Herpes Virus Encephalitis in Adults

Current Knowledge and Old Myths

Alejandro A. Rabinstein, MD

KEYWORDS

• Herpes simplex virus • HSV • Encephalitis • Diagnosis • Prognosis • Treatment

KEY POINTS

- Herpes simplex virus (HSV) is the most common cause of sporadic encephalitis and should be suspected in patients presenting with acute alteration of consciousness that is otherwise unexplained. However, it remains an infrequent diagnosis in clinical practice.
- Identification of the viral DNA in the cerebrospinal fluid via polymerase chain reaction is sensitive and specific for the diagnosis of HSV encephalitis.
- HSV-1 encephalitis nearly always shows characteristic signs on the MRI scan (hyperintensity on fluid-attenuated inversion recovery in medial temporal, insular and inferior frontal areas).
- Delay in the administration of acyclovir is the most common modifiable risk factor for poor prognosis in patients with HSV encephalitis. Therefore, acyclovir must be immediately initiated whenever HSV encephalitis is in the differential diagnosis.

Herpes simplex virus (HSV) is the most frequent cause of sporadic acute viral encephalitis across the world. Although brain infection by HSV is a major problem in neonates, this review focuses only on infections in adults. HSV-1 is responsible for the great majority of cases of encephalitis, but HSV-2 infection also can present with encephalitis and therefore it will be included in this review. HSV encephalitis has been a recognized nosologic entity for many decades, but some of the classic teaching about this disease is outdated or plainly wrong. In this article I will try to dispel some of these old myths as I present up-to-date information on this grave but treatable infection.

BASIC EPIDEMIOLOGIC CONCEPTS

HSV-1 seropositivity is high among healthy adults and increases with age; it has been estimated to be 50% to 55% in middle-age and 60% to 90% among older adults.[1,2]

Disclosures: No relevant disclosures.
Department of Neurology, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905, USA
E-mail address: rabinstein.alejandro@mayo.edu

Neurol Clin ■ (2017) ■–■
http://dx.doi.org/10.1016/j.ncl.2017.06.006 **neurologic.theclinics.com**
0733-8619/17/

Yet, HSV encephalitis is an infrequent diagnosis. Despite being more common than other causes of sporadic infectious encephalitis and accounting for up to 20% of all cases of acute encephalitis, the annual incidence of HSV encephalitis worldwide is only 2 to 4 cases per 1,000,000.[3,4] Among adults, most cases occur in patients older than 50 without sexual predilection. HSV-2 encephalitis tends to affect immunocompromised patients.[5,6]

PATHOPHYSIOLOGY

HSV-1 and HSV-2 are large, double-stranded DNA viruses belonging to the Herpesviridae family. Other members of this family include the varicella zoster virus, Epstein-Barr virus, cytomegalovirus, and human herpes viruses-6, -7, and -8. Although infections from these other viruses can also involve the brain, their characteristics differ and thus deserve a separate discussion.

HSV gains access to humans through mucous membranes or damaged skin. It then infects sensory neurons and travels by fast retrograde axonal transport to neurons in the dorsal root ganglia.[7] How HSV enters the central nervous system is less clear. Retrograde transport through the olfactory or trigeminal nerves appears most plausible, as it would explain the preferential involvement of the frontal and mesiotemporal lobes in cases of encephalitis. It is also unclear whether acute encephalitis is caused by viral reactivation from a latent state or by a primary infection. It is known, however, that HSV can survive in sensory neurons (including the trigeminal ganglia) for a very long time and then become reactivated. The immune response triggered by HSV appears to be crucial to the pathophysiologic changes in patients with acute encephalitis. Details on the molecular mechanisms of this immune response can be found in a recent monograph.[8]

SIGNS AND SYMPTOMS

The signs and symptoms of HSV encephalitis are not pathognomonic and resemble those of other causes of acute encephalitis. Confusion, headaches, nausea/vomiting, focal deficits (aphasia, hemiparesis, abnormal sensory perception), and seizures (usually focal or with focal onset) are the most common clinical manifestations (**Box 1**).[5,9] These signs and symptoms develop rapidly, usually within 1 to 5 days of hospital admission. Depression in the level of consciousness can be seen in more severe or advanced cases (in fact, coma may occur in up to one-third of patients). Fever is common but not uniformly present.[5] Patients may appear very ill, but they generally do not develop a full sepsis syndrome (in particular, hypotension in rare in the absence of medication effects). Meningeal signs are typically not present in patients with HSV-1 encephalitis, but can occur in patients with HSV-2 infection. Actually, HSV-2 can present with meningitis only.[10]

Over the course of the disease, seizures may occur in up to 40% of cases and new focal deficits in 20%.[5] Status epilepticus is uncommon, but it can also ensue. More frequent are agitation or decline in level of consciousness with periodic epileptiform changes on electroencephalography (EEG) but without continuous electrographic seizures.

DIAGNOSTIC INVESTIGATIONS

Blood tests are useful to exclude alternative diagnoses but cannot confirm the presence of herpes simplex encephalitis. Some patients present with leukocytosis or leukopenia and others develop it during the hospitalization; however, normal white