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DIAGNOSTIC DILEMMAS WITH HERPES SIMPLEX ENCEPHALITIS

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Introduction

Herpes simplex encephalitis is the most common cause of sporadic acute common viral encephalitis in the United States and abroad. Beyond the neonatal period, herpes simplex virus type 1 (HSV-1) is the principal agent of herpes encephalitis. Herpes-induced myelitis and aseptic meningitis are primarily caused by herpes simplex virus type 2 (HSV-2).1,2

Clinical manifestations of herpes encephalitis range from minimal symptoms to hemorrhagic necrosis of the temporal lobes with high rates of morbidity (20% to 30%) and mortality (70%).3,5 Although brain biopsy is the definitive diagnostic procedure, the clinical presentation, along with temporal lobe abnormalities detected by electroencephalogram (EEG) and magnetic resonance imaging of the brain, can be highly suggestive of the diagnosis.6,8 Response to appropriate antiviral therapy gives further support to the proper diagnosis of HSV encephalitis. The following case of herpes encephalitis in a child with leukemia highlights diagnostic dilemmas associated with early recognition and therapy.

Case Presentation

A 10-year-old girl developed acute lymphocytic leukemia (ALL) eight months prior to admission. Allogeneic bone marrow transplant four months after diagnosis of ALL was complicated by chronic graft-versus-host disease (GVHD). Pulmonary aspergillosis six months prior to presentation was successfully treated with a left upper lung lobectomy and amphotericin B. Relapse of leukemia required reinduction with chemotherapy.

In the third month of hospitalization, the patient developed fever of 101.5 degrees Fahrenheit. She was confused and unable to recognize her mother or caretakers but was able to identify inanimate objects. She was frustrated with her inability to recognize people. Initially, medication including diphenhydramine HCl, alprazolam, and methylprednisolone sodium succinate was thought to be at least partly responsible for her symptoms. She also was receiving cefazidime and sulfamethoxazole/trimethoprim to resolve typhlitis. She was awake and alert with no photophobia, neck stiffness, or focal central nervous system findings. Cardiovascular, respiratory, and abdominal examinations were unremarkable. The differential diagnosis at this point included bacteremia or corticosteroid-induced psychosis. Blood and urine cultures were taken, and vancomycin was added to her antibiotic regimen. On the next day, her fever persisted at 102 degrees Fahrenheit, but unchanged from baseline. Computed tomography (CT) of the brain without contrast was unremarkable. Lumbar puncture was performed. Cerebrospinal fluid (CSF) studies yielded the following values: white blood cell count, 12 (0-5) x 10^6/L with 92% polymorphonuclear leukocytes; red blood cell count, 16 x 10^6/L; protein, 43 (15-45) mg/dL; and glucose 139 (50-80) mg/dL. The Gram stain of the CSF was negative. India ink stain showed no encapsulated yeasts. Amphotericin B was prescribed for possible cryptococcal infection. Cultures of the CSF for bacterial, fungal, and viral elements were sterile. The initial serum HSV, cytomegalovirus, and toxoplasmosis IgM antibody titers were negative. The HSV IgG was positive at 1:3 and the CMV IgG at 64.

Her low-grade fever persisted (100.6 degrees Fahrenheit). She remained cooperative, appropriate, and able to recognize people, but she was aphasic. Four days after the onset of her symptoms, a repeat lumbar puncture showed that the level of CSF protein had increased to 65 (15-45) mg/dL. Acyclovir in a dose of 10 mg/kg given intravenously every eight hours was begun for a presumed HSV encephalitis. The patient’s mental status then worsened, and she developed incontinence. A magnetic resonance image with gadolinium enhancement 12 days after onset of symptoms showed abnormalities in the temporal lobes (Figs 1A-B). An EEG showed no evidence of epilepsy but indicated the presence of frontal rhythmic intermittent delta discharges. After 14 days, vancomycin and ceftazidime were discontinued, but acyclovir was continued. Her mental status improved slowly. She required assistance in ambulation to maintain her balance, but her incontinence resolved. Over the next few days, she developed a Klüver-Bucy-like syndrome9 manifesting as inappropriate behavior and overt sexual expressions toward her healthcare providers. A repeat HSV serology one month into her illness showed an IgG titer elevated to 1:2560, while IgM was still negative. The patient was eventually discharged home to finish a 28-day course of high-dose acyclovir treatment. On follow-up, she had clinically improved, was able to walk without assistance, but was still unable to name certain objects.

