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A Multicenter Study on Symptomatic Neonatal Herpes Simplex Virus Infection in Korea From 2008 to 2017

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ABSTRACT

Background: Neonatal herpes simplex virus (HSV) infection is rare but can cause severe disease, even death. However, data on neonatal HSV infection is limited in Asia. Thus, this study estimated the incidence of neonatal HSV infections and evaluated the characteristics in hospitalized patients in Korea, where seroprevalence of HSV infection in child-bearing age women is not well known.
Methods: This is the first multicenter retrospective study in 12 university hospitals in Korea. Neonates aged ≤ 28 days with confirmed HSV infection were identified from January 2008 to December 2017, and a chart review was performed.
Results: Among 12 medical centers, 16 patients were identified in 6 centers. The estimated incidence rate was 1/7,888 in hospitalized neonates. Eight (50%) patients were males, and the median age at diagnosis was 11 days (range, 4–28 days). Ten (62.5%) patients were HSV-1-positive, and 6 (37.5%) patients were HSV-2-positive. Four (25%) patients had disseminated infection, 11 (68.8%) patients had central nervous system disease, and 1 (6.2%) patient had skin, eye, and/or mouth disease. All the patients received intravenous acyclovir, with a median treatment duration of 19 days (range, 3–68 days). Four (25%) patients received additional oral acyclovir suppressive therapy, with the median treatment duration of 5 months (3–6 months). Four patients (25%) developed seizures (one case with disseminated disease and 3 cases with central nervous system disease), and 2 of them recovered without

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Presentation

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Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Kim KR, Park SE, Lee BK, Han SB, Cho EY. Data curation: Kim KR, Park SE, Cho EY, Cho HK. Formal analysis: Kim KR, Choi JS, Cho HK. Funding acquisition: Choi JS. Investigation: Kim KR, Choi JS, Han SB, Kim YK. Methodology: Choi JS, Lee BK, Han SB, Eun BW, Kim YK. Project administration: Park JY, Han SB, Jo DS, Kim KH. Resources: Park JY, Lee BK, Lee H, Jo DS, Kim YK. Software: Park JY, Lee BK, Lee H. Supervision: Kim YJ, Park SE, Eun BW, Jo DS, Kim KH. Validation: Kim D, Kim KR, Park JY, Park SE, Lee H, Cho EY, Eun BW. Visualization: Cho EY. Writing - original draft: Kim YJ, Kim D, Kim KR, Lee H, Eun BW. Writing - review & editing: Kim D, Kim KR.

neurologic complications. Two (12.5%) patients with disseminated disease died within 30 days from the diagnosis, and one of them had a maternal history of previous genital herpetic lesions. Medical records of maternal genital herpes were not available in 10 (62.5%) patients with neonatal HSV infections.

Conclusion: Although uncommon, neonatal HSV infection occurs in Korean babies with a high 30-day mortality of 12.5%. Increased awareness is warranted among Korean pediatricians for the early diagnosis and treatment of neonatal HSV infection.

Keywords: Neonatal Herpes Simplex Virus Infection; Acyclovir; Incidence; Mortality; Korea

INTRODUCTION

Neonatal herpes simplex virus (HSV) infection can cause severe, potentially fatal, disease classified as skin, eye, and/or mouth (SEM), central nervous system (CNS), and disseminated (DIS) diseases.[1] Neonatal HSV infection occurs in 3 distinctive periods: intrauterine infection (5%), perinatal infections (85%; direct contact with genital herpes lesions during delivery), and postnatal infection (10%; close contact with someone's active HSV infection).[2] Neonates born to mothers with primary HSV infection during late pregnancy are at high risk for HSV transmission.[3]

With high suspicion of neonatal HSV infection, proactive diagnostic work-up and treatment are important. This diagnosis should be considered in neonates with sepsis-like illnesses or asymptomatic neonates born from a mother with the first episode of primary or non-primary HSV infection at delivery.[3] However, this intervention is not commonly performed in Korea.

