Neurological Complications of Herpes Simplex Virus Type 2 Infection

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Herpes simplex virus type 2 (HSV-2) infection is responsible for significant neurological morbidity, perhaps more than any other virus. Seroprevalence studies suggest that as many as 45 million people in the United States have been infected with HSV-2, and the estimated incidence of new infection is 1 million annually. Substantial numbers of these persons will manifest neurological symptoms that are generally, although not always, mild and self-limited. Despite a 50% genetic homology between HSV-1 and HSV-2, there are significant differences in the clinical manifestations of these 2 viruses. We herein review the neurological complications of HSV-2 infection.

The herpes viruses are responsible for significant neurological morbidity. Three of the 8 human herpes virus types—herpes simplex virus type 1 (HSV-1), HSV-2, and varicella zoster virus—establish latency in the peripheral sensory ganglia and persist in the host for a lifetime. Primary infection occurs at a mucocutaneous surface with retrograde transportation of the virus to the peripheral sensory ganglia, maintenance of the viral genome within the peripheral sensory ganglia, and periodic reactivation with antegrade transmission to the nerve endings and mucocutaneous surface.

Latency and Reactivation

Neurons in the sacral ganglia traditionally have been considered to be the site of HSV-2 latency. Examination of HSV-2 latency using polymerase chain reaction (PCR) techniques have demonstrated HSV-2 latency in ganglia throughout the central nervous system (CNS) axis, albeit at significantly lower frequencies than in the sacral ganglia. Latency of HSV-2 has also been demonstrated to occur in trigeminal ganglia. The widespread latency of HSV-2 suggests that the virus may reach ganglia far removed from the site of primary infection. The molecular mechanisms underlying HSV latency are incompletely understood.

Primary Infection

Herpes simplex virus type 2–associated neurological disease may result from primary infection or reactivation of latent HSV-2. Neurological disease after primary HSV-2 infection is seen most often in neonates. After the neonatal period, HSV-2 infection is principally, but not exclusively, acquired through sexual activity. Primary HSV-2 infection is delayed in most individuals until adolescence and early adulthood with the advent of sexual activity. By the time of HSV-2 infection, most individuals have already been infected by HSV-1. Primary HSV-2 infection in immunocompetent adolescents and adults is usually asymptomatic, with most patients being unaware of their HSV-2 exposure.

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Although reactivation of latent HSV primarily has been studied in HSV-1–infected cells, it is likely that similar mechanisms underlie reactivation of HSV-2. Latent HSV infection is reactivated by local and systemic stimuli. Current evidence suggests that the most plausible mechanism for HSV reactivation is stimulation of latently infected cells through

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pathways yet to be determined. The fate of neurons supporting replication of reactivated HSV remains undecided. Many patients with HSV-2 infection shed low levels of virus continuously without demonstrated reactivation.

**EPIDEMIOLOGY**

Humans are the only known reservoir of HSV-2. The frequency of HSV-2 seropositivity varies by population. An estimated 45 million persons in the United States have genital herpes infection, with new infections occurring at an estimated rate of approximately 1 million per year. Approximately 85% to 90% of infections are unrecognized and therefore remain undiagnosed. Seropositivity for HSV-2 correlates with the number of sexual partners, the age of sexual debut, increasing age, black or Hispanic race, female sex, and the presence of other sexually transmitted diseases, including human immunodeficiency virus (HIV) infection. Despite the widespread adoption of safer sex methods with the advent of the AIDS pandemic, seroprevalence studies in the United States suggest that the frequency of HSV-2 infection is increasing. Seroprevalence rates for HSV-2 in the developed world are not very different than those of the United States.

**NEUROLOGICAL COMPLICATIONS**

Although HSV-1 has a predilection for the development of encephalitis after intracerebral injection in the mouse model, HSV-2 generally causes meningitis. However, the me- ninges are not the only component of the CNS involved in HSV-2 infection. Virtually any part of the neuraxis may be affected by this virus, including the retina, brain, brainstem, cranial nerves, spinal cord, and nerve roots.

**NEONATAL HERPES SIMPLEX ENCEPHALITIS**

When HSV-2 infection is mentioned, neonatal herpes simplex encephalitis (HSE), a devastating disorder, is the disease most commonly considered. Seventy percent of affected neonates are born to mothers without symptoms or signs of genital herpes. Recent studies suggest that as much as 30% of neonatal HSE is due to HSV-1. The risk of acquisition during a primary infection with HSV-1 or HSV-2 is 50%. The risk of development of neonatal HSE is reduced if a mother with primary HSV-2 genital herpetic infection is seropositive for HSV-1. Risk factors for neonatal HSV disease include first-episode maternal infection in the third trimester, invasive monitoring, delivery before a gestational age of 38 weeks, and maternal age of less than 21 years. Delivery by cesarean section significantly reduces the risk of HSV acquisition. In mothers who are seropositive for HSV-2 only, the risk to the neonate is less than 1%.

