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Briefly Legal: Delay in Diagnosis of Neonatal Herpes Simplex Virus Infection in a NICU

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"A 26-year-old G5P1 Ab3 presented at 35 weeks gestation with rupture of membranes and contractions. Her childhood was spent in foster care, where she was sexually abused. Her medical history included bipolar disorder, hepatitis C, and chlamydia. She had Group B streptococcal urinary tract infections during this pregnancy, and her recto/cervical culture was positive for GBS. She denied having had genital herpes."

A 26-year-old G5P1 Ab3 presented at 35 weeks gestation with rupture of membranes and contractions. Her childhood was spent in foster care, where she was sexually abused. Her medical history included bipolar disorder, hepatitis C, and chlamydia. She had Group B streptococcal urinary tract infections during this pregnancy, and her recto/cervical culture was positive for GBS. She denied having had genital herpes. Her labor was quite prolonged, during which time she received multiple doses of penicillin prophylactically for her positive GBS status. She eventually reached full dilatation three hours prior to birth. With the onset of pushing, the fetus showed increasingly severe variable decelerations in response to which an amnioinfusion was performed using the previously inserted intrauterine pressure catheter (IUPC). After 43 hours of rupture of membranes and labor, a 2451g male infant was born by a normal spontaneous vaginal delivery. The Apgar scores were 8^{1} and 9^{5}. The baby was admitted to the Newborn Intensive Care Unit (NICU) because of prematurity. After the initial assessment, he was placed in an open crib wrapped in a blanket under a radiant warmer. His physical examination was unremarkable and consistent with a late preterm infant. He was breastfed and noted to have a strong suck. A peripheral intravenous line was placed to supplement fluid. A complete blood count was sent and found to be normal; a blood culture was drawn and ultimately reported as negative.

Three days after birth, the baby required gavage feeding because of an increasing lack of interest in oral intake. Additionally, he was hypothermic and required extra blankets to maintain his temperature. ***On deposition, the nurses did not acknowledge that the temperature and feeding issues documented in the records could be secondary to illness but emphasized that premature babies often have problems with feeding and temperature regulation. The plaintiff neonatologist pointed out that the baby would be expected to be better at feeding and needing less support to maintain temperature with time.*** *B*ased on his progress notes, the treating neonatologist was unaware of these issues. By DOL 7, he began having periodic breathing and desaturations and was placed on a nasal cannula.

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In depositions, both nursing and physicians again attributed this symptomatology to late prematurity. The baby also developed intermittent tachycardia and watery green stools. A complete blood count (CBC) and C-reactive protein (CRP) were unremarkable, and blood and urine cultures were sent and ultimately read as negative. A lumber puncture (LP) was not done. ***The plaintiff's neonatologist was critical of their failure to perform an LP.***

By DOL 11, he developed lethargy, hypotonia, intermittent apnea with bradycardia, and deteriorating temperature instability. An LP was still not performed. Ampicillin and gentamicin were started but discontinued after 48 hours when the blood cultures were again negative. The cranial ultrasound was unremarkable. A neurologist was consulted at 2 weeks to rule out neurological etiologies of hypotonia. The consulting neurologist noted altered mental status and was concerned about inborn error of metabolism and recommended serum and urine assessments as well as CSF tests to rule out metabolic diseases.-The note pointed out that since t holiday was upcoming the following day, there was no urgency in performing the laboratory evaluation until after the holiday. Two days after the neurology consult, blood, urine, and CSF were sent to rule out various inborn errors of metabolism. A lumbar puncture was done; the CSF was sent for amino acids, lactate, and glucose. The CSF findings: glucose 29 mg/dL, protein 137mg/dL, 2 red blood cells and 1110 white blood cells.

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In her note, the **neurologist** wrote that the low glucose was concerning for GLUT-1 deficiency, a rare disorder that causes decreased transport of glucose across the blood-brain barrier caused by an abnormality in SLC2A1. Later that day, the ***neonatologist*** was apprised of the CSF findings and immediately ordered ampicillin, cefotaxime, acyclovir, and PCR for HSV on blood and CSF. The PCR on the blood and CSF was positive. An MRI performed the following day showed multiple small foci of ischemic changes. The baby remained in the NICU for six weeks. During his hospitalization, the mother's cervix was culture-positive for HSV. On follow-up, the baby had developmental delay and recurrent seizures. The neonatologist and the hospital were sued and settled without going to court.

Allegations:

1. The neonatologist should have properly and timely evaluated the baby's symptomatology beginning DOL 3 and worsened with each passing day.
2. The evaluation should have included a lumbar puncture and HSV PCR, surface cultures, and PCR for herpes
3. It was below a reasonable standard of care to attribute the signs and symptoms to prematurity without a thorough evaluation of other potentially harmful causes. This illustrated the dysfunctional hospital culture that resulted in an adverse outcome
4. The evaluation should have included a lumbar puncture and HSV PCR, surface cultures, and PCR for herpes
5. The dysfunctional hospital culture resulted in an adverse outcome

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Discussion:

Neonatal herpes is usually the result of HSV-2 infection, which is the primary type of HSV associated with genital infection and be transmitted from mother to Infant via three different routes:

Intrapartum:

