Review:

Diagnosis and Management of Congenital, Neonatal and Perinatal HSV Infections

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ABSTRACT

Herpes simplex virus (HSV) infection is one of the most common viral diseases that might occur during pregnancy and during foetal delivery and can transmit vertically from infected mother to foetus or neonate. In infants, the infection is usually fatal if untreated and most of the cases are asymptomatic. Therefore, early diagnostic of both mother and baby is essential and required to save their life. Fortunately, there are many virological and serological techniques are available to detect the virus with a high accuracy rate and help the initiation of treatment with antiviral therapy, particularly with high dose of intravenous acyclovir that has found to be significantly effective in treating the neonatal HSV infection, however, it may associate with neurologic complication in survivors from central nervous system disease.

Keywords: Diagnosis of Neonatal HSV, Management of Neonatal HSV, Diagnosis of Perinatal HSV, Management of Perinatal HSV, Diagnosis of Congenital HSV

INTRODUCTION

Perinatal and congenital herpes simplex infection can occur predominately during delivery and infrequently in utero from mother with primary or recurrent herpes infection but mostly with primary infection (Knezevic, et al. 2007). Congenital herpes infection is rare in comparison to other congenital viral infection while perinatal or neonatal infection with herpes simplex virus is frequent and divided into 3 categories; disseminated disease, central nervous system and localised diseases (skin, eye and membrane). The disseminated and central nervous system forms are associated with high morbidity and mortality rate, despite to the availability of many virological and serological tests for diagnosis of and antiviral therapy for treatment of the disease. Among the recent advanced diagnostic technology is polymerase chain reaction which can be applicable to the majority of suspected babies and pregnant mothers and it characterized by its high accuracy rate and can assist in early and effective treatment. This is beside to recent treatment of neonatal HSV disease with high dose of intravenous acyclovir has saved and controlled significant rate of neonate lives, although it follows less significant adverse effect and neurologic sequelae, especially among survivors from central nervous system disease. In addition to all of these advances, the period for initiation of antiviral therapy is still not reduced substantially for the past two decade. Therefore, the most effective way in this case is to raise awareness about neonatal HSV disease in order to provide earlier diagnosis and rapid initiation of antiviral therapy (Kimberlin and Whitley, 2005).

VIRAL STRUCTURE

Neonatal herpes simplex infection is caused by both HSV-1 and HSV-2 which are belonging to the family of herpesviridae, they are enveloped, double-stranded DNA virus with an icosahedral nucleocapsid. Their genomes are significantly similar and have two covalently linked components named L (long) and S (short). Their envelopes have spikes (glycoproteins) which are 12 types (gB, gC, gD, gE, gG, gH, gI, gJ,
gK, gL, gM, and gN). The gG is providing antigenic specificity by resulting in antibody response to distinguish between HSV-1 (gG-1) and HSV-2 (gG-2) (Kimberlin, 2004).

**DIAGNOSIS**

Generally, clinical manifestations of mother and baby peripartum or postpartum, and laboratory assessments can play in important role in clinical diagnosis of herpes simplex infection.

1. **Clinical manifestations:**

Clinical findings may have a role in early diagnosis of the HSV disease when available diagnostic tests are failed to do that (Gosch et al., 1993). Herpes simplex infection in neonate can be acquired either during pregnancy (in utero) or during and after the birth and the consequence may be perinatal and congenital herpes infection.

