Autopsy Case Reports

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Fatal Disseminated Herpes Simplex in a very premature neonate

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ABSTRACT

Herpes Simplex Virus infections (HSV) are ubiquitous. The neonatal HSV infection (NHSV) is rare. The incidence is estimated globally at only 10.3 per 100,000 births, but it can cause devastating disease in premature infants. Both HSV-1 and HSV-2 can be the etiologic agents in this type of vertically transmittted NHSV infection. Here we describe the pathological findings from a complete autopsy of a very low birth weight infant who succumbed to the infection despite early institution of antiviral treatment. We urge more awareness of this disease with continued surveillance; every effort should be taken to make an early diagnosis and thus prevent this devastating disease.

Keywords
Pathology; Infant, Newborn; Premature birth; Herpes Simplex; Pregnancy Complications, Infectious; Neonatal Sepsis; Intranuclear Inclusion Bodies; Infant, Low Birth Weight.

CASE REPORT

The deceased was a 6-day-old premature female newborn who was born to an 18-year-old gravida one woman. The mother presented with fever and prolonged premature rupture of membranes (PPROM) for one week prior to admission at 27 weeks. On admission, she received two doses each of betamethasone, ampicillin, and gentamicin. Due to worsening maternal respiratory distress needing mechanical ventilation, failure to progress after induction, PPROM, and suspected chorioamnionitis, she underwent emergency cesarean section delivery. The infant was born at 28 weeks and 1 day gestation, weighing 1140 gm. At birth, the baby needed mechanical ventilation and was started on intravenous ampicillin and gentamicin, which were discontinued when the blood cultures were negative at 48 hours of age.

While in the neonatal intensive care unit, the patient was extubated successfully after one day and placed on noninvasive ventilation. On the fourth day, the baby was less active and had temperature instability with bradycardia, and she was started on vancomycin and cefotaxime. Later the same day, due to multiple episodes of apnea, deteriorating bradycardic spells, desaturation, and hypercarbia, she was re-intubated and placed on synchronized intermittent mandatory ventilation. The antibiotics were changed to cefepime, fluconazole, and acyclovir. After an additional 24 hours (then day 5), with increasing metabolic acidosis and worsening respiratory failure, she was placed on high frequency oscillating ventilation; however, her condition continued to deteriorate. She became hypotensive with poor perfusion despite vasopressors, and blood products. A bedside echocardiogram

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revealed a normal-appearing heart with a patent ductus arteriosus, a left-to-right shunt, pulmonary hypertension, a small pericardial effusion, and moderately decreased left ventricular function, with signs of low cardiac output. The patient was in sepsis with a severe metabolic acidosis and disseminated intravascular coagulation, despite antibiotic, antifungal, and antiviral therapy. After 40 hours since the onset of symptoms (on day 6), the patient went into cardiopulmonary arrest and passed away. Of note, the mucocutaneous culture sampled on the day of symptom onset returned positive for HSV, many days after the patient's death.

Placental Pathology

The placental pathology report described a third-trimester placenta with moderate intervillous fibrosis, but did not show any evidence of chorioamnionitis or funisitis.

Autopsy Findings

A complete autopsy performed within 24 hours revealed a normally developed premature female infant with no dysmorphic features or congenital anomalies.

The weight of the body was 1525 gm (actual birth weight of 1140 gm). Pertinent gross findings included serous fluid in the right pleural cavity (20 ml), left pleural cavity (25 ml), and pericardial sac (3 ml). There was 25 ml of serosanguineous ascites. The cardiovascular system revealed a normal-sized heart without any significant abnormalities, and microscopy revealed unremarkable immature myocardium. The ductus arteriosus and foramen ovale were open. The lungs revealed hemorrhagic right upper and middle lobes.

Sections through the right and left lung showed thickened septa. The lungs were in the saccular stage of development. The airway epithelium had disorganized large cells without cilia, and viral nuclear inclusions were present (Figure 1).

An immunohistochemical stain for HSV-1 and HSV-2 was positive. There were diffuse fibrin plugs in bronchioles throughout the lungs, and diffuse alveolar hemorrhage was present primarily in the right middle lobe.

