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Review Article

Herpes Simplex Virus Infections In Neonate

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Abstract

Introduction: Although neonatal herpes infection is relatively uncommon, neonatal HSV causes serious morbidity and mortality, and survivors may need to live with permanent sequelae.

Aim of Work: In this review, we will discuss the most recent evidence regarding neonatal herpes simplex virus, methods of diagnosis, and management.

Methodology: We did a thorough search for most recent available evidence regarding the diagnosis and management of herpes simplex virus (HSV) in neonate.

Conclusion: The disease is classified clinically to three main types: SEM, CNS herpes simplex virus; disseminated HSV infection. Physicians' high index of suspicion is essential to consider neonatal HSV. Polymerase chain reaction (PCR) is more sensitive than viral culture for CSF samples. However, false negative results could be seen and should not exclude the diagnosis in case of high suspicion. The Adequate Neonatal HSV management consists of support measures and antiviral therapy. Supporting steps are especially important for CNS involvement and for disseminated HSV. Acyclovir have led to sharp decrease in the mortality rate and considered the drug of choice. Ganciclovir IV was suggested to be the first-line alternative to acyclovir.

Keywords: *Neonatal Herpes Simplex Virus; Neonatal HSV; Complication of HSV; Pregnant with HSV; Simplex with CNS Involvement.*

Introduction

According to many estimates, herpes simplex virus (HSV) affects approximately 3 - 10 per 100,000 live births in the United States (US) and other countries. The condition is associated with serious morbidity and mortality, and survivors may live with permanent consequences [1-6]. Although these numbers are considered of a relatively low prevalence, neonatal HSV is responsible for 0.6 percent of hospital neonatal deaths in the United States and contributes to substantial healthcare burden and resource utilization [7-10].

Most cases of neonatal herpes are acquired by transmission of maternal infection, this usually occurs during birth canal delivery of a mother with asymptomatic genital herpes. The risk of neonatal herpes increased in case of maternal primary genital infection (30 - 50%) compared with recurrent genital infection (< 3%) [2].

Neonatal HSV infection is usually classified into three main categories: localized skin, eye, and mouth (SEM); CNS disease; and disseminated disease. About one-third of neonatal HSV develops meningoencephalitis, in addition, CNS involvement could also be observed in SEM or disseminated disease [11].

Since 1930s, when neonatal HSV firstly discovered, important breakthroughs in understanding the method of transmission, diagnosis, and treatment strategies have improved diagnosis and treatment [7]. However, despite these advances, neonatal HSV remains a clinical challenge.

Methodology

For the most recent available evidence regarding neonatal herpes simplex virus (HSV) infections, a systematic search was conducted using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant available full articles were reviewed and included. The terms used in the search were: Neonatal Herpes simplex virus; Neonatal HSV; Neonatal meningoencephalitis; newborn viral infection; Herpes simplex localized and disseminated disease.

Virology and transmission

Herpes simplex viruses are classified into HSV type 1 and HSV type 2 based on serologic and molecular variability. It contains a double-stranded linear DNA genome. The DNA of HSV-1 and HSV-2 contain many homologous sequences distributed over the entire genome of both types, which produce antigenically similar polypeptides that explain the cross-reactivity between HSV-1 and HSV-2 glycoproteins [7]. Therefore, most commercially available serologic assays are not able to distinguish between HSV-1 and HSV-2 antibodies. The virus enters the human host through breaks in skin of inoculation in mucosa of oral, genital, or conjunctiva. Then it transports by retrograde axonal flow through sensory nerve endings to the dorsal root ganglia, where it remains latent for the entire life. When the virus is latent, it is not susceptible to antiviral drugs and hence the infection is perpetual. Virus ability for reactivation are responsible for recurrent infections in the host.

HSV could be transmitted to fetus and neonate in three distinct periods: intrauterine, perinatal, and postnatal. The first of which rarely occurs with an estimated incidence of 1 in 250,000 deliveries. The vast majority of neonatal HSV infections (85 percent) are acquired perinatally [11]. Neonates acquire HSV from the genital tract of the pregnant woman at the time. This occurs regardless of the presence of symptoms in the mother. Many factors influence viral transmission as the type of maternal HSV infection (primary or recurrent), maternal antibody status, duration of ruptured membranes, fetal scalp monitors, and cesarean versus vaginal delivery [2]. It is worth mentioning, however, that most neonatal cases occur without mothers' history of HSV infection or other identifiable risk factors [12]. The remaining 10-15 percent are thought to be acquired postnatally [11]. This occurs in case of close contact with active HSV infection individuals.

Clinical features

Herpes simplex infection of neonate is classified into three main categories: localized skin, eye, and mouth (SEM); CNS involvement; and disseminated disease. These three categories may overlap, CNS affection may occur with SEM and/or disseminated HSV. Both HSV-1 and HSV-2 may cause SEM, CNS, or disseminated disease; however, HSV-2 infection is more frequent and has been associated with worse outcome [2,7,13,14].

