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Review Article

Neonatal Herpes Simplex Virus and Central Nervous System Involvement

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Abstract

Introduction: Despite the relatively low prevalence, neonatal HSV causes serious morbidity and mortality, and survivors may live with permanent consequences.

Aim of Work: In this review, we will discuss the advances regarding neonatal herpes simplex virus with some focusing on neonatal HSV meningoencephalitis.

Methodology: We did a systematic search for most recent available evidence regarding neonatal herpes simplex virus (HSV) infections and central nervous system (CNS) involvement.

Conclusion: Cases of HSV meningoencephalitis are considered challenging, this is due to nonspecific early manifestation and similarity with other bacterial and viral conditions. HSV PCR is more sensitive than viral culture for CSF samples. Electroencephalography (EEG) carries high sensitivity for neonatal HSV meningoencephalitis and often is abnormal before computed tomography (CT) or magnetic resonance (MR) imaging abnormalities. Supportive measures and antiviral therapy are the mainstay of neonatal HSV treatment.

Keywords: *Neonatal Herpes Simplex Virus; Neonatal HSV; Neonatal Meningoencephalitis; Herpes Simplex Meningoencephalitis;*

Introduction

It is estimated that neonatal infection with herpes simplex virus (HSV) affects approximately 3-10 per 100,000 live births in the United States and other countries. The condition causes serious morbidity and mortality, and survivors may live with permanent consequences [1-6]. Despite the seemingly low prevalence, neonatal HSV is responsible for 0.6 percent of in-hospital neonatal deaths in the United States and contributes to substantial healthcare burden and resource utilization [7-10].

In addition, encephalitis by HSV (HSE) is identified as the most common cause of sporadic fatal encephalitis in the United States and other industrialized nations [11-14]. About 10 - 20% of all cases of viral encephalitis are HSV encephalitis (HSE) [15]. Hjalmarsson., *et al*. reported in Sweden-wide retrospective study that 2.2 per million people had annual confirmed incidence of HSE [16]. While HSV-1 is known to cause more than 90% of HSE cases in adults, HSV-2 infection 2 is a common cause of acute generalized encephalitis in neonate and typically causes aseptic meningitis [17]. However, an increasing number of neonatal herpes cases caused by HSV-1 is identified in the United States and some European countries [18]

Most neonatal herpes result from transmission of maternal infection, this usually occurs during passage through the contaminated infected birth canal of a mother with asymptomatic genital herpes. The risk for infection is higher in case of primary genital infection (30- 50%) than mothers 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 [19].

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 and central nervous system (CNS) involvement, 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; Herpes simplex meningoencephalitis; HSV CNS affection.

Virology and transmission

HSV is a member of the *Herpesviridae* family of viruses. The virus can be classified into HSV type 1 and HSV type 2 using serologic and molecular techniques. 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]. Hence, most commercially available serologic assays cannot distinguish between HSV-1 and HSV-2 antibodies.

HSV invade the human host through breaks in skin of inoculation in mucosa of oral, genital, or conjunctiva. Then it transports through sensory nerve endings by retrograde axonal flow 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. However, in addition to Latency property, HSV has the biologic properties of reactivation, which 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 [19]. Neonates acquire HSV when HSV is present in the genital tract of the pregnant woman at the time of delivery regardless of presence of symptoms. The transmission could be influenced by many factors as the type of maternal HSV infection (primary versus recurrent), maternal HSV antibody status, duration of ruptured membranes, use of fetal scalp monitors, and cesarean versus vaginal delivery [2]. It is worth mentioning, however, that most neonatal HSV occurs without mothers' history of HSV infection or other identifiable risk factors [20]. The remaining 10 - 15 percent of neonatal HSV infections are acquired postnatally [19]. This occurs in case of close contact with active HSV infection individuals.

Clinical manifestation

For therapeutic and prognostic purposes, neonatal HSV is classified clinically 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 is more common and has been associated with a poorer outcome [2,7,21,22].

Neonatal meningoencephalitis (also called neonatal HSV CNS) accounts for one-third of neonatal HSV conditions [19,23]. 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 [23]. 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 [19].

The clinical manifestations include focal or generalized seizures, lethargy, poor feeding, irritability, tremors, temperature instability, and full anterior fontanel [21,24,25]. However, all of these signs may not appear at the early course.

Cerebrospinal fluid (CSF) analysis classically shows increase in mononuclear cells, normal or slightly decreased glucose concentration may, and mildly elevated protein. Similar to the illness signs, CSF studies may be normal in the early course and could be pronounced as CNS disease progresses. The electroencephalogram (EEG) changes manifest very early in HSV meningoencephalitis. The EEG abnormalities may appear as focal or multifocal periodic epileptiform discharges [7,26]. Brain imaging using Computed tomography (CT) and magnetic resonance (MR) may appear normal in the early course. Later on, neuroimaging studies may show parenchymal brain edema or attenuation, hemorrhage, or destructive lesions [7,24].

In the absence of vesicles, the initial presentation is similar and indistinguishable from other causes of neonatal sepsis or meningitis [19,27]. Many experts recommend initial evaluation with DNA polymerase chain reaction (PCR) and other CSF investigations and starting empiric treatment with acyclovir in all neonates with aseptic meningitis or signs and symptoms of meningoencephalitis without an obvious bacterial clues [28,29].

Investigation and diagnosis

Cases of HSV meningoencephalitis are considered challenging, this is due to nonspecific early manifestation and similarity with other bacterial and viral conditions. Prompt treatment requires a high index of suspicion of neonatal HSV as a possibility in neonates presented with mucocutaneous lesions, central nervous system (CNS) affections, or a sepsis-like picture.