The stomach contained a small amount of bloody mucus with normal mucosa. The liver weighed 65 gm (reference range: 45.5 gm +/- 15 gm). The parenchyma was red-brown with centrilobular congestion, with hemorrhage around portal areas and under the capsule (Figure 2).

Hepatocyte nuclei showed viral inclusions with chromatin displaced to the nuclear membrane (margination or wine red appearance) (Figure 3A to 3C). Immunohistochemistry for HSV-1 and HSV-2 was positive in hepatocytes. (Figure 3D)

The kidneys had peripelvic hemorrhage, but no evidence of herpetic infection. The spleen showed karyorrhexis and perivascular cell fragments (Figure 4).

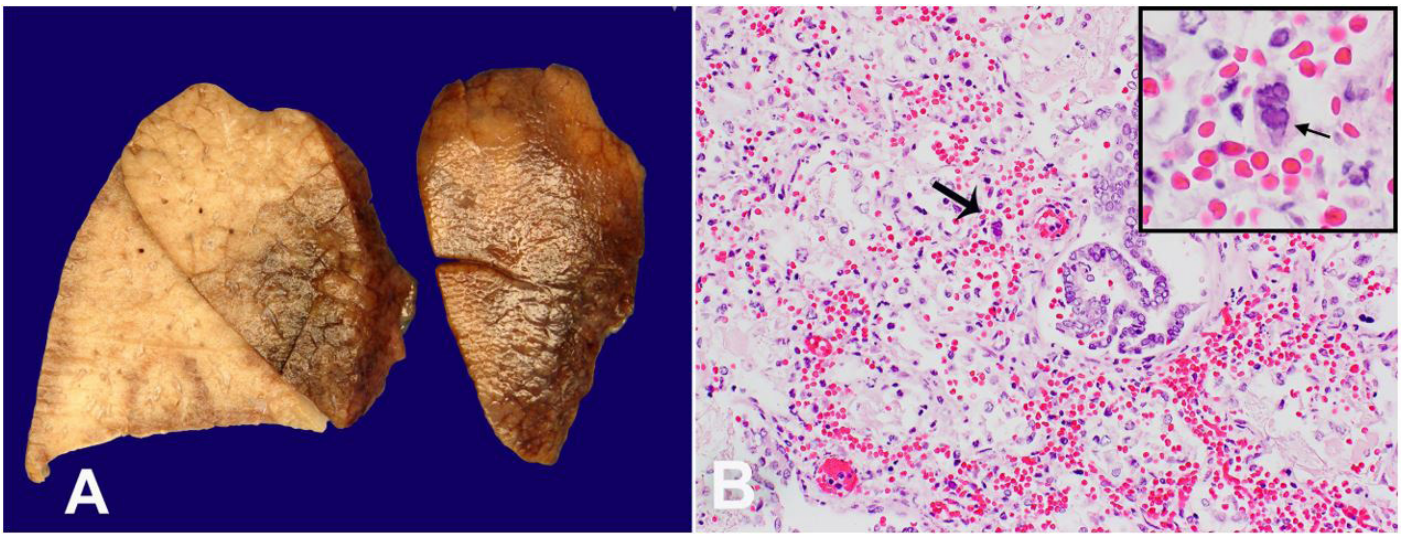

Figure 1. A – Macroscopic view of the lung showing hemorrhagic lobes; **B –** Microphotograph of the lung showing HSV-infected cell in the lung and multinucleated cell (arrow) with margination of chromatin and molding- Viral nuclear inclusion (H&E, 40 X). Inset shows the detail of the multinucleate cell (60X).