The first global estimated neonatal HSV rate was 10.3 per 100,000 births with wide regional differences.[4] The incidence of neonatal HSV infection influences empirical treatment strategies for sepsis-like illnesses and pre-emptive management for asymptomatic neonates.

This study aimed to estimate the incidence rate of neonatal HSV infections and evaluate their characteristics in Korea, where seroprevalence of HSV infection in women of childbearing age is not known well.

METHODS

Data collection

A retrospective chart review of hospitalized neonates aged ≤ 28 days with confirmed HSV infection and their maternal history from 2008 to 2017 in 12 university hospitals was performed. A total number of hospitalized patients aged ≤ 28 days during the study period was collected to calculate the incidence. Neonatal HSV infection was defined as positive results of HSV culture from skin vesicles and surface specimens, including the conjunctivae, mouth, nasopharynx, and anus, or HSV polymerase chain reaction (PCR) from surface specimens, blood, and cerebrospinal fluid (CSF). The surface specimens were obtained 24 hours after birth to avoid contamination after intrapartum exposure.[1] Diagnosis of CNS disease was defined by obtaining PCR-positive CSF specimens.[3] Information including modes of birth, skin lesions, initial and peak of alanine transaminase (ALT) level, and seizure presence was collected.

Definition

Neonatal HSV infection can manifest in 3 types: DIS disease, localized CNS disease, and localized SEM disease. The DIS disease involves multiple organs, predominantly the liver, lung, skin, eye, and/or CNS. CNS disease was defined as positive CSF PCR or HSV culture with or without SEM involvement. SEM disease was defined as an HSV infection localized to the SEM.[1]

Ethics statement

The Institutional Review Board of Samsung Medical Center reviewed and approved this study protocol. Informed consent was waived by the board (approval number 2024-08-003-001).

RESULTS

During the study period, 126,203 neonates were hospitalized in 12 centers. Sixteen patients were identified in 6 centers (**Table 1** and **Fig. 1**). The estimated incidence was 1/7,888 in hospitalized neonates. The median birth weight was 3,405 g (range, 780–4,080 g). One (6.3%) neonate had a low birth weight (< 2,500 g). Eight (50%) patients were males, with the median

Table 1. Characteristics of patients with neonatal HSV infection

Parameters	Values
Total	16
Sex, male	8 (50.0)
Age at diagnosis in days	11 (4–28)
Viral type	
HSV-1	10 (62.5)
HSV-2	6 (37.5)
Disease classification	
DIS	4 (25.0)
CNS	11 (68.8)
SEM	1 (6.2)
Skin lesions present	7 (43.8)
By disease forms	
DIS	3 (75.0)
CNS	3 (27.3)
SEM	1 (100.0)
By viral type	
HSV-1	5 (71.4)
HSV-2	2 (28.6)
Age at the start of antiviral therapy in days[a]	12.5 (7–32)
Treated with acyclovir	
IV therapy	16 (100.0)
Treatment duration in days	17.5 (3–68)
Oral suppression therapy	4 (25.0)
Treatment duration in months	5 (3–6)
F/U duration in days	181 (12–1,426)
Neurologic sequelae	
Seizure	4 (25.0)
Developmental delay[b]	0/11 (0)
30-day overall mortality	2 (12.5)
Overall mortality	4 (25.0)

Values are presented as median (interquartile range) or number (%).
HSV = herpes simplex virus, DIS = disseminated, CNS = central nervous system, SEM = skin, eye, and/or mouth, IV = intravenous, F/U = follow-up.
[a]In one patient, the date of the neonatal HSV test was unknown, but the IV acyclovir therapy was started at the age of 10 days.
[b]Among 16 patients, 4 patients died, and 1 patient was lost to F/U.