Skin, eye, and mouth (SEM) herpes simplex infection accounts for most cases (about 45 percent) of neonatal HSV [11,15]. This variant of neonatal HSV may appear benign initially, however, if not treated, is associated with a high risk of progression to CNS or disseminated disease. SEM disease usually presents in the first two weeks of life. Later presentation could occur up to the first six weeks [16].

Skin disease usually appears as coalescing or clustering vesicular lesions with an erythematous base [7]. Vesicles may begin at the presenting part, or at sites of localized trauma (as scalp monitor site) and may present late in the course of disseminated disease. Eye involvement may initially appear asymptomatic. Early signs include excessive watering of the eye, crying from apparent eye pain, and conjunctival erythema. Skin vesicles around the eye may or may not occur. Eye involvement could be complicated to cataracts and chorioretinitis leading to permanent vision impairment [7,17]. Similarly, oropharyngeal HSV may initially be asymptomatic, but also may be characterized by localized ulcerative lesions of the mouth, palate, and tongue. It should be differentiated from other causes of oral lesions. If SEM disease is treated early, before CNS or disseminated disease occurs, the outcome is favorable.

Herpes simplex virus encephalitis (HSE) is considered as the most common cause of sporadic fatal encephalitis in the United States and other industrialized nations [18-21]. Herpes simplex encephalitis accounts for 10 to 20 percent of all cases of viral encephalitis [22] and for one-third of neonatal HSV conditions [11,16]. In a national retrospective study from Sweden, 2.2 per million people had annual confirmed incidence of HSE [23]. The type 1 herpes simplex virus (HSV-1) is incriminated in more than 90% of HSE cases in adults. In neonate, however, HSV-2 infection is a common cause of acute generalized encephalitis and typically causes aseptic meningitis [24]. it is worth mentioning that an increasing number of neonatal herpes cases caused by HSV-1 is identified in the United States and some European countries [25]. The condition may occur at any time during the first 6 weeks of life, however, it usually presents in the second or third week of life [16]. The virus may reach the CNS through either a localized retrograde spread from the nasopharynx and olfactory nerves or through hematogenous spread in neonates with disseminated disease. HSV meningoencephalitis may occur with or without SEM involvement and with or without disseminated disease. About two-third of neonates with HSV meningoencephalitis show skin lesion (vesicles) at some point during the course [11]. The clinical manifestations include focal or generalized seizures, lethargy, poor feeding, irritability, tremors, temperature instability, and full anterior fontanel [13,26,27]. However, all of these signs may not appear at the early course.

In the absence of vesicles, the initial presentation is similar and indistinguishable from other causes of neonatal sepsis or meningitis [11,28]. it is recommended by experts that initial evaluation should be done with DNA polymerase chain reaction (PCR) and other CSF investigations, meanwhile, empiric treatment with acyclovir in all neonates with aseptic meningitis or signs and symptoms of meningoencephalitis without an obvious bacterial clues should be initiated before confirmatory result [29,30].

Disseminated HSV in neonate accounts for less than 25% of all cases. The conidian is similar to sepsis presentation, with multiple organs involvement [5,7,11,16,20,30,31,36]. The liver involvement occurs in the form of hepatitis with elevated liver transaminases, ascites, and direct hyperbilirubinemia. This could progress to liver failure with need of liver transplantation [32]. Lungs affection appears as pneumonia and hemorrhagic pneumonitis, with or without effusion, with the possibility of progression to respiratory failure [33]. Severe cases of disseminated HSV infection may affect the heart in the form of myocarditis and myocardial dysfunction. Bone marrow involvement may lead to disseminated intravascular coagulation (DIC), thrombocytopenia, and neutropenia. Adrenal gland, kidney, and gastrointestinal tract (GIT) could be affected as well.

Diagnosis

Physicians' high index of suspicion is essential to consider neonatal HSV. The presence of the following presentation in the first 6 weeks of life should raise the suspicion of Neonatal HSV infection [8,16]: Mucocutaneous vesicles; Cerebrospinal fluid (CSF) pleocytosis; Focal neurologic signs and/or Seizures; Abnormal neuroimaging; Elevated liver enzymes; Sepsis-like illness; Respiratory distress; Thrombocytopenia; Conjunctivitis, excessive tearing, or painful eye symptoms. Early in the HSV infection course, some neonates may present with persistent fever with negative bacterial cultures. Neonatal HSV infection remains a possibility in infants born to women who received suppressive therapy during pregnancy. Although suppressive therapy markedly reduces the risk of asymptomatic shedding, it does not completely eliminate it. Neonates with perinatal exposure to HSV (particularly maternal active genital lesions) should be monitored for evidence of HSV infection.

