Neonatal herpes simplex virus (HSV) disease is a rare but sometimes highly lethal infection. The reported incidence in Australia is approximately four cases per 100,000 live births. HSV type 2 (HSV-2) is the predominant serotype that causes infection in the newborn in the United States, whereas in Australia, neonatal infection is usually caused by HSV type 1 (HSV-1), most likely due to greater prevalence of oral and genital HSV-1 disease in this country.

Diagnosis of neonatal infection requires a high index of clinical suspicion as signs are non-specific, and is usually confirmed by isolation of HSV from skin vesicle or detection of HSV DNA in the cerebrospinal fluid, blood or surface swab. Treatment requires intravenous aciclovir for 14-21 days depending on the form of disease.

Presentation and route of infection

The majority (85%) of infants become infected with HSV at the time of delivery by passage through an infected birth canal. A further 10% acquire the infection from contact with infectious lesions, usually on the hands or lips of a caregiver after delivery. The remaining 5% of HSV infected infants have a congenital infection, i.e. become infected in utero by transplacental spread of virus.

Congenital HSV infection presents with distinct manifestations at birth – usually eye abnormalities, skin scarring, microcephaly and sometimes central nervous system calcification on imaging. Perinatal HSV infection, acquired at the time of delivery or in the postnatal period, may present in three ways. Disease may be confined to the skin, eye, or mouth (SEM disease), to the central nervous system alone, or the infection can present with multi-organ ‘septic shock’ with or without encephalitis.

Neonatal HSV pneumonitis is a highly lethal variant of disseminated infection which presents as respiratory distress in a term infant typically on Day 3-5 of life. SEM disease carries a very low to no risk of mortality, but carries a high risk of spread to the central nervous system if untreated with antiviral therapy and a risk of neurological impairment in late infancy. Neonatal HSV encephalitis has a high mortality rate which is significantly reduced by prompt initiation of systemic antiviral therapy, but survivors have a high risk of neurological sequelae. Multi-organ HSV disease in the newborn is also often lethal, even with antiviral therapy.

The strongest risk for vertical transmission of HSV is primary genital infection during late pregnancy. Some studies suggest that genital HSV-1 disease is more readily transmissible to the neonate than HSV-2, but this requires confirmation. If virus is in the genital tract at delivery, invasive obstetric procedures such as instrument deliveries and fetal scalp electrodes increase the risk of transmission to the newborn.

The diagnosis of neonatal herpes

Clinical features

The presenting features of neonatal HSV infection are non-specific, which may result in missed or delayed diagnosis. Typical skin vesicles may be absent in up to 30% of infected infants, particularly in those with encephalitis or multi-organ disease. Fever is only present in just under half of the infected infants. Systemic disease may manifest as lethargy, seizures, jaundice or respiratory distress.

Laboratory diagnosis

Viral culture, PCR and direct immunofluorescence

Specimens that should be collected from an infant with suspected neonatal HSV disease include cerebrospinal fluid (CSF), surface swabs from skin vesicles, conjunctiva, nasopharynx and rectum, and blood for full blood count, liver function tests, and coagulation studies (if systemic disease is suspected). Central nervous system imaging (computer tomographic scan or magnetic resonance imaging) and chest radiographs may also be indicated.

Surface swabs may be analysed by viral culture and/or polymerase chain reaction (PCR) for HSV DNA. HSV induces a typical cytopathic effect in 2-4 days on cell monolayers which can be subsequently serotyped. Rapid confirmation of HSV infection can be obtained by direct immunofluorescence of surface swabs that have been plated on to a glass slide. The sensitivity of this technique is only 40-50%, so a negative result does not exclude the diagnosis.

CSF from neonates should be analysed for cell count and biochemistry, and should always be set up for viral culture in...
addition to PCR; positive CSF cultures have been reported in up to 20% of infants with neonatal HSV disease in contrast to the low yield obtained from adults with HSV encephalitis. The sensitivity of HSV PCR in the CSF is reportedly lower for neonatal herpes (71–100%) than for adults with HSV encephalitis (>95%). The rate of detection of HSV DNA in the CSF decreases in most cases after infants have been on antiviral therapy for over a week. A repeat CSF specimen should be performed at the end of therapy to confirm the absence of HSV DNA, which can be associated with early relapse and late neurological sequelae. Some groups have used quantitative HSV PCR on CSF samples to provide prognostic information in adults with HSV encephalitis, with an HSV viral load >100 copies/ml being associated with poor neurological outcome. This is not in routine clinical use, and similar studies have yet to be conducted in neonates.