One month later, the patient was readmitted to the hospital with severe respiratory insufficiency that proved fatal. An open lung biopsy was consistent with diffuse alveolar damage. At autopsy, the brain tissue showed marked atrophy of both temporal lobes with cystic softening, diminution of gray matter, and numerous calcifications. Microscopic examination demonstrated subcortical gray matter infaracts with widespread gliosis and dystrophic calcifications. Penetrating arteries within the white matter and overlying meninges showed prominent perivascular cuffing with lymphocytes and plasma cells. Immunostaining for HSV-1 and -2 were inconclusive for herpes encephalitis. No viral particles in the temporal lobe gray matter were seen on electron microscopy.

Discussion

This case presents the typical diagnostic challenge often faced in patients with fever and changes in mental status. The patient presented with fever, features of...
encephalitis, nonspecific EEG changes, and magnetic resonance imaging (MRI) of the brain suggestive of HSV encephalitis. The later rise in the serum IgG HSV titer may have been caused by herpes simplex encephalitis, but it also has been observed in reactivation of acute oral labial herpes, latent viral activation in febrile illnesses, lymphoproliferative disorders, and renal transplant patients. A significant increase in the quantity of both CSF and serum antibodies has been noted in these settings. Neuropsychologic changes such as naming deficits, behavioral disturbances (Klüver-Bucy syndrome), abnormalities in language, memory, and visual perception (especially of faces and objects) are well recognized in association with HSV encephalitis.

The gold standard for diagnosis of herpes simplex encephalitis is cerebral biopsy, and with appropriate histologic and cultural techniques, this approach has a 100% specificity. Since this method is not without risk, there is controversy as to when to use biopsies in patients with nonspecific encephalitis symptoms. Because of this dilemma, less reliable diagnostic tools have been used. Serum and CSF serologies with a fourfold increase in IgG titers or a CSF-to-serum ratio of ≥20 and positive CSF cultures for HSV are reported to be diagnostic. The EEG may show diffuse slowing of brain waves, unilateral or bilateral periodic discharges in the temporal lobe. CT, technetium brain scanning, and MRI may show abnormalities that can indicate edema, hemorrhage, or localized uptake in the temporal lobes. These neurodiagnostic procedures have varying degrees of sensitivity and specificity. MRI is probably the most sensitive, especially when gadolinium enhancement is used.

Polymerase chain reaction, a method that was not yet available for our patient, uses primers from an HSV DNA sequence in the CSF. Investigators report sensitivity over 95% and specificity approaching 100% in patients with biopsy-proven herpes simplex encephalitis. This test will likely aid and augment current diagnostic methods, particularly when a nested PCR approach is followed, especially if a brain biopsy cannot be performed or shows nonspecific results.

Although reactivated mucosal HSV is common in cancer patients, HSV encephalitis is rare. This patient is the only patient diagnosed with HSV encephalitis out of 19,810 patients treated at our center. Prompt administration of high-dose intravenous acyclovir of 10 to 15 mg/kg every eight hours is indicated when HSV encephalitis is a diagnostic possibility. Our patient responded to therapy, albeit with residual neurologic deficits before her untimely death. The MRI with gadolinium enhancement detected prominent changes in the temporal lobes and confirmed the clinical diagnosis of HSV encephalitis without resorting to brain biopsy. The autopsy confirmed the nature of the temporal lobe changes after HSV-induced damage despite the absence of active HSV infection at the time of death.

References