

Prevention, Diagnosis and Treatment of Neonatal Herpes Simplex Virus Infections: A Review

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Abstract:

Herpes simplex virus (HSV) infections of the neonate are associated with very high mortality and survival frequently carries neurologic sequelae. The infection is generally acquired from infected maternal genital tract. The risks of neonatal HSV infection have become magnified by the recent increase in the incidence of genital herpes. Recognition of the high risk pregnant patient, detection of maternal genital herpes by culture or histopathology, followed by delivery of the child by cesarean section will prevent intrapartum exposure to infection. Treatment of neonatal herpes with adenine arabinoside and acyclovir significantly decreases the morbidity and mortality of the disease.

Incidence

The past decade has witnessed the epidemic spread of genital herpes among sexually active young adults in the United States. Herpes genitalis is the most common venereal disease identified in patients from middle and upper socioeconomic strata. Private physicians in the United States are seeing more patients with herpes than gonococcal infections. Several million new cases of genital herpes are occurring every year and it has been estimated that 10 to 35 percent of the women of child-bearing age already have genital herpes. This has been associated with an increase in the incidence of neonatal herpes.¹ It is estimated to affect 1/8,000 to 1/10,000 live births. The incidence is higher in premature births. Media coverage given to this infection makes it appear as though it is a new disease. However, infections with herpes simplex virus (HSV) have been described for centuries and it is estimated that one-third of the world's population has been infected with this agent. The virus remains latent in the sensory ganglia after the primary infection and once infected the person harbors the virus for the rest of his life. The majority of primary HSV infections are asymptomatic and only 1 percent cause severe disease.

Types of Herpes Infection

Since the 1960s it is known that there are two types of HSV. Type I is primarily transmitted by contact with oral secretions and is chiefly responsible for oral,

ocular and encephalitic infections in adults and older children, whereas Type II is largely a venereal disease primarily causing genital and neonatal infections.²

The most reliable method of differentiating the two types is the use of restriction enzymes to cut the viral DNA into fragments and subsequent gel electrophoresis of these DNA fragments. This gives rise to patterns characteristic of Type I and Type II. Using multiple enzymes we can differentiate between strains of the same HSV type. This provides a useful epidemiologic tool.

The disease spectrum produced by the two types overlaps. Type II causes 70 to 80 percent of the genital herpes but up to 30 percent may be caused by HSV type I. The presentation is similar but the genital infections caused by HSV type I are less likely to recur. There is no cross protection and a person infected with one type can become infected with the other type of HSV.

Pathogenesis

Most neonatal HSV infections are acquired from the infected birth canal of a mother with acute primary or recurrent genital herpes at term. This is why recognition of the infection in the mother and her sexual partner is the first step towards preventing this devastating illness in a newborn. In men the typical lesion is a cluster of small vesicles on the glans or penile shaft. In women the cervix and vagina are most commonly involved, although the vulva, perineum or buttocks may be affected as well. The cervical lesions may not always be detectable clinically and vulvovaginal lesions may rapidly ulcerate becoming quickly covered with a greyish white exudate. Pain is the predominant complaint. Obviously painful ulceration of the vulvovaginal area is a fairly nonspecific complaint and diagnosis should be confirmed by viral culture.

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Following a six-day incubation period, primary genital infections are associated with fever, malaise, and bilateral, tender, inguinal lymphadenopathy. Lesions heal in 14-17 days. Following the primary infection the virus becomes latent. There is a high incidence of recurrence in the first year after primary infections occurring in 67 to 89 percent of the patients, usually about 6 months after the primary infection. The recurrent lesions heal in seven to 10 days. The rate of future recurrences varies in individuals but may be as frequent as every month. During each recurrence the patient is infectious and if the recurrence is near the time of delivery in a pregnant woman, the chances of the baby becoming infected are about 1 in 10. The frequency of the infection and persistence of virus are both increased during pregnancy increasing the likelihood of neonatal transmission. Eighty percent of infected neonates are delivered prematurely. Fifty percent will develop disseminated infections with 70% mortality and most survivors will have severe neurologic sequelae.

Prevention of Neonatal Herpes Infection

The terrible consequences of neonatal herpes demand that we do everything possible to protect the newborn from infection. The baby is most likely to be exposed to the virus at the time of delivery, by contact with an infected birth canal, or by ascending infection after rupture of the membranes and rarely by ascending infection with chorioamnionitis in the presence of intact membranes. Therefore if genital herpes is present, the only practical way to protect that baby from exposure is to deliver it by cesarean section soon after rupture of the membranes. There is no controlled study to demonstrate that delivery by cesarean section reduces the incidence of neonatal herpes. Nevertheless, there is general agreement that when primary maternal genital herpes is present at birth, the risk for the baby is sufficiently great to justify this mode of delivery. It is assumed but not proven that cesarean section within four hours of rupture of the membranes can reduce the risk from 90 percent to 4-6 percent.