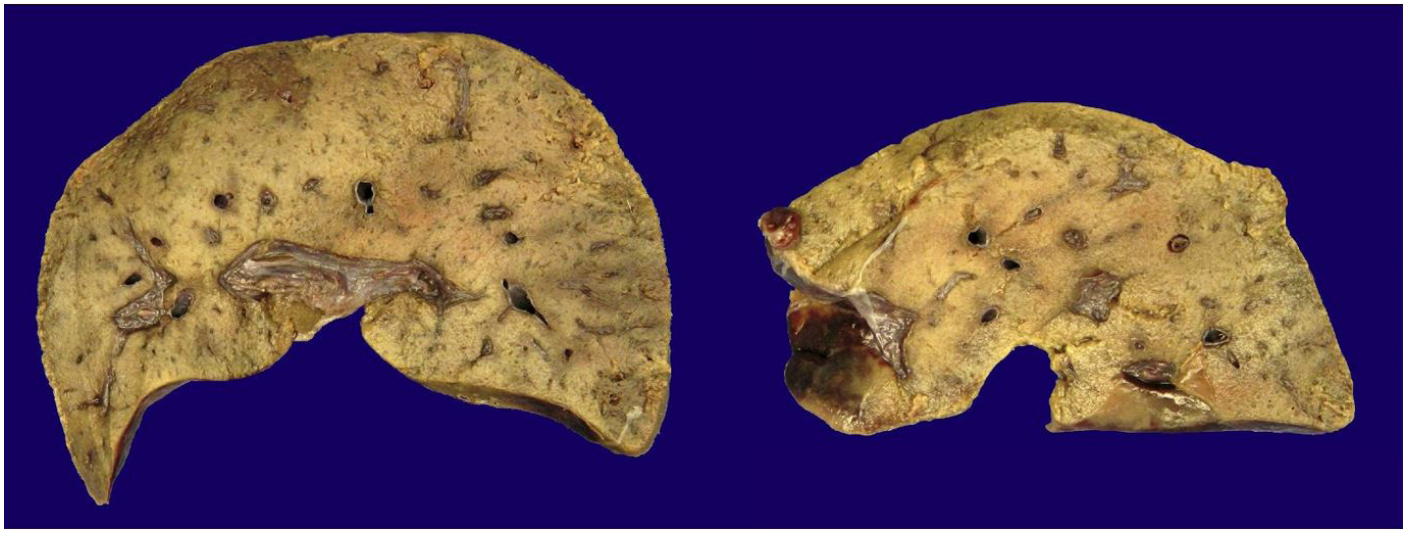

Figure 2. Macroscopic view of the liver- showing hemorrhage in the portal region.

