Herpes Simplex Virus-2 Meningoencephalitis With Abducens Nerve Palsy With Literature Review

Sachin Patil 1, Phillip Beck 1, Taylor B. Nelson 1, Andres Bran 1, William Roland 1

1. Infectious Disease, University of Missouri, Columbia, USA

Corresponding author: Sachin Patil, drsmp1@gmail.com

Abstract

Herpes simplex virus (HSV), a human alpha herpes virus, is responsible for most infections caused by herpes viruses worldwide. Among the herpes simplex viruses, both HSV 1 and 2 cause significant morbidity. HSV-2 accounts for most genital infections with extragenital complications involving the groin, thigh, or other pelvic areas. HSV-2 is the leading viral cause of sexually transmitted diseases. Viral dissemination via the blood or the cutaneous route during primary infection can affect joints, liver, lungs, spinal cord, and brain. HSV-2, by nature of its higher reactivations frequency, leads to clinical reactivation or subclinical shedding, resulting in increased transmission risk during unprotected sexual encounters. HSV-2 reactivation can result in lesions involving the fingers, skin, eyes, brain, and visceral organs such as the esophagus, lung, and liver. Ocular involvement results in keratitis, blepharitis, conjunctivitis, and rarely necrotizing retinitis. Oculomotor cranial nerve involvement by HSV is a rare entity even in patients with human immunodeficiency virus infection. Clinical features associated with reactivation are seen in primary infections, especially in children and adolescents. A medical literature search resulted in a few cases caused by a varicella-zoster virus but none by HSV. Here we describe a young female with a newly diagnosed meningoencephalitis and abducens nerve palsy (first case) due to a primary HSV infection. She came to the emergency department with headache, confusion, abnormal behavior and later developed diplopia as an inpatient. She was treated successfully with two weeks of acyclovir.

Keywords: herpes simplex virus, meningitis, encephalitis, abducens nerve palsy, cranial nerve palsy

Introduction

Herpes simplex viruses (HSV 1 & 2) are deoxyribonucleic acid viruses belonging to the human herpesvirus family’s alpha herpesvirus group. Humans are the only known natural reservoir with no known animal vectors. HSV-1 infection acquisition is earlier and frequent than HSV-2 based on epidemiological data [1]. HSV-2 infection is acquired frequently during puberty due to sexual activity initiation, whereas HSV-1 infection occurs commonly during the first decade of life. Risk factors for HSV-2 infection include human immunodeficiency virus infection. Clinical features associated with reactivation are seen in primary infections, especially in children and adolescents. A medical literature search resulted in a few cases caused by a varicella-zoster virus but none by HSV. Here we describe a young female with a newly diagnosed meningoencephalitis and abducens nerve palsy (first case) due to a primary HSV infection. She came to the emergency department with headache, confusion, abnormal behavior and later developed diplopia as an inpatient. She was treated successfully with two weeks of acyclovir.

Case Presentation

A 19-year-old white female came to the emergency department (ED) with altered mentation and abnormal behavior. Three days earlier, she developed headache, malaise, nausea, confusion with fever, behavioral changes, and agitation, which prompted her parents to bring her to the ED for evaluation. Her medical history was relevant for anxiety, depression, and obesity. She endorsed social alcohol consumption and routine recreational marijuana use. She denied any intravenous drug abuse and reported being sexually active. At the ED, she had stable vital signs. Clinical exam revealed a young obese female with somnolence, intermittent agitation, a Glasgow coma score of seven, spontaneous limb movements with no nuchal rigidity. Ocular examination revealed a left-sided esotropia. The genital examination was negative for lesions indicative of sexually transmitted disease.

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Comprehensive laboratory workup revealed a normal metabolic panel and blood count revealing a normal white cell count with neutrophilia (absolute granulocyte count of \(9.02 \times 10^9/L\)), lymphopenia (absolute lymph count of \(0.59 \times 10^9/L\)). Lactic acid was increased with a normal creatine kinase, thyroid-stimulating hormone, and troponin. Urinalysis was not indicative of urinary infection. The testing for rapid influenza A/B and SARS-CoV-2 nasopharyngeal polymerase chain reaction (PCR) was negative. The urine drug screen revealed cannabinoids (Table 1). Chest X-ray revealed no acute cardiopulmonary abnormality (Table 1). Sedatives and antipsychotics were required to control her agitation in the ED. Computed tomography of the head was done, which was normal (Figure 1). Due to her restlessness, fundoscopy could not be performed.

Her clinical course was concerning for meningitis/encephalitis, so she underwent a lumbar puncture for cerebrospinal fluid (CSF) and two blood culture sets. The CSF opening pressure was 30 centimeters (cm) of water. Immediately after obtaining the CSF, empiric antibiotics (vancomycin, ceftriaxone), acyclovir, and steroids were initiated. CSF analysis was suggestive of a viral infection with a negative CSF Bio fire PCR and cryptococcal antigen test (Table 1). The empirical regimen was continued, and she was admitted to internal medicine service.