Dissemination to the CNS occurs in 70% of all infected neonates and is most commonly heralded by the appearance of focal or generalized seizures. Skin lesions are observed in 66%. Laboratory test results often show abnormal liver function and disseminated intravascular coagulation. The cranial magnetic resonance images (MRIs) and computed tomograms initially show diffuse edema and cerebral atrophy, calcifications, and cystic encephalomalacia. Electroencephalography shows slow background and paroxysmal discharges. Results of cerebrospinal fluid (CSF) analysis are remarkable for a lymphocytic pleocytosis, increased protein levels, and PCR findings that are positive for HSV-2. Neonates with HSE due to HSV-1 have a better prognosis than those with infection due to HSV-2. The latter group has a higher frequency of seizures, greater CSF pleocytosis and protein concentration, and more CNS structural disease on radiographic images.

**ACUTE ASEPTIC MENINGITIS IN ADULTS**

Aseptic meningitis occurs in 36% of women with primary HSV-2 genital infection and 13% of men; it results in hospitalization for 6.4% of infected women and 1.6% of infected men. Aseptic meningitis is a rare manifestation of primary HSV-1 genital infection and a rare complication of recurrent genital infection due to HSV-1 and HSV-2. During the prodrome of genital herpes and concomitant with the herpetic eruption, affected patients experience headache, neck stiffness, and low-grade fever. Back, buttock, perineal, and lower extremity pain may be associated with urinary retention and constipation. Analysis of CSF reveals a lymphocytic pleocytosis. Viral cultures of CSF may yield diagnostic findings, but PCR for HSV-2 is recommended. For samples obtained after the acute infection, measurement of intrathecal antibody levels for HSV-2 may be diagnostically valuable.

**RECURRENT ASEPTIC MENINGITIS**

Disease Description

Recurrent aseptic meningitis due to HSV-2 may occur with or without symptomatic herpetic mucocutaneous disorder. The manifestations of this disorder are identical to that observed with primary genital herpes. In 1 series, recurrent meningitis has been observed in 19% to 42% of patients who experience meningitis with their first episode of genital herpes. Headaches occur in as many as 15% of patients with recurrent genital herpes. Anecdotal experience suggests that suppressive prophylactic therapy with acyclovir sodium, famciclovir, and valacyclovir hydrochloride prevents these recurrences.

Many of these cases were previously diagnosed as Mollaret meningitis, before the recognition that HSV-2 may be causative. Confusion, focal neurological manifestations, and cranial neuropathies may be observed. Analysis of CSF often reveals a large mononuclear cell with an indistinct cytoplasm referred to as the Mollaret cell. Herpes simplex virus type 2 is not the only virus responsible for Mollaret meningitis, and some authorities have suggested that the term be restricted to recurrent aseptic meningitis without an identifiable cause.

**Report of a Case**

A woman aged 33 years presented with a 4-day history of intractable headache, photophobia, nausea, and...
neck and back discomfort. She had 3 previous hospital admissions for a similar disorder, the first and most severe of which occurred concomitantly with her initial outbreak of genital herpes. Results of her examination were remarkable for a low-grade fever and stiff neck. A contrast-enhanced MRI of the brain yielded normal findings. Results of CSF analysis showed a white blood cell count of 56/μL (90% lymphocytes), a protein level of 66 mg/dL, and a glucose level of 54 mg/dL. Results of PCR were positive for HSV-2. Her symptoms resolved shortly after treatment with intravenous acyclovir, and no further episodes were observed during a suppressive regimen of daily acyclovir in the ensuing 3 years.

ADULT HSV-2 ENCEPHALITIS AND MENINGOENCEPHALITIS

Herpes simplex virus type 2 accounts for 1.6% to and 6.5% of all HSE in adults. 