To minimize these chances, a history of vesicular lesions in the father and painful vesicles or ulcers in the mother is asked during each pregnancy. If the history is negative at the initial visit, routine followup includes questions about the occurrence of suspicious lesions. If lesions are seen or the history is suggestive of herpes genitalis, viral cultures are done. If the initial culture is positive in either parent, the mother should have weekly cervical culture in the last six weeks of pregnancy. When she goes into labor, a speculum examination is done to look for lesions. If any lesions are seen, she is delivered by cesarean section. If no obvious lesions are seen, the entire vulva is

palpated with a dry cotton tipped swab. Pre-eruptive herpes is tender and delivery by cesarean section is indicated. If the mother's examination is totally benign and the last cervical culture was negative, she may be delivered vaginally.³

Early Recognition

Infection of the newborn can occur by postnatal contact with nongenital infections in family members, hospital personnel and from other infected neonates. The infectious lesions in these contacts range from the common cold sore on the lip to herpetic whitlow which may be clinically indistinguishable from bacterial or candida infection. These lesions are infectious until they become dry and crusted.

In utero, transplacental spread may occur if the mother has viremia but this is very uncommon. Death in utero is the likely outcome of such pregnancies. Intrauterine Growth Retardation (IUGR), psychomotor retardation, microcephaly, encephalitis, intracranial calcification, chorioretinitis and recurrent skin vesicles are described in the occasional survivor.

After delivery, early recognition of infection and prevention of nosocomial spread from an infected mother to the infant or from an infected infant to other neonates becomes the objective. To ensure this, babies born to potentially infected mothers are kept in isolation while in the nursery.⁴ Eventually the baby will go home with the mother and take its chances on becoming infected but it is our responsibility to prevent infection in the hospital. The baby may visit the mother who washes her hands with a virucidal, iodine-containing scrub, e.g. Betadine, and dons a clean gown. The baby's throat and conjunctivae are swabbed for viral culture and he is examined daily for mucosal or skin lesions. As for the eyes, which form an important portal, prophylactic application of vidarabine, idoxuridine or tri-fluorothymidine ophthalmic ointment during the first five days of life should be considered. When the baby is discharged home, the mother is told to look for skin and mucosal vesicles and any sign of sepsis, e.g. poor feeding or lethargy until six weeks of age. The mothers may use the same procedures at home when they have recurrent genital herpes and the baby is less than six weeks old.

Overall, the risk of neonatal herpes when the baby is delivered vaginally is approximately 10% in women with evidence of recurrent genital herpes after 32 weeks gestation and 40-60 percent when primary genital infection is present after 32 weeks gestation. This is because in primary infections the extent and duration of genital lesions is greater and virus is present in higher titers and for a longer time and the cervix is almost always involved and the baby may not receive any transplacental antibody to modulate the severity of the disease.

Diagnostic Tests

More than one-half of pregnant women with active genital herpes are asymptomatic⁵ and typical lesions are present in only 35-50 percent of cases with positive cultures. Virus isolation in cell culture is the most sensitive and accurate methods of diagnosis. Its sensitivity varies with the stage of the disease at the time the sample is taken, adequacy of sample and how it is handled. Patients should be cultured as early in the course of the infection as possible when a greater amount of virus is shed. 90 to 95 percent of cultures are likely to be positive when vesicles are seen. Cells swabbed from the base of these vesicles should be placed in cold transport medium and taken to the laboratory on ice and immediately inoculated into cell cultures. 60% causes typical cytopathic effect within 24 hours, 85% are positive in 48 hours and 95% will be positive by 72 hours. Obviously a method of sensitive, rapid diagnosis is needed to use when a suspected woman presents in labor.

Cytology is the most widely used method. Cells from the base of vesicular lesions or ulcers are gently spread on a slide, fixed and stained. These and Pap smears from the cervix may show multinucleated giant cells and enlarged epithelial cells with eosinophilic intranuclear inclusion bodies. Cytology is less sensitive than viral culture and a Pap smear is almost never diagnostic in culture-positive recurrent herpes. Some laboratories use immunofluorescence or immunoperoxidase staining of these slides to detect viral antigens and to increase the sensitivity. Overall, these techniques are one-half as sensitive as viral culture.

Serologic diagnosis is unsatisfactory even for primary infections as it does not differentiate between HSV type I and HSV type II as past oral infection with HSV-1 may mask antibody response to a new HSV-2 genital infection.

At present it is not feasible to monitor all pregnant women for genital herpes, so certain high risk groups have been identified for close followup. These include:

- Women with a history of active genital herpes during the present pregnancy.
- Women whose sexual partners have a history of genital or oral herpes.
- Women with herpes lesions below the waist or on the hand.

Such mothers account for 50% of neonatal herpes only. Others are born to totally unsuspected mothers. Women should be advised against sexual contact with men having active herpes especially in late pregnancy and to use spermicidal foams, which are also virucidal, with condoms.