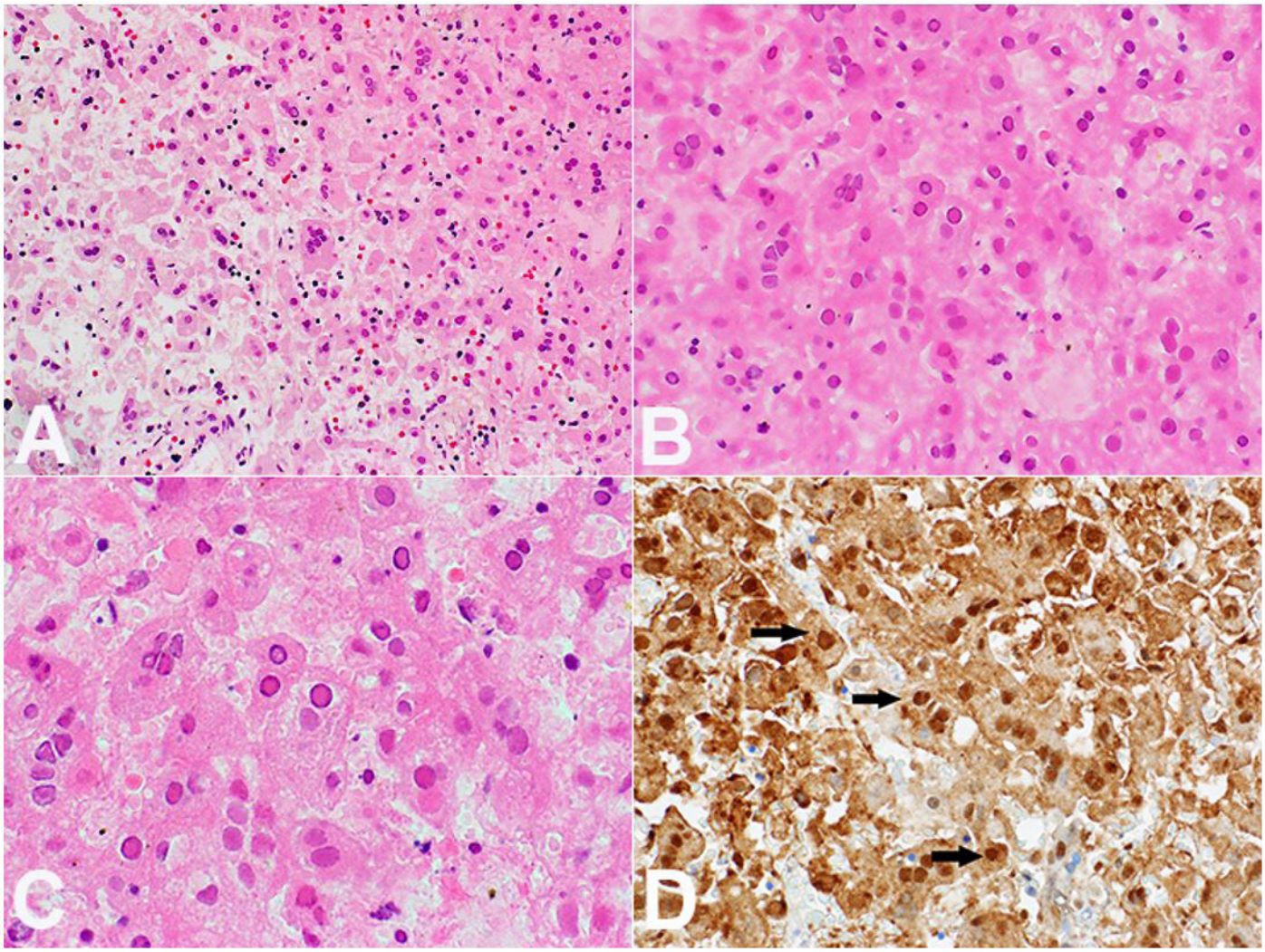

Figure 3. Photomicrograph of the liver showing in **A, B** and **C –** HSV infected hepatocytes showing multinucleation, margination of chromatin and molding and hepatocytes with HSV Nuclear viral inclusions with nuclear chromatin pushed against nuclear envelope and those with clear halo around (Cowdry type A/wine red nuclear inclusions) (H&E, 40X, 40X, 60 X respectively); **D –** Immunostain for HSV1/2 showing nuclear staining (40X) - arrows reflect viral intranuclear stain.

Central nervous system (CNS) examination was unremarkable except for sections through the midbrain and thalamus, which showed microglial nodules (Figure 5).

HSV was isolated from postmortem lung cultures. The final pathologic diagnoses were a premature female infant with resolving hyaline membrane disease of lungs along with disseminated HSV infection of the liver, lung, and brain with microglial nodules in the midbrain and thalamus. In addition, ascites, pleural effusion, persistent ductus arteriosus, involution of thymus, and medullary congestion and pelvic hemorrhage of the kidneys.

DISCUSSION

HSV infections are ubiquitous in the adult population and are caused either by HSV-1 or HSV-2.[1] In contrast, neonatal HSV (NHSV) is rare. NHSV is generally transmitted from pregnant women to their newborn infants, and both HSV-1 and HSV-2 have been implicated. HSV, along with cytomegalovirus, varicella-zoster virus, Epstein-Barr virus, and human herpes virus 6-8 belongs to the human herpes virus family.[2] These are enveloped, double-stranded DNA viruses, and an important characteristic is their ability to remain latent in some tissues and reactivate at a later