It is typically observed in immunosuppressed individuals. Unlike HSV-1, HSV-2 affects mesial temporal or orbitofrontal lobes less often and may demonstrate a predilection for the brainstem. Herpes simplex encephalitis due to HSV-2 may occur without meningitic features. Neurological manifestations may include altered level of consciousness, cranial neuropathies, hemiparesis, and hemisensory loss. In contrast to HSE due to HSV-1, which typically demonstrates progressive deterioration, a fluctuating course may be observed. The MRI may show normal findings, nonspecific white matter lesions, or lesions of orbitofrontal and mesial temporal lobes suggestive of HSE due to HSV-1. These lesions are best seen on T2-weighted or fluid-attenuated inversion recovery images.

HSV-2 ASCENDING MYELITIS

Thoracic or lumbosacral ascending myelitis is also seen with HSV-2 infection but almost exclusively in immunocompromised patients, particularly those with HIV infection. The lesions may be necrotizing and, if so, have a poor prognosis. Recurrent disease also has been described. The clinical presentation is characterized by pain, often anogenital or radicular, with associated limb numbness, paresthesias, and weakness. Herpetic skin lesions may accompany the neurological manifestations. An MRI of the spine typically shows enlargement of the lower cord or conus medullaris with an increased signal on T2-weighted images and contrast enhancement of adjacent nerve roots.

HSV-2 RADICULOPATHY

Disease Description

In autopsies studies, 40% of sacral dorsal root ganglia contain dormant HSV-2. Only 5% of these individuals had recognized genital herpes infection during life. This disorder is almost always misdiagnosed unless it occurs concomitantly with the initial outbreak of genital herpes. Obtaining a history of recurrent genital herpes outbreaks occurring contemporaneously with the radicular symptoms is very helpful diagnostically. Unfortunately, the patient may be unaware of the infection and the physician may be reluctant to inquire about sexually transmitted disease. Radiculopathy caused by HSV-2 infection typically affects the lumbar or sacral nerve roots and is often recurrent. In addition to radicular pain, paresthesias, urinary retention, constipation, anogenital discomfort, and leg weakness may be observed. Although there are few descriptions of HSV-2 radiculitis and radiculomyelitis, nerve root or lower spinal cord edema, enlargement, and hyperintensity on T2-weighted MRI and contrast enhancement are anticipated; however, the lumbosacral MRI may show normal findings. The disorder is typically self-limited, resolving after days or weeks, but recovery appears to be hastened by the use of antiviral medications.

Report of a Case

A woman aged 43 years presented with a burning, shooting pain radiating down the back of her left leg and a sense of weakness in the leg of 2 months' duration. Driving and climbing stairs were difficult. She commented on a similar, self-limited discomfort occurring with variable frequency since the birth of her second child 10 years earlier. She had her initial outbreak of genital herpes at that time. Results of the examination showed minimal weakness of the extensor hallucis longus, normal reflexes, and decreased pinprick sensation in an L5 distribution. Titers of IgG HSV-2 antibody were elevated in the blood. Lumbosacral spine MRI with and without contrast showed normal findings. Analysis of CSF showed 12 white blood cells (84% lymphocytes) and a protein level of 54 mg/dL. Results of CSF PCR for HSV-2 were positive. Therapy consisting of acyclovir sodium, 800 mg 3 times daily, was initiated, with prompt resolution of her symptoms. While receiving daily acyclovir suppressive therapy, she had no further recurrences.

CRANIAL NEUROPATHY

Although it has been argued that the presence of detectable viral DNA in the geniculate ganglia of most humans cannot explain the annual incidence of Bell palsy of 20 to 30 per 100 000, there has been increasing acceptance of HSV-1 and varicella zoster virus as the cause of Bell palsy. Other infectious diseases have been implicated as well. Although sites of viral latency differ between HSV-1 and HSV-2, likely owing to their latency activity transcripts, HSV-2 can certainly be harbored by the trigeminal ganglia. In a study of more than 1000 people, 3.2% shed HSV-2 in their saliva on at least 1 occasion. Bell palsy has been reported after the discontinuation of acyclovir therapy in a patient being treated for HSE due to HSV-2.

ACUTE RETINAL NECROSIS

Acute retinal necrosis is heralded by red eye, periorbital pain, and impaired visual acuity. Examination results will show episcleritis or scleritis, keratic precipitates, retinal vasculitis, and necrosis with retinal detachment. Typically, this sight-threatening disorder has a bimodal age distribution, with varicella zoster virus and HSV-1 infections affecting older patients and HSV-2 infections affecting patients with a median...
age of 20 years. Acute retinal necro-
sis may occur in association with
HSV-2 meningoencephalitis.

