Neonatal Herpes Simplex Virus Infection

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KEYWORDS

• Neonatal herpes • Herpes simplex virus • Genital herpes
• Mother-to-child transmission • Antiviral therapy

KEY POINTS

- Most women who transmit herpes simplex virus (HSV) to their infants have no known history of genital herpes.
- The clinical classifications for neonatal HSV infections (skin, eye, and/or mouth; central nervous system; and disseminated disease) are predictive of morbidity and mortality.
- Intravenous acyclovir, 60 mg/kg/d divided every 8 hours, remains the treatment of choice for the acute management of neonatal HSV infections.
- Six months of suppressive-dose oral acyclovir following the initial treatment course improves neurodevelopmental outcomes and reduces the frequency of skin recurrences, although some patients still have significant morbidity from their disease.

INTRODUCTION

Herpes simplex virus (HSV) infections are extremely common worldwide and account for a large burden of disease, including potentially life-threatening infections, in all age groups. HSV genital infections are particularly common in adolescents and adults, and carry the risk of mother-to-child transmission (MTCT) when occurring in pregnant women. Neonatal HSV infection occurs with less frequently, especially considering the high prevalence of HSV infections in the general population, but it is a serious and often invasive infection of which clinicians must be aware. Although advancing diagnostic and therapeutic modalities have improved clinical outcomes in the past several decades, neonatal HSV infections remain a significant cause of morbidity and mortality in this vulnerable population. This article offers an overview of the disease process, epidemiology, clinical diagnostic and therapeutic considerations,

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outcomes, and potential complications. Ongoing and future avenues of investigation designed both to prevent MTCT and optimize therapeutic intervention in affected infants are highlighted.

PATHOGEN DESCRIPTION

HSVs exist as 2 distinct viral types: type 1 (HSV-1) and type 2 (HSV-2), both of which are associated with neonatal disease. HSV-1 and HSV-2 are categorized in the alpha herpesvirus subfamily of the Herpesviridae family of DNA viruses, along with varicella-zoster virus. As a subfamily, alpha herpesviruses are characterized by short replicative cycles, host cell destruction, and the ability to establish lifelong latency in sensory neural ganglia following primary infection.[1]

Both HSV-1 and HSV-2 are large enveloped virions marked by an icosahedral nucleocapsid arranged around a core of linear, double-stranded DNA. The lipid envelope and nucleocapsid are separated by a tightly adherent proteinaceous tegument. The HSV lipid bilayer envelope is embedded with surface glycoproteins that mediate attachment and entry into host cells and are responsible for evoking the host response. The envelope glycoproteins gB, gD, gH, and gL have been shown to be essential to cell entry.[2] Viral replication within an HSV-infected cell occurs through a cascade of steps including cell surface attachment, entry of the viral genome into the nucleus, transcription, DNA synthesis, capsid assembly, DNA packaging, envelopment via passage through the trans-Golgi network, and egress of new virions as the host cell is destroyed.

The genomes of HSV-1 and HSV-2 share approximately 50% homology, resulting in significant antigenic cross reactivity.[3] Type-specific glycoproteins, such as glycoprotein G (gG-1 and gG-2 for HSV-1 and HSV-2, respectively), allow differentiation of the 2 virus types via an antigen-specific antibody response. Differentiation of HSV type can also be achieved by restriction endonuclease fingerprinting, DNA sequencing, and increasingly by real-time polymerase chain reaction (PCR).[4–6]

RISK FACTORS

Neonatal HSV infections are most commonly acquired in the setting of maternal genital herpes infection in which there is viral shedding from the genital tract at or around the time of delivery. Risk factors for acquiring genital herpes include:

- Female gender
- Low family income
- Minority ethnic group
- Longer duration of sexual activity
- Past history of other sexually transmitted infections
- Higher number of sexual partners[7]

Women with no serologic evidence of prior HSV infection have a nearly 4% chance of acquiring HSV-1 or HSV-2 during the course of pregnancy (a first-episode primary infection), whereas women who are seronegative for HSV-2 but seropositive for HSV-1 have a 2% chance of acquiring HSV-2 during pregnancy (a first-episode nonprimary infection).[8] Viral reactivation from latency and subsequent antegrade translocation of virus from sensory neural ganglia to skin and mucosal surfaces can occur during pregnancy as well (a recurrent infection). Recurrent genital lesions pose a significantly lower risk for transmission to an exposed infant than first-episode primary infections (2% vs 57%), likely because of the transplacental passage of protective antibodies as well as lesser amounts of virus for a shorter period of time in the genital tract in recurrent infections.[9]