<table>
<thead>
<tr>
<th>Laboratory test/Others</th>
<th>Result</th>
<th>Laboratory test/Imaging</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature max</td>
<td>39.5°C</td>
<td>CSF Color</td>
<td>Clear</td>
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<tr>
<td>Complete Blood count</td>
<td>Hemoglobin 11.1 g/dL, Platelet count 263,000/mL</td>
<td>CSF white cell count</td>
<td>808</td>
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<tr>
<td>Metabolic Panel</td>
<td>normal</td>
<td>CSF Neutrophil %</td>
<td>12%</td>
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<tr>
<td>Hemoglobin A1c</td>
<td>5.5% (4 – 6)</td>
<td>CSF Monocytes %</td>
<td>36%</td>
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<tr>
<td>Lactic acid</td>
<td>3.3 mmol/L (0.5 – 2.2)</td>
<td>CSF Lymphocytes %</td>
<td>52%</td>
</tr>
<tr>
<td>Creatinine Kinase</td>
<td>50 units/L (20 – 180)</td>
<td>CSF Red Blood cell count</td>
<td>182</td>
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<td>Lipid Panel</td>
<td>Within Normal Limits</td>
<td>CSF VDRL</td>
<td>Negative</td>
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<tr>
<td>Troponin T</td>
<td>&lt; 0.01 ng/mL</td>
<td>CSF Cryptococcal Antigen test</td>
<td>Negative</td>
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<td>Thyroid-stimulating hormone level</td>
<td>3.290 mIU/L (0.27 – 4.2)</td>
<td>CSF Culture</td>
<td>Negative</td>
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<td>Urine Analysis</td>
<td>Negative for UTI</td>
<td>CSF Bio Fire PCR Panel</td>
<td>Negative</td>
</tr>
<tr>
<td>Urine Drug Screen</td>
<td>Positive for cannabinoids</td>
<td>CSF HSV 1 &amp; 2 DNA PCR</td>
<td>Positive for HSV-2 DNA</td>
</tr>
<tr>
<td>Nasopharyngeal COVID-19 PCR</td>
<td>Negative</td>
<td>Blood Culture</td>
<td>Negative</td>
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<tr>
<td>Nasopharyngeal Influenza A &amp; B Antigen Testing</td>
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<td>Serum Pregnancy test</td>
<td>Negative</td>
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<tr>
<td>HIV 1 &amp; 2 Antigen Antibody testing</td>
<td>Negative</td>
<td>Serum Ferritin</td>
<td>65.2 ng/mL (13 – 150)</td>
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<td>Syphilis IgG and IgM testing</td>
<td>Negative</td>
<td>Serum Iron</td>
<td>14 mcg/dL (37 – 145)</td>
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<td>TB Gold QuantIFERON</td>
<td>Negative</td>
<td>Chest X-ray</td>
<td>No acute abnormality</td>
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<tr>
<td>Ehrlichia chaffeensis / canis / ewingii CSF and Blood PCR</td>
<td>Negative</td>
<td>Computed Tomography of Head</td>
<td>No acute intracranial abnormality</td>
</tr>
<tr>
<td>Anaplasma Serology</td>
<td>Negative</td>
<td>Magnetic Resonance Imaging of Brain</td>
<td>No acute intracranial abnormality</td>
</tr>
</tbody>
</table>

**TABLE 1: A summary of laboratory and imaging findings**

COVID-19 = Coronavirus disease 2019, CSF = Cerebrospinal Fluid, VDRL = Venereal Disease Research Laboratory Test, PCR = Polymerase chain reaction.
On day 2 of her hospitalization, she was febrile and encephalopathic with a leukocytosis of 17,550/mL. The infectious disease (ID) team recommended CSF PCR for HSV, VDRL (Venereal Disease Research Laboratory Test), CSF, and blood serology for Ehrlichia, Anaplasmosis. Doxycycline was added to the empirical regimen. Tuberculosis gold QuantiFERON, serology for HIV, and syphilis were negative. Magnetic resonance imaging of the brain revealed no abnormalities (Figure 2). On day 3, her mentation and leukocytosis improved with new onset of diplopia. She informed the medical team of her unprotected sexual encounter with a new partner three weeks before. On day 4, CSF and blood cultures returned negative. CSF and blood PCR for Ehrlichia, Anaplasmosis were negative. Both vancomycin and doxycycline were stopped. A neurology evaluation confirmed left abducens nerve palsy. By day 6, CSF HSV PCR returned positive for HSV-2 DNA, confirming meningoencephalitis (ME) diagnosis, whereas the CSF VDRL was negative. Ceftriaxone was discontinued, and she was discharged on IV acyclovir to complete two weeks of antiviral therapy. An eye patch over the left eye was recommended to prevent diplopia. At the time of her discharge (day 5), her encephalopathy had resolved.
At two weeks follow-up with primary care, ophthalmology, and occupational therapy, she continued to improve with residual diplopia. She was continued on conservative management with an eye patch and physical therapy. Per ophthalmology, it may take six months for her diplopia to resolve completely. At two months follow-up, her diplopia had improved, and she was cleared for driving with a left eye patch.

