seizures, and non-focal neurological deficits. This case underscores the critical importance of maintaining a broad differential diagnosis when evaluating other etiologies that may mimic ischemic stroke.

The differential diagnosis for truncal ataxia secondary to cerebellitis in an adult is broad and encompasses various inflammatory, autoimmune, metabolic, neoplastic, vascular and infectious etiologies. Clinically, acute cerebellitis can manifest with ataxia, nystagmus, dysarthria, dysmetria, vertigo, and nausea [12].

Inflammatory diseases with cerebellar involvement include celiac disease which is associated with HLA-DQ2/DQ8 and can have positive autoantibodies against transglutaminase and endomysium. Autoimmune thyroiditis can manifest with cerebellar symptoms in Hashimoto's encephalopathy. Post-infectious conditions such as Miller Fisher syndrome, a variant of Guillain-Barré syndrome, can present with areflexia, ataxia, ophthalmoplegia, sometimes with anti-GQ1b antibody positivity [12].

In the realm of autoimmune encephalitis presenting with ataxia, specific antibodies such as mGluR1, CASPR-2, and GABA-B receptor antibodies have been associated [12]. Recently, the paraneoplastic antibody Purkinje cell cytoplasmic autoantibody 1 (PCA-1) has been associated with isolated acute cerebellitis with an underlying gonadal malignancy, the most common being epithelial ovarian cancer [9].

Metabolic causes of ataxia can arise from B12 deficiency, thiamine and vitamin E deficiency. Neoplastic etiologies of cerebellitis are most commonly low-grade gliomas in adults but more aggressive medulloblastomas and lymphomas can occur [5]. Vascular causes such as cerebellar strokes also contribute to the differential diagnosis of acute cerebellar syndrome.

Infectious causes of cerebellitis are frequently attributed to viral pathogens, with Epstein-Barr virus (EBV), Varicella-Zoster virus (VZV), being among the most common [14]. Bacterial pathogens including *Mycoplasma pneumoniae* and *Borrelia burgdorferi* have also been associated with cerebellitis. *Listeria monocytogenes* is particularly notable as it can cause rhombencephalitis involving the brainstem and cerebellum, especially in immunocompromised individuals [14].

While HSV is a well-known cause of encephalitis, it is not commonly considered an infectious cause of cerebellitis. HSV-1 encephalitis most commonly involves the temporal and frontal lobes. The occurrence of HSV isolated cerebellar involvement is rare and not well-documented in medical literature.

Acyclovir, antiviral agent, is the standard of care for HSV encephalitis treatment. Acyclovir has significantly reduced the mortality associated with HSV encephalitis, from an estimated 70% to 15-20% [7]. Despite this reduction in mortality, patients can still experience long-term neurological sequelae. Only 50% of patients achieve a full neurological recovery one-year post-treatment with acyclovir [7]. Thus, adjunctive therapy in combination with acyclovir has been proposed to minimize long term neurological deficits from HSV encephalitis.

Adjunctive glucocorticoids have been considered as a potential adjunctive therapy as their anti-neuroinflammatory properties which have proven benefit in other central nervous systems infections like bacterial meningitis[6]. It has been hypothesized that overactivation of the host immune system leads to an extensive inflammatory cascade which damages neurons and glia cells contributing to neurological deficits, rather than direct damage by HSV infection [6]. However, the use of glucocorticoids in conjunction with acyclovir is controversial due to the theoretical risk of immunosuppression, which could lead to further HSV activation. Glucocorticoids inhibit the transcription factor NF-KB, crucial for cell-mediated immunity comprised of natural killer cells and CD8+ lymphocytes. These immune pathways are essential for eliminating an intracellular viral infection like HSV, by decreasing viral replication. Suppression of these pathways via glucocorticoids could be detrimental in the context of an active infection [13]. Thus, the benefit of glucocorticoids could outweigh the theoretical risk of HSV activation if there is extensive cerebral edema or increased intracranial pressure.

Currently there is no clear consensus on the role of glucocorticoids in HSV encephalitis treatment. In a retrospective case series glucocorticoid treatment in combination with acyclovir was correlated with improved outcomes [8]. However, a meta-analysis did not demonstrate a clear benefit for adjunctive steroid treatment in the treatment of viral encephalitis [6]. A prospective randomized controlled trial, GACHE, aimed to explore whether acyclovir combined with dexamethasone was

superior to acyclovir with placebo in patients with confirmed HSV encephalitis. Unfortunately, the trial was terminated prematurely due to low enrollment, and the limited data gathered from 41 patients randomized showed no significant difference between the two study arms [10]. The results of the completed prospective DexEnceph trial, which addresses long term neurological status after adjunctive steroid treatment has not yet been published [15]. With the recent discovery that HSV encephalitis can trigger post infectious encephalitis [15], it remains to be seen if immunomodulating treatment will affect this new entity.

The literature on HSV encephalitis treatment with isolated cerebellitis in adults is very limited. After an extensive search, the authors identified three cases in the medical literature to the best of their knowledge: Two patients—a 24-year-old female and a 19-year-old female with HIV on antiretroviral therapy—were treated with acyclovir and glucocorticoids. Both patients showed symptomatic improvement after two weeks and did not appear to suffer any long-term neurological sequelae in subsequent follow up [4]. A 29-year-old female treated with acyclovir showed symptom improvement and decreased cerebellar inflammation one month later MRI, although her long-term neurological status remains unknown [3].