**HSV-2 IN THE SETTING OF HIV INFECTION**

An association between HSV-2 and HIV has been recognized since the onset of the HIV/AIDS pandemic. Recent studies have demonstrated synergism between HSV-2 and HIV. Infection with HSV-2 increases the risk of HIV acquisition 2- to 4-fold compared with patients without HSV-2 infection., increases the risk of transmitting HIV to partners, and accelerates the progression of HIV infection to AIDS. Reduction of HSV-2 infection, increases the risk of the development of intrathecal antibodies limits their usefulness. Type-specific serological testing can detect prior infection in most HSV-2-infected individuals who are unaware of prior infection. Two serological methods have been validated for the diagnosis of HSE. The HSV-specific antibody index and HSV-specific immuno blotting of oligoclonal IgG require comparison of HSV-specific antibody reactivity in CSF and serum to ensure that serum HSV antibodies have not reached the CSF by means of a sink mechanism.

**DIAGNOSIS**

Polymerase chain reaction assays are rapid, sensitive, and specific for HSV-2 and HSV-1 and constitute the criterion standard for the diagnosis of HSV infections of the nervous system. The development of real-time PCR and methods for identifying HSV-1 and HSV-2 allow rapid identification of HSV in CSF, serum, and other tissues.

The sensitivity and specificity of CSF PCR for HSE due to HSV-1 or HSV-2 infection exceeds 90% in most studies for children and adults. Polymerase chain reaction analysis has been helpful in detecting HSV in perhaps 15% to 20% of patients with mild or atypical forms of HSE, including those with radiculomyelitis, Mollaret meningitis, and Bell palsy. However, an initially negative result for HSV PCR in a patient with a high probability of an HSV neurological disorder significantly reduces but does not exclude the diagnosis.

Viral culture, although frequently negative, and serological-assays for HSV antibodies are still useful in several settings. A study of neonatal HSV showed 40% of CSF cultures were positive. Viral cultures may be of more limited value in HSV-2 recurrences. Serological assays have limited value in the diagnosis of HSV-2-associated neurological diseases. Although several serological assays will differentiate between HSV-2 and HSV-1, the delay in the development of intrathecal antibodies limits their usefulness. Type-specific serological testing can detect prior infection in most HSV-2-infected individuals who are unaware of prior infection. Two serological methods have been validated for the diagnosis of HSE. The HSV-specific antibody index and HSV-specific immunoblotting of oligoclonal IgG require comparison of HSV-specific antibody reactivity in CSF and serum to ensure that serum HSV antibodies have not reached the CSF by means of a sink mechanism.

**TREATMENT**

Vidarabine phosphate was the first agent to demonstrate efficacy in HSE. Two large subsequent studies demonstrated the superiority of acyclovir, and it has been widely adopted as standard therapy. The current recommendation for HSE in adults and children older than 3 months is intravenous acyclovir sodium at a dosage of 10 mg/kg every 8 hours for 14 to 21 days. A clinical trial of oral valacyclovir after intravenous acyclovir for 14 to 21 days is currently being conducted to determine whether prolonged antiviral therapy will improve the outcome and decrease the recurrence rate. Age, level of consciousness at presentation, duration of encephalitis, and HSV viral load all affect the treatment of HSE. In neonates with suspected or proved neonatal HSE, acyclovir sodium is recommended, with a regimen of 20 mg/kg every 8 hours for 14 to 21 days. If HSV-2 DNA is detected in the CSF after 21 days of therapy, intravenous acyclovir therapy is continued for another 14 days and the CSF is reexamined for HSV DNA by means of PCR. Intravenous acyclovir therapy is stopped when the CSF no longer contains HSV DNA. There have been only anecdotal reports of the treatment of other HSV-2–related neurological disease, which suggests that acyclovir sodium at a dosage of 5 to 10 mg/kg 3 times daily is sufficient for the treatment of HSV-2 meningitis and that a dosage of 10 mg/kg 3 times daily is sufficient in myelitis and radiculitis. In patients with HSV-2 myelitis, the addition of high-dose intravenous glucocorticosteroid therapy to antiviral therapy has been suggested to decrease the risk of the development of an ascending myelitis.

Acyclovir-resistant HSV strains have been isolated from immunocompetent and, more commonly, immunocompromised patients. Increasing the dose of acyclovir for the treatment of drug-resistant HSV infections is rarely successful because mutations in the thymidine kinase gene are responsible for drug resistance. Successful treatment with valacyclovir of resistant HSE due to HSV-2 has been reported. Acyclovir-resistant HSV responds to foscarnet sodium and, possibly, cidofovir.

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