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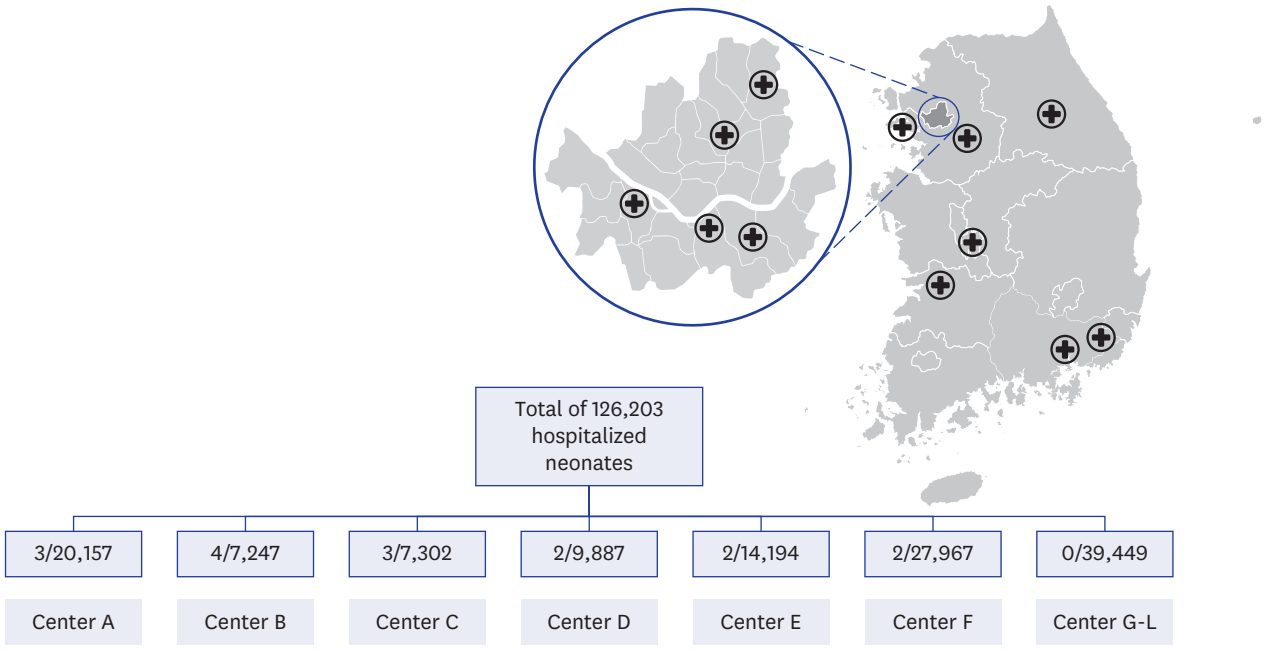


Fig. 1. Incidence of neonatal HSV among hospitalized neonates from 2008 to 2017 in Korea. The cross symbol showed the location of enrolled hospitals.
HSV = herpes simplex virus.

postnatal age at diagnosis of 11 days (range, 4–28 days). Initial symptoms included fever, decreased activity, seizure, skin vesicles. There were no cases in which the diagnosis was made through preemptive testing considering the mother's history of HSV infection.

All patients' ALT levels showed below 40 IU/L at the initial test. Peak ALT level was a median 151 IU/L (range, 18–1,711 IU/L), and 3 patients (75%) developed hepatitis (**Table 2**). Four (25%) patients had DIS disease, 11 (68.8%) patients had CNS disease, and one (6.2%) patient had SEM disease. Ten (63%) patients were positive for HSV-1, and 6 (37%) patients were positive for HSV-2 (**Table 1**). The most common HSV positive specimen was CSF (n=13), followed by blood (n = 3) and SEM (n = 3). Among 11 CNS disease cases, 6 (54.5%) and 5 (45.5%) were positive for HSV-1 and HSV-2, respectively (**Table 2** and **Fig. 2**). Maternal history of genital herpes was not recorded in 10 (62.5%) neonates.