PCR assays for HSV DNA have also been performed on blood from infants with neonatal HSV infection. HSV DNA was detected in PBMC or plasma from 60-70% of infected infants in one study.

Serology

Type specific IgM or IgG serology for HSV has a limited role in the acute diagnosis of HSV infection in the neonate. Only 40% of infants develop HSV-type specific IgM responses in neonates and their response is usually too slow to guide therapy. Serology may play a role in counselling parents postnatally as to the origin of neonatal HSV disease as most women who deliver an infant with neonatal HSV disease are unaware of their own genital HSV disease until the infant is diagnosed. Serology may also assist in the diagnosis of nosocomial infections.

Routine antenatal type specific serology is controversial and probably not indicated in countries with low HSV-2 seroprevalence like Australia. However, it may play a role in isolated cases for counselling serodiscordant couples about risks of vertical HSV transmission in future pregnancies.

The treatment of the neonatal HSV disease

Current recommendations for antiviral therapy for neonatal HSV disease are listed in Table 1. Clinical trials have confirmed that vidarabine and aciclovir are equally efficacious in reducing mortality from neonatal HSV disease; however, intravenous aciclovir has become the standard therapy because it has less toxicity and is easier to administer. The duration of therapy depends on the type of neonatal HSV disease. Infants with SEM disease should be treated for 14 days, whereas infants with disseminated infection, encephalitis or where a lumbar puncture has not been performed, should be treated for 21 days.
The dose and duration of IV aciclovir for neonatal HSV disease has been increased over the last decade to 60mg/kg/day, administered in three equal doses in order to reduce disease progression and mortality from disseminated infection or encephalitis. These changes have not been formally studied in randomised controlled trials due to the low frequency of the condition, but were reported in an open label study to result in increased survival for infants with disseminated HSV disease and to reduce long-term neurological sequelae compared to historical controls. Infants on high dose aciclovir should have their neutrophil counts and hydration monitored throughout therapy, and dose should be adjusted for renal function.

Other antiviral agents are not generally used to treat neonatal HSV disease. Foscarnet has been used in neonates with severe viral disease, or on the rare occasion where aciclovir resistance is suspected. Oral aciclovir should not be used for the acute treatment of neonatal HSV disease due to low bioavailability and the failure to achieve adequate CNS concentrations that will inhibit viral replication. There are no current data available about the use of oral antiviral preparations with better bioavailability for the treatment of this condition.

Suppressive antiviral therapy to prevent long-term neurological sequelae from neonatal HSV disease has been trialled. However, this practice is associated with a high rate of drug induced neutropenia, and isolated reports of late CNS recurrences on therapy and isolation of aciclovir-resistant mutants, so is not routinely recommended.

The use of antiviral therapy in pregnant women or their partners to prevent vertical transmission of HSV disease is reviewed elsewhere.

Conclusion

Neonatal HSV disease remains an uncommon but important cause of infant death and childhood neurological morbidity. As clinical signs at presentation are non-specific, and a history of maternal genital disease often absent, diagnosis requires a high index of clinical suspicion and prompt laboratory investigation.

Table 1. Aciclovir therapy for neonatal HSV disease.

<table>
<thead>
<tr>
<th>Type of neonatal HSV disease</th>
<th>Duration of therapy</th>
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<tbody>
<tr>
<td>Skin, eye, mouth</td>
<td>14 days</td>
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<tr>
<td>Central nervous system</td>
<td>21 days*</td>
</tr>
<tr>
<td>Disseminated infection</td>
<td>21 days*</td>
</tr>
<tr>
<td>LP not performed at diagnosis</td>
<td>21 days*</td>
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</tbody>
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Dose: 60mg/kg/day divided into three equal doses and given every 8 hours intravenously as 1 hour infusion

* Duration should be extended if HSV DNA PCR remains positive at the end of therapy.

References

7. Yfet, K.L. Herpes simplex virus infections of the central nervous system: encephalitis and meningitis, including Mollaret’s. Herpes 2004; 11 Suppl 2, 57A-64A.