Neonatal herpes simplex virus infection

Tom Wong, Sandra Burton, Marc Steben

Epidemiology

Neonatal herpes simplex virus (HSV) infections may be caused by either herpes simplex virus type-1 (HSV-1) or herpes simplex virus type-2 (HSV-2). In the United States, HSV-2 is responsible for 75% of genital and neonatal infections, while HSV-1 causes the rest. HSV-1 more commonly affects the oropharynx, the eyes and the central nervous system.[1,2] It is estimated that 20 to 30% of sexually active adults are seropositive for HSV-2.[3] According to a recent study, white patients were four times more likely to acquire HSV-1 via oral sex than black patients.[4] The majority of subjects with HSV infections most likely have unrecognized symptomatic infection.[5,6] Sixty to eighty percent of children with neonatal herpes are born to women with no known history of genital herpes.[7]

Eighty to ninety percent of neonatal herpes is perinatally acquired at time of delivery through an infected maternal genital tract, or *in utero* by ascending infection, sometimes even through apparently intact membranes.[8] Postnatal acquisition is rare but has occurred from hospital personnel and other caregivers with orolabial herpes.[8,9]

A recent study has shown that about 3% of mothers are susceptible to acquiring primary genital HSV infection during pregnancy.[10] Among this 3%, if the infection is acquired near the time of labor, the risk of transmission during birth can reach 50%. A pregnant woman with a primary genital HSV-2 infection who has HSV-1 antibodies in her blood may have partial protection against HSV-2 vertical transmission (risk of about 20%).[11] Mothers with recurrent episodes of genital HSV have the lowest risk of transmission—between 0% to 5%.[12,13]

The reported rate of neonatal herpes infection varies in the United States between 20 to 50 cases per 100,000 live births, while in the United Kingdom and Australia it is about two or three cases per 100,000 live births. Canadian data are incomplete, although studies are currently under way to define the incidence of neonatal herpes and estimate the prevalence of genital herpes in specific populations.

Preliminary results from the ongoing Canadian Street Youth Study reveal a 9% prevalence rate of HSV-2 antibodies among street youths aged 15 to 24.[14] Studies in Ontario[15] and British Columbia (BC)[16] showed an HSV-2 seroprevalence among

pregnant women aged 15-19 years old of 5 % and 7.1% respectively, and among those aged 40-44 years old of 15.8 % and 28.1% respectively. In BC, the corresponding seroprevalence for HSV-1 ranged from 52.1% to 65.2%.

Clinical manifestations

Neonatal herpes infections occur in infants at a mean age of 14 days, but can happen up to four to six weeks after birth. Clinical manifestations of neonatal infection can be localized to the skin, eye or mouth (SEM) or to the central nervous system (CNS), such as encephalitis with or without skin lesions. They can also show as disseminated infections involving the liver, lungs, adrenals and other organs, such as the larynx, trachea, esophagus, stomach, lower gastrointestinal tract, spleen, kidneys, pancreas, and heart. Systemic signs are irritability, seizures, progressive respiratory distress, jaundice, bleeding and shock.[8,11]

Diagnosis and treatment

In the presence of skin lesions, other causes of such exanthems should be excluded, such as varicella-zoster, enteroviral disease, and disseminated cytomegalovirus. Serologic specimens and other viral cultures should be obtained to exclude toxoplasmosis, rubella and syphilis.[9]

Diagnosing neonatal herpes infection is becoming more difficult due to the decreasing incidence of the clinical presentation of skin lesions.[17-19] Forty percent of infants with HSV encephalitis do not show skin lesions.[9] Clinical signs of disseminated infections, where there are no skin lesions, are non-specific and the mortality rate in this group is high (50%) with one third of the survivors having significant neurological sequelae.[20] Signs include: psychomotor retardation associated with microcephaly, hydrocephaly, spasticity, visual impairment, and significant learning disabilities.[9] Early diagnosis and prompt treatment are essential to increase the chance of survival and limit disabilities.

