NEONATAL HERPES IN SERBIA: IS IT A PROBLEM OR NOT?

ALEKSANDRA KNEŽEVIĆ1,*, JELENA MARTIĆ2, MAJA STANOJEVIĆ1, B. JANKOVIĆ2 and TANJA JOVANOVIĆ1

1 Virology Department, Institute of Microbiology and Immunology, Faculty of Medicine, University of Belgrade, 11000 Belgrade, Serbia
2 Neonatology Department, Mother and Child Health Institute "Dr Vukan Čupić", Faculty of Medicine, University of Belgrade, 11070 Belgrade, Serbia

Abstract - With 20-80% mortality, neonatal infection caused by herpes simplex virus (HSV) or neonatal herpes is among the most severe of all perinatal infections. The majority of neonatal HSV infections are acquired during delivery, although in utero and postnatal infections do occur. Primary maternal infection is associated with a high rate of transmission (~50%), compared to <3% in infants of women with reactivated disease. Other factors that influence transmission include HSV type, premature delivery, etc. Clinical manifestations have been classified into three forms: skin-eye-mouth disease, CNS and disseminated disease. The diagnosis of neonatal HSV infection includes the detection of HSV DNA by PCR in samples from neonate and mother. The incidence of neonatal herpes differs widely between different countries. In Serbia, the data about neonatal herpes incidence are scarce. The results of our pilot study showed that the minimal estimation of the national incidence of neonatal herpes is 7.5 per 100 000. Therefore, the set up and implementation of a national neonatal herpes surveillance system might provide valuable information for the accurate assessment of disease burden and development of an effective prevention strategy in Serbia.

Key words: Neonatal herpes, HSV, neonates, surveillance

INTRODUCTION

Neonatal infection caused by the herpes simplex virus (HSV) or neonatal herpes was first reported and described in the mid-1930s. Over the subsequent decades, the spectrum of the disease that HSV can cause in the newborn has been well characterized and the efficacy of the antiviral therapy in neonatal HSV infections has been established. However, even today, neonatal herpes is among the most severe of all perinatal infections, with 20-80% mortality, primarily due to the fact that 60 to 80% of women who deliver an HSV-infected infant have no evidence of infection (Kimberlin, 2004a; Malm, 2009).

Virus, transmission and epidemiology

Herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) are ubiquitous, enveloped and double-stranded DNA viruses, belonging to the family Herpesviridae. HSV-1 and HSV-2 are closely related viruses, although the differences in DNA genome are sufficient for type identification and diagnosis. Two biological properties of HSV that directly influence human disease are latency and neurovirulence. The transmission occurs across mucosal membranes and nonintact skin by direct contact. After attachment to the host epidermal or mucosal cells, viruses are transported via axons to the nuclei of sensory neu-
rons. A lifelong latency with reactivation properties is established which might be influenced by host or environmental factors. Reactivation can result in clinically apparent disease (vesicular lesions) or clinically inapparent (asymptomatic or subclinical) infection (White and Fenner, 1999).

HSV-1 is usually found in the oropharyngeal region with latency in the trigeminal ganglia, whereas HSV-2 is most commonly found in the anogenital region with latency in the lumbosacral ganglia. However, these viruses can infect both areas. Recently, the increased incidence of HSV-1 as a cause of genital herpes has been reported in some developed countries. This may be explained by sexual behavior changes mainly in young adults (Malm, 2009; Gardella and Brown, 2011).

HSV infection of the newborn can be acquired in utero (intrauterine), intrapartum (perinatal) and postpartum (postnatal). The mother is the most common source of infection for the first two routes of viral transmission. The vast majority (85%) of neonatal HSV infections are acquired during delivery when the infant comes into direct contact with infected maternal secretions in the birth canal. An additional 10% of infected neonates acquire the virus postnatally (e.g. from someone shedding HSV from the mouth who then kisses the baby, from exposure to HSV from a breast lesion, or from herpetic whitlow exposure in the nursery). Intrauterine or congenital HSV infection is a rare disorder and accounts for 5% of HSV infections in neonates. Intrauterine infection may occur either because of ascending infection from the cervix uteri or because of transplacental transmission (Kimberlin, 2007; Anzivino et al., 2009).

The most important factors that influence the transmission of HSV to the neonate are the type of maternal infection (i.e., primary infection, symptomatic or asymptomatic reactivation), transmission of maternal transplacental antibodies (less maternal-fetal transfer of HSV neutralizing antibodies), duration of ruptured membranes in the presence of active infection (i.e., longer than 6 h) and the use of a fetal scalp monitor at delivery (Kimberlin, 2004b).