Congenital herpes disease is thought to be caused by both primary and recurrent maternal infection during first trimester (McIntyre and Newell, 2000), although the risk after primary infection is higher. Congenital infection is rare with HSV and its clinical manifestation is non-specific because of similarity to other congenital infections. It is usually symptomatic and has clinical abnormalities at birth including microcephaly, chorioretinitis and hydrocephalus (Corey and Wald, 2009) whilst the neonatal or perinatal infection is frequent with HSV and mostly result from exposure to the virus during delivery, especially from mothers with primary HSV infection (50%) (Ural, 2013). The majority of neonatal HSV infections are asymptomatic which is responsible for delay in diagnosis and treatment (McIntyre and Newell, 2000). However, the symptomatic form may also occur and assist in early treatment. The symptomatic form is generally classified into three categories including disseminated disease, CNS disease and SEM disease (localised infection of skin, eyes or mouth). Disseminated disease is a generalized form which spreads throughout the body and affects multiple organs, especially liver, lungs and it is associated with highest mortality rate than other forms (around 85%) in untreated infants (Kimberlin, 2004; Kimberlin and Whitley, 2005; Knezevic et al., 2007) whilst the CNS form is characterized by the presence of both focal and generalized seizures, fever, lethargy, irritability, tremors and poor feeding. It may also associate with skin vesicles (about 60-70%). Its mortality is also high without treatment (50%), this is due to devastating destruction of brain tissue. Whereas SEM disease has relatively low mortality rate without treatment and it is limited to skin, eyes and mouth (Kimberlin, 2004).

2. **Laboratory diagnostic assessments**

The clinical signs of neonatal herpes simplex infection are nonspecific and not sufficient alone due to presence of other similar conditions. In addition, most of infants are asymptomatic. Therefore, laboratory diagnostic tests are essential for confirming herpes simplex infection in both mother and baby (Simon, 2010). There are many laboratory tests that can be used to diagnosis of HSV which can basically be divided into two groups including virological tests which are used to detect either the virus itself, its nucleic acid (DNA) or its antigen from the samples available and serologic tests to detect antibodies produced against the virus. The way of application of both virological and serological tests is different according to the sample type that is being tested. Therefore, it is necessary for the clinician to speak with the virologist during suspicion of any cases of neonatal herpes simplex infection (Kimberlin, 2004). Virologic techniques include: viral isolation and culture of the throat swab (oropharynx or nasopharynx), blood, cerebrospinal fluid (CSF), stool and urine; polymerase chain reaction (PCR) testing of blood and CSF; direct immunofluorescent antibody (DFA) staining of skin lesions if present; enzyme immunoassays (EIA) for the virus antigens whilst serologic techniques include ELISA, Immunoblot, Biokit HSV-2 and Western Blot Tests (Ashley, 1993; UMMC, 2011).
2.1. Virological tests: They are generally divided into three groups including:

2.1.1. Direct virus detection:

Viral culture: HSV isolation and culture is still one of the standard lab techniques for diagnosis of HSV diseases, especially when characteristic skin vesicles are present. Sample are scraped from the lesions and then transported on a suitable ice medium to the virology laboratory for diagnosis, where the samples are inoculated into cell culture systems to detect the characteristic cytopathic effects produced by the replication of HSV and then viral typing is determine by other techniques (Ashley, 1993; Singh et al, 2005). Blood, CSF, urine, stool and oropharynx are other available sources for viral isolation. Specimens can also be obtained from other sites of the body to culture the virus based on the form and location of HSV infection. For example, in infants with hepatitis, necrotizing enterocolitis or other gastrointestinal manifestations of HSV disease, samples may be aspirated from duodenum for virus culture or in case of SEM form of HSV disease, specimens may routinely isolated from eyes or conjunctivae. Even in sometimes, specimens from multiple body sites, with the exception of CSF, may be combined prior to plating in cell culture in order to reduce costs (Kimberlin, 2004).

Basically, it is better to obtain samples from the babies during 48 hours after birth because they may represent active replication of herpes virus whereas samples isolation within the first 24 hours after birth are represent colonisation and not replication (Allen, 2006). Another virological test is Tzanck smear test which is an older virological testing which is used in diagnosis of neonatal herpes simplex if lesions are present. In this method, the obtained samples from the lesions are stained and examined under microscope to detect specific intranuclear inclusion bodies within the multinucleated giant cells (syncytia) that are representing herpes simplex viruses. This test is now uncommon and unreliable for definitive diagnosis, although it is a fast test. This is because it has relatively low accuracy rate around 50 - 70% and it is also unable to differentiate between herpes virus types (Kimberlin, 2004; UMMC, 2011; CDC, 2014).