Anecdotally, these case reports suggest a potential beneficial role for steroids in the treatment of HSV cerebellitis. A limitation of this case report and Campos et al. [3] is that the long-term neurological status of the patient could not be accessed. The use of adjunctive glucocorticoids in the treatment of HSV cerebellitis and encephalitis remains unclear and is a subject of ongoing investigation. While glucocorticoids may be considered to reduce cerebral edema, routine use remains limited due to the risks of possible immunosuppression, and interference with viral clearance. Treatment decisions should be guided by clinical presentation, patient-specific factors, and new emerging evidence.

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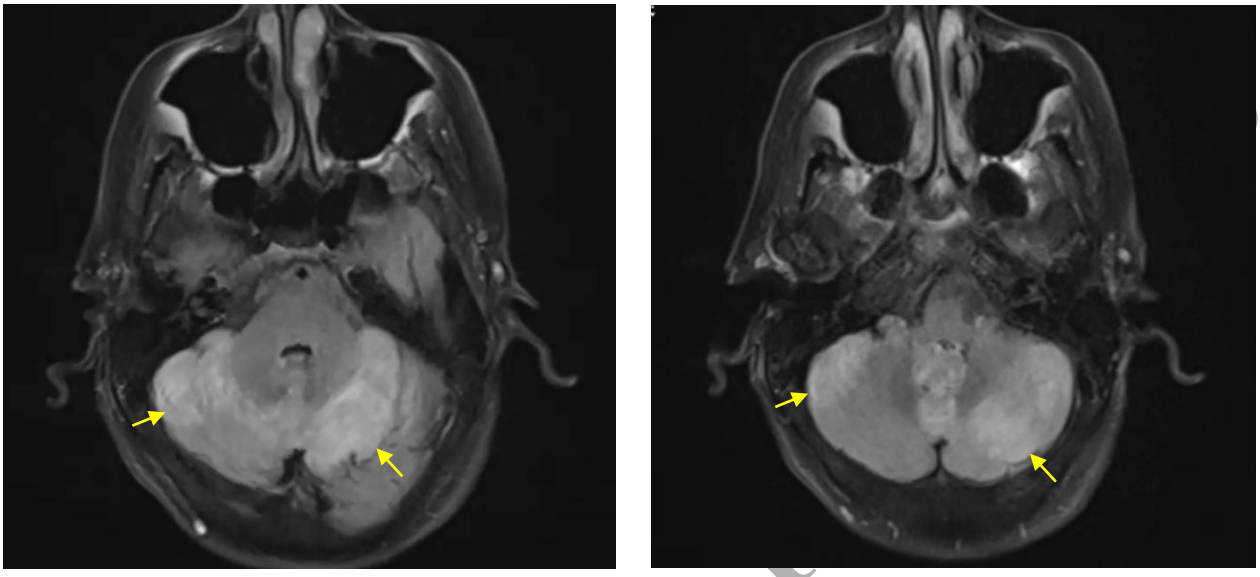
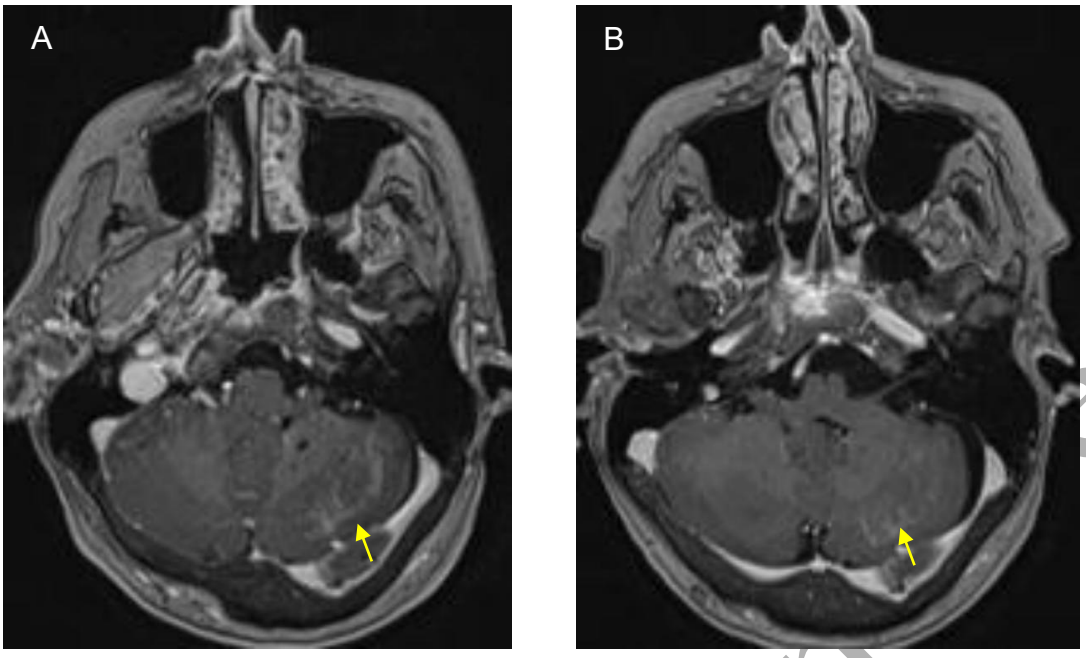
FIGURES AND TABLES.

Figure 1: Axial T2 FLAIR brain MRI showing diffuse hyperintense signal throughout the cerebellar hemispheres, consistent with cerebellar edema.



Legend: Yellow arrows indicate areas of prominent signal abnormality in both hemispheres.

Figure 2. (A) Pre- and (B) post-treatment axial contrast-enhanced MRI (MG-RAGE sequence) showing left cerebellar enhancement.



Legend: The left image shows diffuse cerebellar swelling and enhancement prior to treatment. The right image demonstrates marked improvement in cerebellar enhancement following 14 days of acyclovir and 5 days of intravenous methylprednisolone.