Primary maternal infection is associated with a high rate of transmission (~50%), compared to <3% in infants of women with reactivated disease. The risk of transmission is increased if the infection occurs late in the third trimester of pregnancy due to the lack of an antibody response prior to delivery in late primary infection. However, most neonatal HSV infections (about 70%) result from exposure to asymptomatic genital HSV infection of the mother near delivery (Kimberlin, 2004b; Straface et al., 2012).

The incidence of neonatal herpes varies widely between different countries from 8-60 per 100 000 live births in the USA to 1.6 per 100 000 in the UK and Switzerland. These differences are probably due to differences in criteria and diagnosis of neonatal herpes infections. Numerous studies have reported an increased incidence of neonatal herpes over the past 10 years worldwide. Therefore, in some developed countries, surveillance and prevention programs of neonatal herpes have been introduced (Malm, 2009; Pascual et al., 2011).

In the majority of countries, HSV-2 is associated with 70% of cases of neonatal herpes. However, recent studies reported an increased prevalence of neonatal HSV-1 infections, which may be explained by an increased prevalence of genital HSV-1 infections worldwide (Malm, 2009; Pascual et al., 2011; Gardella and Brown, 2011). In addition, concomitant neonatal infection with HSV-1 and HSV-2 has been reported (Knezevic et al., 2007).

**Clinical manifestations**

The clinical disease of neonatal herpes usually presents in the first 3 weeks of life. The symptoms of neonates have been classified into 3 forms of presentation: skin-eye-mouth manifestations (SEM disease) without visceral or CNS involvement, CNS form without other visceral organs being involved, and disseminated form (DISS) with sepsis-like
symptoms, disseminated intravascular coagulopathy (DIC) and visceral involvement (liver, lungs, adrenal glands) with or without CNS symptoms (Kimberlin, 2004a).

SEM disease accounts for 45% of infants and is characterized by vesicular lesions on the skin, eye and mouth without CNS or organ-system involvement. Usually, this form presents at 10-11 day of age. In the absence of antiviral treatment, 60-70% of infants with SEM disease progress to either CNS or disseminated disease. With treatment, the outcome is good, although these children may have recurrent outbreaks of cutaneous herpes during childhood (Kimberlin, 2004b; Gardella and Brown, 2011).

Infection of the CNS accounts for 30% of infected infants. Disease presentation is usually around day 16-19 of life. Clinical manifestations of this form include seizures (both focal and generalized), lethargy, irritability, tremors, poor feeding and temperature instability with or without skin lesions. The mortality rate is 50% in untreated infants and is the result of devastating brain destruction. Although response to therapy is generally good, moderate to severe neurological sequelae are evident in 50% of surviving neonates (Kimberlin, 2007; Gardella and Brown, 2011).

Disseminated disease is seen in 25% of HSV infected neonates, and mortality in the absence of treatment is high (~85%). Clinical manifestations usually appear between 9 and 11 days of age, however the infant may be ill on the first day of life. Neonates commonly present with viral sepsis, including respiratory collapse, liver failure and DIC. CNS involvement occurs in 60-70% of infants with DISS. If treated, 70% of infants survive and about 15% of these neonates subsequently suffer from neurological abnormalities (Kimberlin, 2004b; Kimberlin, 2007).

Laboratory diagnosis

The laboratory diagnosis of neonatal HSV infection includes demonstration of the virus (viral nucleic acid) by PCR in samples from the neonate (vesicles, nasopharynx, eye, blood and CSF) and mother ( cervix uteri, vesicles, and nasopharynx). The viral culture or immunofluorescence test can be also used (Malm, 2009).

The PCR method allows for the rapid diagnosis of neonatal herpes, particularly HSV infections of the CNS. Not only is it more sensitive than viral culture, but it also avoids many problems associated with the culture methods (e.g., inadequate quantity of specimen, inactivation of the virus through suboptimal handling and transport delays, etc.). However, the interpretation of PCR results, either positive or negative, must be correlated with the infant’s clinical presentation and disease course in determining their ultimate clinical or diagnostic significance (Kimberlin, 2004b; Kimberlin, 2007).

Serology or detection of IgM and IgG antibodies from blood and CSF is not of great clinical value due to the presence of transplacentally acquired maternal IgG antibodies. Currently, these methods are used for complementary diagnostic confirmation in doubtful cases. Serological investigation of HSV type specific IgM and IgG antibodies with an avidity test in the mother can be used for the determination of the type of maternal infection (primary or reactivating infection) (Enright and Prober, 2002; Malm, 2009).