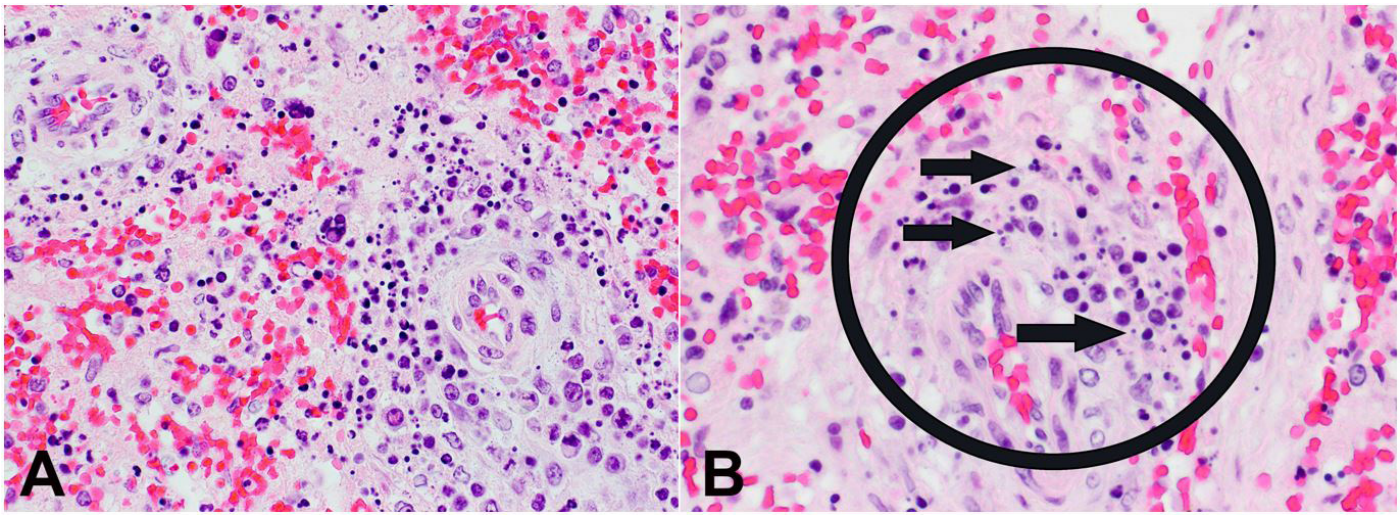

Figure 4. Photomicrograph of spleen showing in **A –** karyorrhexis and perivascular cell fragments (40X H&E); **B –** in detail with arrows.

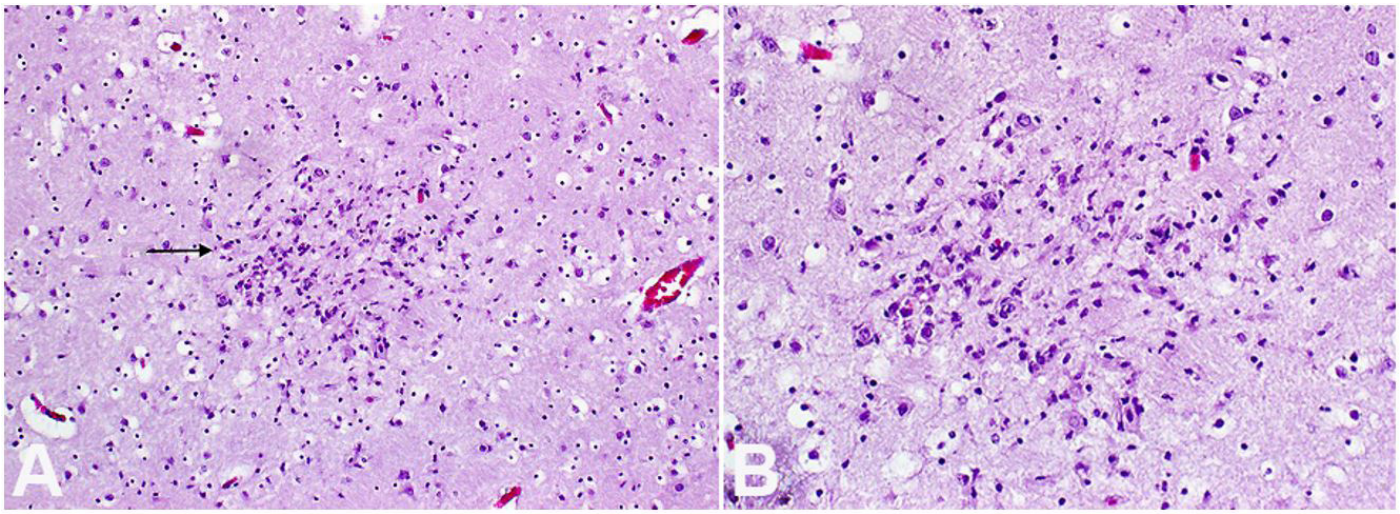

Figure 5. Photomicrograph of the CNS showing in **A –** thalamus with microglial nodule (arrow) (H&E, 10X); **B –** detail of the microglial nodule (H&E, 20X).