Clinical Features of Neonatal Herpes

Neonatal illness generally presents within 3 days of birth but may present as early as 1 day or as late as 3 weeks after birth. The presentation is nonspecific and

the usual signs and symptoms of sepsis neonatorum are encountered with fever, poor feeding, vomiting and lethargy. Temperature instability and jaundice may also be present. Fifty percent of neonates with disseminated infections will have central nervous system involvement signified by irritability, seizures, paralysis or coma. Detailed maternal history should be a part of any neonatal evaluation. A history of penile lesions in sexual partners should also be asked. Affirmative answers greatly raise the suspicion of neonatal herpes. Any neonate who is being worked up for sepsis should have a careful examination of skin and mucous membranes. Skin vesicles of neonatal herpes are most likely to be seen at the presenting part which remains in contact with the maternal genital canal for the longest time. Sites of fetal scalp electrodes and scalp vein blood sampling sites, eyes, mouth and especially in breach presentation the anal canal should be inspected for herpes vesicles. The mucosal lesions consist of friable vesicles on an erythematous base. The vesicles on mucous membranes break down very easily and only shallow, erythematous ulcers may be seen. The suspected lesions should be swabbed for viral culture and smears for immunofluorescent staining should be prepared. Infants who are suspected of bacterial infection but have negative cultures should be suspected of herpes. Neonatal HSV infection can occur in the absence of mucocutaneous lesions and should be considered in high risk infants with a picture of sepsis especially if seizures develop.⁶ A characteristic EEG pattern has been described in full term neonates with herpes simplex encephalitis. Further support of suspected diagnosis of herpes encephalitis can be obtained by cranial nuclear medicine and computerized tomograms with contrast. CT scans at the end of therapy are useful to delineate the extent of damage.^{7, 8} In disseminated disease there is hematogenous spread of the virus. The liver, adrenals and lungs are most severely affected although nearly every system can be involved. Untreated, mortality is approximately 80%. Central Nervous System disease (CNS), disseminated intravascular coagulation and pneumonia are the major causes of mortality. Most infectious disease specialists would state that they have not seen any baby with HSV pneumonia survive even with maximal support.

Generalized disease and CNS involvement can be associated with conjunctivitis, keratitis or chorioretinitis. Localized disease with mild systemic signs and symptoms is seen and has been correlated with a high titer of maternal HSV neutralizing antibodies.⁹ Vesicles may be seen on the skin, mucous membrane or keratoconjunctivitis may be present. These localized infection manifestations may be accompanied by CNS involvement which gives a 40% mortality and 40% incidence of severe neurologic sequelae. It seems that viremia occurs even in apparently localized disease, estimation of liver enzymes might show evidence

of visceral involvement and developmental defects may become evident even after an apparently innocuous cutaneous attack.

The mortality and morbidity of untreated neonatal herpes can be reduced by antiviral therapy with Vidarabine 15mg/kg daily as a 12 hour IV infusion.^{10,11} This treatment has been shown to decrease the mortality of neonatal disseminated herpes from 85% to 57% and that of localized CNS infection from 50% to 10%. This occurred although the mean duration between onset of illness to initiation of therapy was seven days and a better outcome with lesser neurologic sequelae can be anticipated with earlier therapy.

Treatment of Neonatal Herpes

Any infant shedding HSV during the first month of life should be considered to have neonatal herpes and treated without delay. Vidarabine, which is a purine nucleoside analog, is phosphorylated by cellular kinases to a triphosphate form which is a competitive inhibitor of DNA polymerase activity. Acyclovir is another nucleoside analog with a high degree of specificity against HSV.

Infection of cells with HSV results in production of viral thymidine kinase which phosphorylate acyclovir to acyclovir monophosphate. Viral thymidine kinase phosphorylate acyclovir much more efficiently than cellular enzymes, so there is 40 to 100-fold more acyclovir monophosphate in infected cells. After subsequent triphosphorylation by cellular enzymes, acyclovir is approximately 60 times more active against HSV than ARA-A. It is being tested in a randomized trial against vidarabine and the last analysis showed them to be equally efficacious.¹² As acyclovir is administered in small fluid volume it may be reasonable to consider its use in encephalitis when fluid overload is causing serious problems. Very little toxicity is associated with either drug in infants. Relapse of infection after therapy and recurrent skin lesions are frequent problems after initial successful treatment. Improvement may be observed within 48 hours.

Newer antivirals are being tested but no dramatically improved compounds are on the horizon. Local application of antiviral ointment can decrease viral shedding and should be recommended for mothers or household contacts with active herpes lesions. The efficacy of oral acyclovir in preventing recurrences of genital herpes has been demonstrated in controlled trials.^{13, 14} However, use of systemic antiviral agents

is not approved in a pregnant patient unless life-threatening disease is present. Therefore, it is unlikely we can use these to minimize chances of intrapartum exposure.

Our knowledge of the structure and replication of HSV has greatly expanded in the last 10 years. This has allowed production of effective antiviral agents. However, many issues concerning viral latency and reactivation remain mysteries.

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