Diagnostic tests

Infants should be tested if:

a) the mother has active genital herpes lesions at the time of delivery, or
b) neonatal HSV infection is strongly suspected

Cultures for HSV should be obtained from neonates in the first 24 to 48 hours of life. Samples should include swabs or specimens of urine, stool, mouth, nasopharynx, skin lesions, and conjunctiva.

For CNS infection diagnosis, cerebrospinal fluid (CSF) HSV-PCR* is recommended.

* PCR = polymerase chain reaction (a nucleic acid amplification test)

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Treatment

Acyclovir 45-60 mg/kg/day IV, in three divided doses for 14 to 21 days,[21] should be initiated when:

- HSV infection is suspected; i.e., infant with skin or scalp rash, especially vesicular lesions;
- CSF findings are abnormal;
- CSF HSV-PCR is positive;
- culture results are positive.

Intravenous acyclovir should be initiated at birth after HSV tests have been obtained in an infant whose mother has primary genital herpes at the time of delivery.[8]

Prevention

For neonatal HSV infection, prevention is a challenge as it implies prevention of genital herpes simplex infection in adults. Neonatal herpes infection is a rare complication of a common infection in mothers, for which there is a treatment but no cure. Although research is underway to develop an effective prophylactic vaccine, more studies need to be done. The best prospect for a vaccine will be to prevent acquisition of primary infection with a potential to reduce the severity, frequency of recurrences, viral shedding and transmission of genital herpes simplex infection.[22,23] In the absence of a licensed vaccine, prevention of neonatal herpes will depend on:

- promotion of consistent safer sex practices and use of condoms during all sexual exposures with new partners to prevent the acquisition and transmission of sexually transmitted diseases in the general population—condoms may reduce the chance of getting or transmitting HSV infection but would not provide absolute protection;
- successful counseling of mothers and their sexual partners on the chronic aspects of the disease, recurrences, anti-viral therapy, transmission and risk of neonatal infection, safer sex practices, especially during the last trimester of pregnancy, and the risk of specific genital and orogenital sexual practices;
- the ability to identify women at high risk of acquiring a primary HSV infection;
- the management of high-risk women and their newborns.

For comprehensive genital HSV prevention strategies, further research needs to be done to explore:

- the benefits of type-specific serology for screening, in high-risk population and pregnant women, and for diagnosis;
- behavioural impact of serologically proven asymptomatic infection; and
- partner management strategies.[24]

RESOURCES

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Questions

1. Clinical manifestations of disseminated neonatal herpes simplex infections include?
   a) vesicular lesions and respiratory distress
   b) irritability and seizures
   c) lethargy and jaundice
   d) a, c
   e) all of the above

2. True or false?
   a) Primary infection in the second and third trimesters increases the risk of HSV transmission to the newborn
   b) About 5% of pregnant women are susceptible to acquired primary herpes infection during pregnancy
   c) In some Canadian studies, the rates of HSV-2 seroprevalence among pregnant women aged 15-19 years old range from 5% to 7%

3. Which laboratory test(s) should be ordered to investigate the possibility of neonatal herpes infection in an infant born 14 days ago who is irritable, and has respiratory distress and swallowing difficulties?
   a) CSF HSV culture
   b) CSF HSV-PCR
   c) HSV IgM
   d) a, b
   e) a, b, c

4. If the CSF HSV-PCR was positive, how would you manage this case?
   a) Acyclovir IV, 30 mg/kg/day in 3 divided doses for 7-10 days
   b) Acyclovir IV, 60 mg/kg/day in 3 divided doses for 21 days
   c) Acyclovir PO, 80 mg/kg/day in 4 divided doses for 5 days
   d) Acyclovir IV, 60 mg/kg/day in 3 divided doses for 14 days and HSV vaccine to the mother

Answers: 1-e; 2-T, F,T; 3-d; 4-b