date.[2] HSV infects through the mucous membranes or via non-intact skin, the incubation period ranging from 2-12 days, with 4-6 days being the most common time frame. Even with major advances in perinatal care and management, the significant morbidity and mortality caused by invasive disseminated NHSV disease have not decreased.[1]

The annual number of NHSV cases between 2010 and 2015 globally was estimated to be 14,257, of which approximately two-thirds were due to HSV-2, and one-third due to HSV-1.[3] The global rate of NHSV infection when averaged is estimated to be 10·3 per 100,000 births.[3] Neonates acquire the disease primarily from the viral shedding from maternal genital tract around the time of the delivery, but the maternal transmission to the neonate can be either peripartum (85%), postpartum (10%), and rarely in utero (5%).[1] The risk of transmission is also much higher if the mother develops a primary infection, especially late in pregnancy.[1]

In neonates, the presentation can generally be as mucocutaneous lesions (45%), neurologic infection (30%), or as disseminated infection (25%).[1] The mucocutaneous lesions are generally seen in the mouth, the eyes, or as clear vesicles on the skin. Neurological manifestations can mimic meningoencephalitis with temperature instability, apnea, seizures, poor feeding, and irritability. The disseminated disease presentation, where multi-organ involvement is present, can rapidly progress to septicemia and septic shock. Extremely premature infants are at risk of acquiring bacterial, fungal, or viral sepsis due to deficiencies in multiple host factors. The differential for the histologic nuclear inclusions includes several DNA viruses: cytomegalovirus, herpes virus, and adenovirus; however, the morphologic features of the inclusions, combined with a pattern of organ involvement and epidemiological context, fit best with HSV.[2,4-6] The types of nuclear inclusions seen in HSV include one with a clear, unstained "halo" around it (formerly called Cowdry A inclusion/body) and one with a fuzzy purple "ground glass" that fills the nucleus. In both cases, nuclear chromatin is pushed against the nuclear envelope and represents different stages of the viral infection. But HSV often has multinucleate cells, a feature that is rare in adenovirus or cytomegalovirus infection. Immunohistochemical analysis of lung and liver shows extensive positive staining for HSV. The stains for HSV use antibodies that react to antigens present in both serotypes of HSV. The confirmation in this case was also supported by the fact that HSV was cultured from the lung.

Few autopsy reports exist of the disseminated neonatal herpes, and fewer of those described in preterm infants.[7-11] This disease is most commonly seen in a context of primary maternal infection involving the placenta or prolonged rupture of membranes. The clinical history of loss of fluid and fever over the week preceding this patient's presentation and delivery is consistent with this type of maternal transmission. Upon identification of HSV in the infant's lung and liver tissue, the placenta was re-examined, and the microscopic sections were stained. The HSV stain on the placenta was negative and no viral inclusions were seen. Based on these findings, ascending infection associated with prolonged maternal rupture of membranes, although rare, is the most likely cause of transmission. The patient's rapid clinical deterioration despite empirical treatment with acyclovir is indicative of the severity of the infection. The disseminated intravascular coagulation and septic shock are explained by the disseminated viral infection.

The clinical differential diagnosis is that of neonatal sepsis and includes bacterial especially gram-negative bacteria, group B *Streptococcus*, and other gram-positive bacteria such as *Staphylococcus aureus*. In preterm infants, fungal infections such as *Candida albicans* could also cause sepsis, although the clinical course may not be as rapid. In addition, viral infections like disseminated enteroviral infection caused by an echovirus or coxsackievirus, disseminated herpes virus, or cytomegalovirus must remain in the differential diagnosis. The massive hepatic necrosis strongly suggests neonatal herpes virus or echovirus infection.

Prevention of neonatal herpes depends both on preventing the acquisition of genital HSV infection during late pregnancy and avoiding exposure of the neonate to herpetic lesions and viral shedding during delivery. The risk for herpes is highest in newborn infants of women who acquire genital HSV during late pregnancy.