Neonatal HSV infection could be diagnosed through virus isolation in traditional or enhanced viral culture, detection of viral DNA by polymerase chain reaction (PCR), or viral antigens detection by rapid direct immunofluorescence assays (DFA). Serology plays a minor rule in the diagnosis at the time of presentation.

Isolation of HSV culture is the gold standard laboratory investigation that ensure the presence of an active HSV infection 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 common and noninvasive investigation to be used [7,23].

Isolation of HSV by viral culture of other samples as CSF or blood are less commonly used, although this can establishes the diagnosis, PCR is preferred over viral culture of these specimens because it has 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 [30,31]. These methods are generally comparable to cell culture, but not all these assays are able to distinguish and type HSV-1 or HSV-2.

The detection of HSV DNA in the CSF of a neonate using PCR confirms the diagnosis of CNS involvement. CSF HSV PCR is more sensitive than viral culture. However, false negative results may occur in case of blood or high protein in the CSF, CSF samples early in the course of illness, and samples obtained several days into antiviral therapy [7,32-37]. Hence, negative CSF does not exclude the diagnosis in case of high suspicion and should be repeated during the first week of illness [38]. 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 [7,20,33,39-41]. 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 [41].

Direct immunofluorescence assays (DFA) and enzyme immunoassays (EIA) are rapid methods that detect the virus antigens in case of localized lesions [31,42]. 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 [42].

EIA is primarily used for screening, especially to screen asymptomatic or pregnant women for HSV genital infection [42]. 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.

Serologic tests have a marginal benefits in the diagnosis of neonatal HSV infection. The importance of serological test reside in attempts to identify HSV-2 infection in pregnant women which help in neonatal HSV prevention.

Electroencephalography (EEG) should be performed in all neonates suspected to have meningoencephalitis, this is especially important in case of seizures, abnormal movements, or abnormal CSF. The test carries high sensitivity for neonatal HSV meningoencephalitis and often is abnormal before computed tomography (CT) or magnetic resonance (MR) imaging. Periodic or quasiperiodic epileptiform discharges in abnormal EEG, especially if they are focal or multifocal, is characteristic of neonatal HSV CNS involvement [26].

Infants with neonatal HSV disease of any clinical class or presentation should have neuroimaging with magnetic resonance imaging (MRI), CT, or ultrasonography [23]. In HSV meningoencephalitis, enhanced CT or MRI brain is recommended to determine the location and extent of brain involvement [7,24]. MRI is more sensitive than, but CT is adequate if MRI cannot be readily performed. In intrauterine HSV disease, prenatal ultrasound may play important role by showing fetal brain damage. By contraries, the modality has limited benefits in neonatal ultrasound because it underrepresents the extent of brain involvement. Thus, it should not be the only Imaging modality in infants with suspected HSV CNS disease.

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 [7,24]. Temporal lobe destructive lesions are classical finding and imaging abnormalities may be multifocal or limited to the brainstem or cerebellum [26].

Treatment and management

The Adequate management of neonatal HSV consists of supportive measures and antiviral therapy. Supportive measures are essential in CNS HSV meningoencephalitis and in case of disseminated HSV. These measures include: Fluid and electrolyte maintenance and avoidance of hypoglycemia; management of shock and systemic inflammatory response; Provision of oxygen and mechanical ventilator support; nutritional support; Control of seizures. Fresh frozen plasma and/or platelet transfusions are important in patients with significant bleeding caused by disseminated intravascular coagulation.

Before the availability of antiviral therapy, neonatal HSV infections carried a high one-year mortality rate that was estimated to be 85 percent and 50 percent for disseminated and meningoencephalitis HSV respectively [43]. After discoveries of antiviral therapy, the mortality rate declined sharply to 29 and 4 percent respectively [19,44,45].

Acyclovir is the antiviral of choice for the treatment of all categories of neonatal herpes simplex virus (HSV) infections [45,46]. Antiviral therapy has been evidenced to improve survival and outcome, especially if treatment is begun early in the illness [44,45,47]. 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 [44]. The two drugs showed similar results, however, vidarabine has systemic toxicity and a more complex dosing schedule [48].

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 [23,27-29].

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 [45]. The dose of acyclovir must be adjusted for neonates with renal impairment. A lower dose is used for older than three months of age.

The benefits of this higher dose of acyclovir was compared with the conventional dose of 30 mg/kg per day in two trials. In the first trial, infant were treated with acyclovir 30 mg/kg per day for 10 days [44]. In the second trial, seventy-two neonates with meningoencephalitis or disseminated HSV were treated with acyclovir 60 mg/kg per day for 3 weeks [45]. The higher dose was associated with increased survival at 24 months.

The American Academy of Pediatrics (AAP) Committee on Infectious Diseases suggest the IV use of ganciclovir as a first-line alternative [49-51]. The dose of ganciclovir is 6 mg/kg every 12 hours IV for infants ≤ 3 months and 5 mg/kg every 12 hours IV for infants > 3 months.

Conclusion

Despite the relatively low prevalence, neonatal HSV causes serious morbidity and mortality, and survivors may live with permanent consequences. The disease us classified clinically to three main types; SEM, CNS HSV (also HSV meningoencephalitis; and disseminated HSV infection. Cases of HSV meningoencephalitis are considered challenging, this is due to nonspecific early manifestation and similarity with other bacterial and viral conditions. HSV PCR is more sensitive than viral culture for CSF samples. Electroencephalography (EEG) carries high sensitivity for neonatal HSV meningoencephalitis and often is abnormal before computed tomography (CT) or magnetic resonance (MR) imaging abnormalities. Supportive measures and antiviral therapy are the mainstay of neonatal HSV treatment.

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