**Discussion**

HSV-2 infection in adults leads to primary genital herpes followed by dormant infection of the sacral nerve root ganglia [1]. HSV-2 can also infect the orofacial area, especially the tonsils or the pharynx. Infrequently during the primary infection, the extragenital spread via blood or cutaneous route can affect local adjoining areas (uterus, prostate, urethra, thigh) in addition to the brain, spinal cord, lungs, liver, or joints. Neurological manifestations include aseptic meningitis, sacral neuralgia, transverse myelitis. Reactivation after the primary infection (HSV 1 & 2) presents as recurrent lesions involving the skin, finger, brain, eyes, and rarely visceral organs (lung, liver, esophagus). Eye lesions include keratitis, blepharitis, conjunctivitis, chorioretinitis, or necrotizing retinitis. HSV encephalitis causes 10% to 20% of all viral encephalitis cases in the United States of America, but it is still the most common recurrent cause [4]. HSV encephalitis incidence is 2.3 cases per one million persons per year. The age distribution is biphasic, with an increased incidence before 30 years and after age 50 [5]. HSV-1 accounts for most cases (>95%) [6,7]. The pathophysiology of encephalitis is different in young adults in comparison to older adults. In adolescence, primary HSV infection can cause encephalitis via the olfactory neurotropic spread, which manifests as a reactivation in elderly patients. Based on our PubMed literature review, neither HSV primary infection nor reactivation has been reported to involve the ocular cranial nerves three, four, or six.

Abducens nerve palsy (ANP) is the most common oculomotor cranial nerve palsy due to multiple underlying disease processes. The incidence of ANP is 11.3/100,000 persons per year, and the proportion of cases...
attributed to infection is minimal [8]. To date, no study has determined the exact percentage of an infectious cause of ANP. It can be bilateral or unilateral. The abducens nerve (AN) has the longest anatomic course of all oculomotor cranial nerves, arising from the contralateral abducens nucleus in the dorsocaudal pons. It innervates the ipsilateral lateral rectus muscle and is responsible for eye abduction resulting in an outward gaze. Isolated abducens paralysis is one of the classical false localizing signs due to raised intracranial pressure. Local processes such as trauma, infection, inflammation, and neoplasm-induced raised intracranial pressure can affect AN in its course. AN injury results in ipsilateral abduction impairment, diplopia, and eso-deviation. Infections may be responsible for ANP by one or more of the following pathophysiologic mechanisms: ischemic vascular neuritis, primary cranial neuritis, perineuritis due to adjacent meningeal inflammation, and compressive effect [9]. Apart from the herpes viruses, oculomotor cranial nerve involvement is infrequent among other viral encephalitides [9-13]. Other viral causes of ANP in adults are the West Nile virus, hantavirus, enterovirus, and dengue virus [14-17]. Among the herpes viruses, it is more common with varicella-zoster infections of the brain than with Epstein-Barr virus and cytomegalovirus. Even in patients with varicella-zoster infections, ANP occurring along with meningitis or encephalitis is a rare entity [10].

Our patient was a young immunocompetent adult female not on any immunosuppressive medications. Her presentation was approximately three weeks after unprotected sexual intercourse with no genital complaints or brainstem localizing signs or symptoms. Her ME was likely due to a primary infection than a reactivation. HSV-2 accounts for about 5% of these cases caused by HSV [6]. The CSF opening pressure was 30 cm of H2O, which was high normal (<25 cm of H2O), and this is a normal variation due to her increased BMI of 45 kg/m² [10]. CSF differential count was suggestive of a viral cause, and PCR testing was positive for HSV-2. In cases with higher clinical suspicion, we recommend continuing acyclovir until a reliable HSV PCR is negative. The occurrence of ocular cranial nerve palsy along with ME is rare. An outpatient eye evaluation confirmed left lateral rectus palsy with no papilledema. No HSV ME cases with ANP were revealed on a PubMed literature review, and our case is the first one documented to our knowledge. With unilateral ANP and a normal MRI brain with no significantly raised intracranial pressure, the possible mechanism could be primary cranial neuritis or perineuritis from ME. The presence of residual ANP at two months post-discharge supports this explanation. Had this been due primarily to raised intracranial pressure, ANP should have resolved once the pressure declined. At one- and two-month follow-up she still had residual diplopia and esotropia. The recovery rates for infectious causes are unknown in comparison to non-infectious causes. Information from anecdotal case reports reveal recovery in most cases by six months [9,13-17].

Conclusions

In younger patients with meningencephalitis and oculomotor cranial nerve palsy, both HSV and syphilis should be considered in the differential diagnosis. HSV-2 should be suspected even in the absence of genital complaints. CSF PCR assay availability has improved the ability to make rapid diagnoses with no delays in treatment. We suggest continuing acyclovir until a dedicated HSV PCR is negative, as in our case. We agree that MRI is the best imaging modality in younger patients with ME and ANP to rule out other causes such as trauma and tumor. Detailed studies on isolated ANP infectious causes, effective antimicrobial therapy duration, immunomodulatory therapy effect, and recovery rates are recommended to improve future treatment and inform these conditions' prognosis.

Additional Information

Disclosures

**Human subjects:** Consent was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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