The ideal methods for diagnosis of HSV are by surface cultures and PCR studies on the blood and cerebrospinal fluid. Serological screening during pregnancy was touted as a preventative measure; however, there is a high false-positive rate of the

screening tests, and the potential anxiety related to diagnosis has been serious enough to suggest that the harms outweigh the benefits for population-based screening for genital HSV infection.[12]

Conclusion: NHSV is rare and more instances are occurring in infants of mothers who have never had a history of HSV infection. In extremely preterm infants at risk for exposure, early diagnosis is the key and treatment after onset of the disease is less likely to be successful. Prevention of the disease and vaccine development may hold promise in the future.

REFERENCES

1. James SH, Kimberlin DW. Neonatal herpes simplex virus infection: epidemiology and treatment. Clin Perinatol. 2015;42(1):47-59. http://dx.doi.org/10.1016/j.clp.2014.10.005. PMID: 25677996.
2. Karr T. Herpes virus infections. In: Procop GW, Pritt BS. Pathology of infectious diseases. Philadelphia: Saunders Elsevier, 2015. p. 17-36.
3. Looker KJ, Magaret AS, May MT, et al. First estimates of the global and regional incidence of neonatal herpes infection. Lancet Glob Health. 2017;5(3):e300-9. http://dx.doi.org/10.1016/S2214-109X(16)30362-X. PMid:28153513.
4. Capretti MG, Marsico C, Lazzarotto T, et al. Herpes Simplex Virus 1 infection: misleading findings in an infant with disseminated disease. New Microbiol. 2013;36(3):307-13. PMid:23912873.
5. Nicoll JA, Love S, Burton PA, Berry PJ. Autopsy findings in two cases of neonatal herpes simplex virus infection: detection of virus by immunohistochemistry, in situ hybridization and the polymerase chain reaction. Histopathology. 1994;24(3):257-64. http://dx.doi.org/10.1111/j.1365-2559.1994.tb00518.x. PMid:8200626.
6. Krehbiel K, Singh V. Disseminated neonatal herpes simplex virus infection with Escherichia Coli Coinfection. J Forensic Sci. 2018;63(3):935-8. http://dx.doi.org/10.1111/1556-4029.13590. PMid:28678413.
7. Pichler M, Staffler A, Bonometti N, et al. Premature newborns with fatal intrauterine herpes simplex virus-1 infection: first report of twins and review of the literature. J Eur Acad Dermatol Venereol. 2015;29(6):1216-20. http://dx.doi.org/10.1111/jdv.12583. PMid:24909064.
8. Knox AT, Powell SB, Logan LK. Intrauterine herpes simplex virus infection in a monochorionic twin gestation. J Pediatric Infect Dis Soc. 2012;1(2):157-9. http://dx.doi.org/10.1093/jpids/pis040. PMid:26619169.
9. Dye DW, Simmons GT. Fatal herpes virus type I infection in a newborn. Am J Forensic Med Pathol. 2010;31(1):89-91. http://dx.doi.org/10.1097/PAF.0b013e3181c2bae2. PMid:19949315.
10. Wu JH, Parsons S. Fatal disseminated neonatal herpes simplex virus type 1 infection in neonates in a forensic setting. Forensic Sci Med Pathol. 2017;13(1):99-101. http://dx.doi.org/10.1007/s12024-016-9834-5. PMid:28101751.
11. Catlin EA, Warren HS, Shailam R, Lahoud-Rahme M, Lew M. Case records of the Massachusetts General Hospital. Case 19-2012. A premature newborn boy with respiratory distress. N Engl J Med. 2012;366(25):2409-19. http://dx.doi.org/10.1056/NEJMcpc1109276. PMid:22716980.
12. Bibbins-Domingo K, Grossman DC, Curry SJ, et al. Serologic screening for genital herpes infection: US preventive services task force recommendation statement. JAMA. 2016;316(23):2525-30. http://dx.doi.org/10.1001/jama.2016.16776. PMid:27997659.

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The authors retain a parental consent and the retrospective case study was approved by the institutional research and ethics review board.

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