Usually, delayed diagnosis for cases presented as disseminated infection occurs until the second week. This is due to wrongly suspicion of bacterial sepsis. When the diagnosis delayed and the condition remained untreated, the mortality rate exceeds 80 percent. Unfortunately, the diagnosis is often made or confirmed at autopsy, after extensive organ damage has occurred. Thus, clinicians must have a high index of suspicion and all efforts should be focused on identifying high-risk neonates with a sepsis-like picture, meningoencephalitis, progressive pneumonitis, or hepatitis, and should tested for HSV and empiric antiviral therapy should be initiated empirically [7,9,12,15,19,34,35,40].

Neonatal HSV infection could be diagnosed by virus isolation in traditional or enhanced viral culture, polymerase chain reaction (PCR) detection of viral DNA, or rapid direct immunofluorescence assay (DFA) detection of viral antigens. At the time of presentation serology

plays a minor role in the diagnosis. Isolation of HSV culture is the gold standard laboratory investigation which ensures that an active HSV infection is present in the neonate. Viral isolation from surface sites of the neonate older than 12 to 24 hours is always a significant finding. This is the most commonly used and suggested investigation as it is noninvasive [7,16].

Alternatively, viral culture of other samples as CSF or blood are less commonly used, although this can establishes the diagnosis and successfully isolate HSV. In these saples, PCR is preferred because its greater sensitivity.

Recent methods as 24 hour shell vial centrifugation fluorescent foci cultures (SVC) and enzyme-linked virus inducible systems (ELVIS), are frequently used and could provide rapid detection of HSV in clinical systems within 24 to 48 hours [36,37]. These methods are generally comparable to cell culture, but not all these assays are able to distinguish different types of HSV.

The detection of virus DNA in the CSF of a neonate using PCR confirms the diagnosis of CNS involvement. This method is more sensitive than viral culture of the CSF. However, false negative results could be seen with contaminated sample by blood or the presence of high protein; CSF samples obtained early in the course of illness, and samples obtained after therapy initiation [7,38-43]. Hence, if there is a high suspicion negative CSF does not exclude the diagnosis and should be repeated later on [44]. In neonates with signs of meningoencephalitis, the detection of HSV DNA confirms the diagnosis. However, neonates may have CNS HSV infection without overt clinical, laboratory, or imaging signs of meningoencephalitis. Approximately one-quarter of neonates with HSV apparently localized to the SEM, and more than 90 percent of neonates with disseminated HSV disease, have HSV DNA detected in their CSF by PCR [7]. Thus, it is imperative to include a CSF examination and CSF HSV PCR in all neonates with suspected or proven neonatal HSV infection. Using PCR to detect HSV DNA in the blood or plasma confirms the diagnosis and aid to early antiviral therapy [7,12,34,39,45,46]. One study showed that blood HSV PCR is mostly accurate in case of disseminated HSV disease with 100% detection by PCR, on the other hand, 64 percent of infant with meningoencephalitis HSV demonstrated positive blood PCR [46].

Direct immunofluorescence assays (DFA) and enzyme immunoassays (EIA) are rapid methods that detect the virus antigens in case of localized lesions [37,47]. DFA has high specificity for HSV infection with easy conducting of HSV type. Despite the high specificity, DFA is not as sensitive as culture; in addition, test accuracy depends greatly on adequate sampling to ensure catching cells from the base of mucocutaneous lesions [47]. EIA is primarily used for screening, especially to screen asymptomatic or pregnant women for HSV genital infection [47]. Test results may be false positive or false negative in not trivial number of cases, hence, combination with cell culture is recommended to optimize accuracy. The role of rapid EIA in neonatal HSV diagnosis is not well-established, highlighting the need for cell culture to confirm the diagnosis of HSV in neonates.

Neuroimaging with magnetic resonance imaging (MRI), CT, or ultrasonography should be recommended for infants with neonatal HSV disease of any clinical class or presentation [16]. In CNS herpes simplex virus infection, enhanced CT or MRI brain is recommended to determine location and extent of brain involvement [7,26]. MRI is more sensitive than CT. Prenatal ultrasound may play an important role in intrauterine HSV disease, by showing fetal brain damage. By comparison, neonatal ultrasound has minimal advantages, as it underrepresents the degree of brain involvement. Thus, it should not be the only Imaging modality in infants with suspected HSV central nervous system involvement.

The finding of neonatal HSV CNS imaging varies. Neuroimaging may be normal early in the course of meningoencephalitis, hence, negative imaging at this time does not exclude the disease. Several days to a week, parenchymal brain edema or abnormal attenuation, hemorrhage, or destructive lesions may appear [7,26]. Temporal lobe destructive lesions are classical finding and imaging abnormalities may be multifocal or limited to the brainstem or cerebellum [48].