Numerous studies showed that the early recognition and diagnosis of neonatal herpes is crucial in decreasing both mortality and the incidence of neurological sequelae in surviving infants. Therefore, neonatal HSV infection should be considered in the differential diagnosis of acutely ill infants less than 1-month-old with mucocutaneous vesicles on the skin, eyes and mouth, with seizures and other CNS disorders (with negative bacterial cultures after 48 h and antiepileptic nonresponders) and in febrile neonates with signs of sepsis with negative bacterial cultures after 48 h associated with hepatitis, DIC, seizures and pneumonia. In these neonates, appropriate laboratory specimens should be taken for HSV PCR, and antiviral therapy commenced immediately (Kimberlin, 2004b; Fidler et al, 2004).
Treatment and prevention

Antiviral therapy with intravenous acyclovir reduces mortality from 85% to 31% among infants with disseminated disease and from 50% to 6% among infants with CNS disease. Acyclovir at a dose of 20 mg per kilogram of body weight given intravenously every 8 h for 21 days is recommended for disseminated and CNS disease, and the same dose for 14 days is recommended for SEM disease. PCR monitoring for HSV DNA should be considered at the end of treatment for CNS and disseminated disease. Neonates who remain PCR-positive should continue to receive antiviral therapy until PCR-negativity is achieved (Kimberlin, 2007; Corey and Wald, 2009).

A number of approaches are employed in the prevention of neonatal HSV infection. Cesarean delivery in women with active genital lesions can reduce the infant’s risk of acquiring HSV and it is recommended when genital herpes lesions or prodromal symptoms are present at the time of delivery (Kimberlin, 2007).

However, due to the high rate of undiagnosed and asymptomatic HSV infection, the primary goal in the prevention of neonatal herpes is the identification of the at-risk mother. The determination of pregnant women's HSV serostatus is used to establish their susceptibility to the infection during pregnancy. The HSV-seronegative women, as well as, women with HSV seropositivity for only one HSV type are at risk of acquiring primary infection. In these cases, the prevention measurements include education and safe-sex counseling. This approach would also identify women with asymptomatic HSV infection and prophylactic administration of acyclovir or valacyclovir in the third trimester of pregnancy should be provided to all pregnant women with frequent genital outbreaks (Anzivino et al., 2009; Gardella and Brown, 2011).

Recently, a more direct prevention strategy has been introduced. It includes the identification of neonates at risk for HSV exposure at the time of delivery by sampling genital secretions for HSV PCR of all women in labor or prior to labor (in the 36th gestational week). In this approach, maternal serology is used for the determination of the type of viral infection (primary or recurrent). For those with recurrent infection, options could include vaginal delivery with acyclovir prophylaxis of the mother and neonate (Anzivino et al., 2009; Gardella and Brown, 2011).

Since neonatal herpes can also be acquired postnatally, postpartum women, family members and health workers with active herpetic lesions on the mouth, skin or breast should take necessary precautionary measures to prevent direct contact with the neonate and/or should be excluded from the neonatal unit until the lesions are fully healed (Anzivino et al., 2009).

NEONATAL HERPES IN SERBIA

In Serbia, the data about neonatal herpes incidence are scarce. There are no neonatal herpes or genital herpes reporting, surveillance and prevention programs. The estimation of neonatal herpes burden in terms of incidence, mortality and prevalence helps to define priorities for preventive, diagnostic and therapeutic strategies in order to reduce disease burden.

Therefore, we conducted a pilot study to evaluate the incidence of neonatal HSV infection in all neonates admitted to the Neonatology Department at the Mother and Child Health Institute “Dr Vukan Čupić” between January 2010 and December 2011.

During the study period, 1 038 neonates were admitted to the hospital. Neonatal herpes was suspected in 35 neonates according to the clinical and laboratory parameters, which include the presence of mucocutaneous vesicles on skin, eyes and mouth, seizures and other CNS disorders (with negative bacterial cultures after 48 h and antiepileptic non-responders) and the presence of febrile syndrome with signs of sepsis with negative bacterial cultures after 48 h associated with hepatitis, DIC, seizures and pneumonia. The diagnosis of neonatal herpes was assessed using type-specific PCR in blood and/or CSF and/or vesicle swabs.
The majority of neonates with suspected neonatal HSV infection were with CNS disease (57.1%), with disseminated disease in 17.2%, and 25.7% had other symptoms indicative for neonatal herpes. There were no suspected neonates with SEM disease. Out of the 35 neonates with suspected neonatal herpes, 11 were positive. Nine were HSV-1 positive (81.8%). The most of positive neonates had CNS infection (63.6%). Overall incidence in this study was 1.06 % (11/1038).

Extrapolating from the obtained data and applied to approximately 70 000 annual live births in Serbia, the minimal estimation of the national incidence of neonatal herpes is 7.5 per 100 000 live births. This finding is higher compared to the reported data of neonatal herpes incidence in other European countries.

In conclusion, neonatal herpes has an important role in morbidity and mortality of newborns in Serbia. Therefore, the set-up and implementation of a national neonatal herpes surveillance system might provide valuable information for the accurate assessment of disease burden and development of effective prevention strategy in Serbia.

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REFERENCES