2.1.2. Antigen detection methods:

There are some virological techniques that are valuably used to detect viral antigens from HSV lesions and they are basically alternative to the viral culture, particularly when rapid diagnosis is desired (Ashley, 1993; Kimberlin, 2004; CDC, 2014) and also in cases where circumstances for handling and transportation of specimens are inappropriate for the viability of any viruses present. However, the sensitivity of antigen detection tests may be similar to than that of culture. One of the common techniques that are used to detect HSV antigen is Direct Immunofluorescence (DFA) staining which is commonly suitable for the smears that are isolated from a skin lesion. It can also be performed on oropharyngeal swab but it is unreliable. It also requires a high-quality specimen to provide a greater sensitivity rate about 90%, especially in early stage of infections (Kimberlin, 2004; CDC, 2014).

2.1.3. Viral DNA detection

PCR technique is now widely used in diagnostic laboratory for herpes infection. It is rapid and requires less labour as well as it is much more accurate than standard viral culture because it detects the DNA of HSV (Corey and Wald, 2009; CDC, 2014). It can produce many amplicons of the viral DNA, so it can demonstrate even a small quantity of DNA present in a specimen (UMMC, 2011). Clinical specimens that are used for perform PCR include CSF and blood. CSF samples are usually recommended by the majority of laboratory for diagnosis of HSV in suspected cases of neonatal herpes encephalitis whilst blood samples are recommended in suspected cases of disseminated herpes diseases. Although PCR can detect HSV DNA from lesions sample, false-positive results are commonly following it; this is mainly due to the contamination of sample before amplification. Therefore, application of PCR in the laboratories require separated areas and cleaned equipment for pre- and post-amplification sample handling to reduce this problem. In addition, the positive results of PCR usually need to be confirmed by a second PCR to ensure the specificity of the amplification (Kimberlin, 2004; Thompson and Whitley, 2011).
Recently, automated PCR has been developed for HSV detection and it is thought to be used widely in the future for many diagnostic purposes. It detects products in a closed-tube system without any post-amplification handling and it can differentiate between herpes simplex types by using HSV1/2 kits. It has a higher sensitivity rate than that of viral culture and also it has less false-positive results than that of PCR. Whereas the disadvantage of this technique is that it cannot be used by many laboratories because of the unreasonable cost of the kits and reagents that are used for this technique (Kimberlin, 2004)

2.2. Serological tests:

There are many serological tests that can be used in the laboratory for diagnosis of HSV infection particularly when other virological methods are unable to be performed or producing negative results and also in asymptomatic infections, however, serological tests are basically not of great clinical value in diagnosis of neonatal HSV infection. This is because of several factors including: it is difficult to differentiate between transplacental IgG antibodies and IgG produced by the babies (Kimberlin, 2004); in some severe cases the infants may be unable to produce antibody; the HSV IgM tests that are commercially available have variable and limited reliability. Thus, the serological tests that are not type-specific having laboratory limitations for diagnosis of neonatal HSV infection.

Although many serological tests can identify HSV antibodies, some of them can differentiate between HSV-1 and HSV-2. This is because of serologically close relationship between both types. Recently, a new HSV type-specific antibody assay has been introduced in order to overcome this problem, they each encode a serologically two distinct glycoproteins G (Glycoprotein gG-1 is associated with HSV-1 and Glycoprotein gG-2 is associated with HSV-2) (Singh et al, 2005).