Prevention and management

Prevention of postnatal transmission of HSV could be achieved by counseling family members with active HSV, a history of recent past cold sores, or HSV lesions to avoid close contact with and avoid kissing the newborn baby. Women with herpetic breast lesions should

not breastfeed from the infected breast until the lesions have been healed because the HSV can be transmitted directly to the infant [49]. Mothers should use careful hand hygiene and cover any lesions with which the infant might come into contact.

Infants born to women with active HSV lesions should be managed with contact precautions during hospitalization, with a private room, or while rooming with the mother [16]. Some experts believes that such precautions are not necessary for infants delivered by cesarean section < 4 hours after rupture of membranes. Contact precautions are not necessary for infants born to women with a history of recurrent genital HSV who have no genital lesions at the time of delivery.

Contact precautions should be used as well for infants hospitalized with HSV infection if they have mucocutaneous lesions [16]. The median duration of viral shedding from skin vesicles and mucosal lesions in infants receiving acyclovir therapy is five to eight days [50]. Infants and children with cutaneous recurrence of neonatal HSV should be counseled to cover the lesions to prevent potential transmission through direct contact [51]. Regarding vaccines, until our search, there is no approved, effective vaccine against HSV-1 or HSV-2 infection. However, a promising HSV-2 gD subunit vaccine is being studied currently in clinical trials [2,7].

The Adequate Neonatal HSV management consists of support measures and antiviral therapy. Supporting steps are important for CNS involvement and for disseminated HSV. Such steps include: prevention of hypoglycemia and avoidance of fluids and electrolytes imbalance; shock management and systemic inflammatory response; oxygen and mechanical ventilator support; nutritional support; seizure control. Fresh frozen transfusions of plasma and/or platelets are important in patients with significant bleeding caused by intravascular coagulation that has spread.

Before antiviral therapy was available, neonatal HSV infections had a high one-year mortality rate estimated at 85 percent and 50 percent respectively for disseminated and meningoencephalitis herpes simplex infection [52]. After discoveries of antiviral therapy, the mortality rate was declined sharply to 29 and 4 percent respectively [11,50,53].

Acyclovir is the antiviral of choice for the treatment of all categories of neonatal herpes simplex virus (HSV) infections [50,54]. Antiviral therapy has been evidenced to improve survival and outcome, especially if treatment is begun early in the illness [50,53,55]. in addition, the early administration of antiviral therapy prevents progression of localized SEM HSV to meningoencephalitis or disseminated disease. More than half of the neonate with localized SEM will progress to CNS or disseminated HSV disease without antiviral therapy. A randomized controlled trial was designed to compare the morbidity and mortality among infant who receive acyclovir versus infants on vidarabine [53]. The two drugs showed similar results, however, vidarabine has systemic toxicity and a more complex dosing schedule [56].

There is no consensus on the specific indication of acyclovir treatment. Empiric acyclovir is usually agreed upon for neonates with clinical features suggestive of HSV infection of any types and in critically ill infants until confirmatory results become available [16,28-30].

For all types and presentation of neonatal HSV, the dose of acyclovir is equal as it is 60 mg/kg per day intravenously divided on three doses [50]. The dose of acyclovir must be adjusted for neonates with renal impairment. A lower dose is used for older than three months of age.

Two trials have examined the benefits of the higher dose of acyclovir compared with the conventional daily dose of 30 mg/kg. In the first trial, 30 mg/kg of acyclovir were administered for 10 days [53]. in the second trial, seventy-two neonates with CNS or disseminated HSV were treated with acyclovir dose of 60 mg/kg daily for 3 weeks [50]. The higher dose was associated with increased survival at 24 months.

Ganciclovir IV was suggested to be the first-line alternative to acyclovir by The American Academy of Pediatrics (AAP) Committee on Infectious Diseases [57-59].

Conclusion

According to many estimates, herpes simplex virus (HSV) affects approximately 3 - 10 per 100,000 live births in the United States (US) and other countries. The condition is associated with serious morbidity and mortality. The disease is classified clinically to three main types: SEM, CNS herpes simplex virus (also HSV meningoencephalitis); and disseminated HSV infection. Physicians' high index of suspicion is essential to consider neonatal HSV. Neonatal HSV infection remains a possibility in infants born to women who received suppressive therapy during pregnancy. Polymerase chain reaction (PCR) is more sensitive than viral culture for CSF samples. False negative results could be seen with contaminated sample by blood or the presence of high protein; CSF samples obtained early in the course of illness, and samples obtained after therapy initiation and should not exclude the diagnosis in case of high suspicion. The Adequate Neonatal HSV management consists of support measures and antiviral therapy. Supporting steps are important for CNS involvement and for disseminated HSV. Acyclovir have led to sharp decrease in the mortality rate and considered the drug of choice. Ganciclovir IV was suggested to be the first-line alternative to acyclovir.

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