Brain ultrasonography or magnetic resonance imaging was performed in 14 (3 cases of DIS disease, 10 cases of CNS disease, and 1 case of SEM disease) patients, with abnormal findings confirmed in 36% of patients (n = 5/14, 1 case of DIS disease, 4 cases of CNS disease). Abnormal image findings included brain parenchymal swelling, cystic encephalomalacia, brain infarction, vasculopathy of basal ganglia, and increased echogenicity of the white matter. Four patients (25%) developed seizures (1 with DIS disease and 3 with CNS disease), and 2 of them recovered without neurologic complications.

All 16 patients with HSV infection received intravenous (IV) acyclovir, with a median treatment duration of 19 days (range, 3–68 days). Among 14 survivors after 30 days, 4 (4/14, 29%; 4/16, 25%) patients received acyclovir suppressive therapy, with the median treatment duration of 5 months (range, 3–6 months). One patient with DIS disease died after 3 months of oral suppressive treatment. Additionally, 30-day overall mortality was 12.5% (n = 2/16)

Table 2. Clinical characteristics by disease form

Variables	DIS	CNS	SEM
Total (N = 16)	4 (25.0)	11 (68.7)	1 (6.3)
Median age, day	6 (4–13)	14 (4–28)	9
Sex, male ratio	2 (50.0)	6 (54.5)	0 (0.0)
HSV serotype			
HSV-1	3 (75.0)	6 (54.5)	1 (100.0)
HSV-2	1 (25.0)	5 (45.5)	0 (0.0)
Modes of delivery			
Vaginal	2 (50.0)	6 (54.5)	1 (100.0)
C-section	2 (50.0)	5 (45.5)	0 (0.0)
Clinical manifestations			
Skin lesions	3 (75.0)	3 (27.3)	1 (100.0)
Seizure	1 (25.0)	3 (27.3)	0 (0.0)
Hepatitis	3 (75.0)	0 (0.0)	0 (0.0)
Laboratory results			
WBC, /mm^3	10,065 (7,580–13,090)	12,740 (3,200–14,900)	10,700
Hb, g/dL	13.6 (11.2–15.3)	15.5 (11.8–20.8)	18.7
PLT, /mm^3	221,500 (184,000–298,000)	373,000 (166,000–476,000)	411,000
AST, IU/L	1,620 (31–8,656)	44 (23–124)	80
ALT, IU/L	151 (18–1,711)	18 (11–71)	61
30-days overall mortality	2 (50.0)	0 (0.0)	0 (0.0)
Mortality	3 (75.0)	1 (9.0)	0 (0.0)

Values are presented as median (interquartile range) or number (%).
DIS = disseminated, CNS = central nervous system, SEM = skin, eye, and/or mouth, HSV = herpes simplex virus, WBC = white blood cell, Hb = hemoglobin, PLT = platelet, AST = aspartate transaminase, ALT = alanine transaminase.

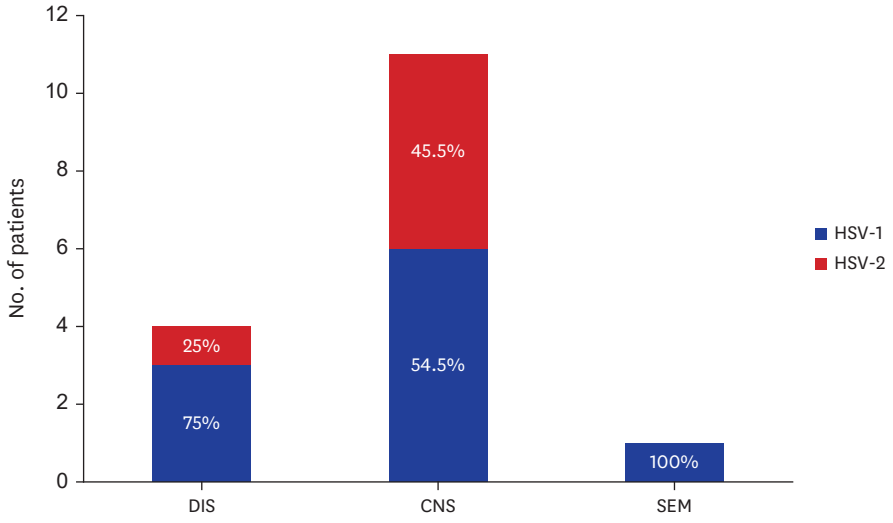


Fig. 2. Viral types by classification of neonatal HSV diseases.
DIS = disseminated, CNS = central nervous system, SEM = skin, eye, and/or mouth, HSV = herpes simplex virus.