MANAGEMENT

Antiviral therapy of at risk baby:

All suspected or diagnosed cases of neonatal HSV infection must be treated with intravenous Acyclovir (60 mg/kg) daily, which is a drug of choice especially in disseminated and CNS herpes form. The duration of treatment is different according to the form of neonatal herpes infections, it is for about 21 days treatment in case of CNS or disseminated HSV infections (McIntyre and Newell, 2000; Hartnett, 2005; Anzivino et al, 2009) and for about 14 days in case of localized SEM form. In addition, suppressive dose of oral Acyclovir is also recommended in case of cutaneous recurrences after SEM disease for several weeks or months (Anzivino et al, 2009), however, it is contraindicated by some studies (Allen, 2006).

Although intravenous administration of Acyclovir with high dose and adequate duration can be effective, the mortality and morbidity rate with the CNS and disseminated herpes disease is still high. This is because Acyclovir can only reduce the virus in infected infants, not eliminate it (Kimberlin and Whitley, 2005; Anzivino et al, 2009). Therefore, careful monitoring of exposed infants is necessary and required for recurrent infection, eye and neurological sequelae (Allen, 2006). Acyclovir is also recommended for 14 days for asymptomatic babies born to mothers who acquired HSV in late gestation period (Corey and Wald, 2009).

Vidarabine is another antiviral drug can be administered intravenously in neonatal herpes disease (15 or 30 mg/kg per day) for 12 hour interval but it may associate with significant side effect such as hepatic toxicity and bone marrow suppression (Hartnett, 2005). In other words, Acyclovir is better than Vidarabine, although the high dose of it may also associate with less significant side effect on the infant such as nephrotoxicity and transient neutropenia. In addition, rare cases of neonatal HSV resistance to this drug have been described (Corey and Wald, 2009).
Antiviral prophylaxes during pregnancy and caesarean delivery

All suspected or diagnosed pregnant women should be treated based on the type of herpes infection, the stage of gestation, the duration of the fetal membranes and the mode of delivery (caesarean versus normal).

In mothers with first episode of herpes infections (primary or non-primary), the rate of viral transmitting to the foetus is high and treatment with suppressive dose of Acyclovir therapy (400 mg) starting at 36 weeks of gestation is recommended prophylactically to prevent neonatal herpes infection. In women who have recurrent genital HSV during pregnancy, Acyclovir suppressive therapy is also considered prophylactically in the late pregnancy. In some cases in mothers with delayed delivery, intravenous Acyclovir (15 mg/kg per day in a 3 doses) is also suggested by some studies.

If there is no obvious clinical findings and the virological and serological tests of the pregnant woman are negative during the last week of delivery, vaginal delivery for the baby is recommended whereas in mother with symptomatic primary herpes infection especially in late trimester of gestation (last 6 weeks of expected delivery) as well as in those with membrane rapture for less than 4-6 hours, caesarean section is recommended immediately in order to minimize the risk of neonatal HSV infection (Kimberlin and Whitley, 2005; Allen, 2006). The problem with caesarean section is that because the majority of babies having herpes infection are delivered from asymptomatic mothers (60-80%), so neonatal herpes diseases in babies cannot avoided by this method. It is also cannot be used when the membrane rupture occur at a stage of pregnancy when the lung of foetus is still very immature (Kimberlin, 2004).

CONCLUSION

Nowadays, there are many serological and virological diagnostic techniques available and have been developed for diagnosis and detection of perinatal and neonatal HSV infections in the laboratories and the most common one is automated PCR which can detect the DNA of the virus in the early stage of infection and it can also differentiate between herpes simplex types HSV1/2 (Kimberlin, 2004). Antiviral drugs are available for treatment of the disease, especially with Acyclovir which has been found to be more effective, however, it can only reduce the virus in infected infants, not eliminate it (Kimberlin and Whitley, 2005; Anzivino et al, 2009). Therefore, careful monitoring of exposed infants is necessary to reduce the chance of recurrent infection and neurological complications (Allen, 2006).

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Conflict of Interest

No conflict of interest

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