(**Table 1**). The lethal cases were diagnosed with DIS disease, and 1 of them had a maternal history of previous genital herpetic lesions. Two patients (DIS and CNS diseases each) died after 30 days from diagnosis at the age of 3 and 5 months, respectively (**Fig. 3**). The cause of death in one patient who died during oral suppressive therapy was pulmonary hypertension. Another patient died after 30 days of infection due to central apnea.

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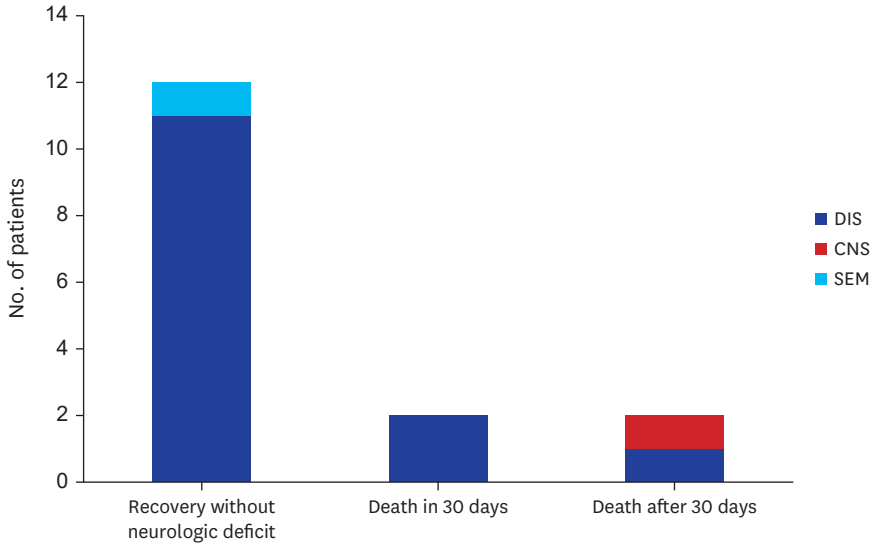


Fig. 3. Outcome of neonatal herpes simplex virus infections in Korea, 2008–2017.
DIS = disseminated, CNS = central nervous system, SEM = skin, eye, and/or mouth.

DISCUSSION

This is the first multicenter study on neonatal HSV infection in Korea. Although we could not measure the incidence of neonatal HSV infection per live birth, the incidence was estimated at 12.7/100,000 hospitalized neonates during the study period from January 2008 to December 2017. CNS disease was the most common, and HSV-1 was a more predominant type. Our study highlights that HSV infection should be considered as a cause in neonates hospitalized sepsis-like illness, including fever and decreased activity as well as blisters and convulsions.

Annual neonatal HSV incidence was reported at 10.3/100,000 live births worldwide and 10.0/100,000 in the Western Pacific region during 2010–2015.[4] In Japan, the estimated incidence rate was 1/28,000 births (3.6/100,000 births) in 2020.[5] In Canada, the incidence of neonatal HSV was 34/100,000 in 2009 and increased to 53/100,000 births in 2015.[6] However, this study only measured HSV infection per hospitalized neonates, not total births. Therefore, this study captured more obvious and severe cases; hence, the true value could have been higher.

Among neonatal HSV infections, SEM disease was reported as the most common clinical manifestation (35–85%).[7] However, CNS disease was the most common (68.8%) in this study, with SEM disease accounting for only 6.2%. Since this study was performed only in neonates admitted to university hospitals, whether the occurrence of SEM disease was truly low in Korean neonates is unclear. SEM disease in this study could have been underestimated.

Neonatal HSV infection is associated with certain HSV type (HSV-1 > HSV-2), type of maternal infection (primary genital lesions > recurrent genital lesions), maternal HSV serostatus, timing of maternal genital herpes infection (close to delivery > prenatal or the first half of pregnancy), mode of delivery (vaginal > Cesarean section), duration of membrane ruptures, and impaired fetal skin barriers.[7] The major HSV virus types in neonatal

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HSV infection differed by region. HSV-1 accounted for more than two-thirds of cases in the US, whereas most cases were HSV-2 in Africa.[2] In this study, 62.5% of patients were positive for HSV-1, and 37.5% of patients were positive for HSV-2. Cesarean delivery is known to reduce the risk of neonatal infection (1.2% cesarean vs. 7.7% of vaginal; odds ratio, 0.14; $P = 0.47$).[8] Neonatal HSV infection can still occur after cesarean delivery. Neonatal HSV infection occurred in 56% of vaginal delivery cases and 44% of cesarean delivery cases.

Infectious Disease Collaborative Antiviral Study Group (ID-CASG) recommended high-dose IV acyclovir (60 mg/kg/day; 14 days for SEM disease and at least 21 days for DIS and CNS diseases). A study showed that oral suppressive acyclovir therapy improved neurodevelopmental outcomes and fewer cutaneous recurrences in neonatal HSV patients.[9] Therefore, oral suppressive acyclovir therapy has been introduced in clinical practice around the world since 2013–2014.[10,11]

Currently, ID-CASG recommends 300 mg/m^2 oral acyclovir suppressive therapy administered 3 times a day for 6 months after IV acyclovir therapy.[1] In our study, the first patient was identified in 2010; hence, he did not receive oral suppressive therapy. However, some patients in this study also started to receive oral suppressive therapy since 2012: 4 patients received acyclovir suppressive therapy in 2012 (n = 1), 2014 (n = 1), and 2015 (n = 2). The median duration of suppression treatment was 5 months (range, 3–6 months).

Attention to neonatal HSV infection, which can be treated with antiviral agents, has been raised with increasing interest in the epidemiology of HSV infection in reproductive women. The genital HSV disease due to the first episode of primary HSV infection is the highest risk of HSV viral shedding from mother to her baby.[12] The rate of HSV transmission from mother to her baby is at the first episode of maternal genital HSV primary infection 57%, the first episode of nonprimary HSV infection (a patient who has seropositive for HSV-2 newly infected HSV-1 during pregnancy) 25%, and recurrent infection 2%.[3,7,13] The American Academy of Pediatrics recommends early diagnostic and therapeutic algorithms for neonates delivered by mothers with active genital herpetic lesions.[3] Oral suppressive therapy at 36 weeks of gestation in women with previous HSV infection reduces asymptomatic viral shedding.[13]

In this study, medical records of maternal genital herpetic lesions were absent in 10 (62.5%) patients. Kim et al.[14] reported that the prevalence of HSV-2 infection in gravida was 17% (85/500) from 2009 to 2010 in Korea. Furthermore, studies on the seroprevalence of HSV-1 and HSV-2 in Korea are scarce. More data on the serostatus of women of childbearing age and their partners are needed in Korea.

This study has some limitations. The study might have included only severe cases since it only included hospitalized neonates from tertiary hospitals. Further studies on the birth prevalence of neonatal HSV disease and disease burden are needed. Birth-related risk factors, such as premature membrane rupture and skin barrier disruption after forceps delivery, were limited in this retrospective study. Assessment and data collection regarding the long-term neurodevelopment of survivors were insufficient.

In conclusion, this is the first multicenter epidemiology study on neonatal HSV infection in Korea. Although uncommon, neonatal HSV infection occurs in Korean babies with a high 30-day mortality rate at 12.5%. Increased awareness about HSV infection in pregnant women and neonates is warranted among Korean pediatricians and obstetricians. A multidisciplinary

approach and risk assessment are critical for the early diagnosis and treatment of neonatal HSV disease in Korea.

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