In the majority of cases (88% to 93%), HSV infection in the newborn is acquired during the intrapartum period as the fetus passes through the birth canal or through ascending infection after rupture of the membranes; typically, the virus is acquired by direct contact of the Infant's skin, eye, or oral cavity with the virus in the mother's birth canal. Because of the importance of direct contact, it is understandable that when the newborn does have vesicular lesions, they are usually over the scalp and face in cephalic presentations and over the buttocks in breech presentations. Overt maternal herpetic lesions are uncommonly present. The chance of a woman who has a history of genital herpes shedding virus at the time of delivery is approximately 1%. However, in most cases of neonatal infection, mothers do not give a history of active genital herpes at the time of delivery. Infants born to mothers who have primary first-episode genital herpes infections at the time of delivery, however, have a 50% risk of developing infection compared with a 25% risk when mothers with an active lesion have antibodies to HSV-1 only (nonprimary first episode) and less than 2% in cases of recurrent infections in seropositive mothers.

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In the United States, the prevalence of neonatal herpes is 0.05 to 0.3 per 1,000 live births, with 1,500 cases occurring yearly. The risk of transmission to the newborn is more than 10-fold greater when the mother is shedding HSV-1 versus HSV-2 at delivery. The five most important factors known to affect the transmission of HSV from mother to neonate are the type of maternal infection (primary vs. recurrent), maternal antibody status, duration of rupture of membranes, the integrity of mucocutaneous barriers (use of scalp electrodes, for instance), and mode of delivery (cesarean vs. vaginal). It is estimated that about one-third of women who asymptomatically shed HSV during labor have been recently infected and that their infants have a 10-fold or more significant risk of being infected than the infants of mothers with recurrent disease.

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Because recurrent infections are so much more common, half of all neonatal HSV-2 infections occur secondary to a recurrent maternal infection, even though transmission from mother to Infant occurs in only 2% of the cases. The higher the amount of neutralizing antibody the mother has at the time of delivery, the less likely the Infant will develop disseminated disease. Prolonged rupture of membranes (>4-6 hours) also increases the risk of viral transmission, presumably from ascending infection. Delivery via cesarean section, preferably before rupturing membranes, but at least before 4-6 hours of rupture, reduces the risk sevenfold. Vacuum extraction increases the risk of HSV infection sevenfold compared to spontaneous vaginal or cesarean delivery. Antenatal

maternal viral culture screening for HSV shedding is not of predictive value in determining who will be shedding the virus at delivery.

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Transplacental:

In 2-5% of cases of neonatal HSV infection is acquired transplacentally with the acquisition of the infection during early gestation with prematurity being uniformly present. Clinically the infants may present with growth restriction, characteristic skin lesions with vesicles and scarring, neurologic damage (intracranial calcifications, microcephaly, hypertonicity, and seizures), and eye involvement (microphthalmia, cataracts, chorioretinitis, blindness, and retinal dysplasia)

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Postpartum:

Individuals with HSV having contact with the baby may transmit the infection, accounting for 5%-10% of OSV neonatal infections. Restriction enzyme DNA analysis has been used to document the postnatal acquisition of HSV and its spread within a nursery by identifying infection with the same herpes strain in infants of different mothers. Symptomatic and asymptomatic shedding among hospital personnel is a concern. Orolabial lesions should be covered with a mask, and skin lesions should be covered with clothing or a bandage. Counseling on good hand hygiene is important.

Presentation of HSV:

Neonatal HSV infection acquired during the intrapartum route typically presents within 1-3 weeks after birth and can be classified into 1 of 3 categories: disseminated disease; CNS infection; or skin, eyes, and mouth (SEM) infection. The disseminated disease involves multiple organs, including, but not limited to, the lung, liver, adrenal glands, brain, and skin. CNS disease involves the brain, with or without skin involvement, but no visceral organ dysfunction. SEM disease is limited only to these areas of the body. Disseminated disease has the most significant mortality, and CNS disease has the most significant morbidity. The localized disease presents as vesicles on the skin, eyes, or mouth. If left untreated, 70% of cases progress to disseminated disease. Nonspecific presentation with the disseminated disease includes poor feeding, temperature instability, lethargy, apnea, respiratory distress, seizures, jaundice, and disseminated intravascular coagulopathy. There are no skin lesions in 40% with disseminated disease and 30% with CNS disease.

Cruz reported in 2021 8 independent predictors of invasive HSV infection on babies who presented to the Emergency Department: age, prematurity, seizure before hospital arrival, ill appearance, abnormal triage temperature, vesicular rash, thrombocytopenia, and CSF pleocytosis. When combined into an invasive HSV risk score, these variables accurately identified infants at extremely low risk for invasive HSV infection and for whom routine HSV testing and treatment can be safely avoided.

The central nervous system (CNS) and its covering membranes may become involved in various infectious processes, devastatingly affecting structure and function. HSV is distinctive among the diseases caused by organisms of the TORCH complex because the infection is acquired during the intrapartum period, and the babies become symptomatic during the neonatal period. **TORCH** is an acronym representing infections caused by **T**oxoplasma gondii, **O**ther agents, **R**ubella, **C**ytomegalovirus (CMV), and **H**erpes simplex virus (HSV). HSV infection is distinctive among the disease caused by organisms of the TORCH complex presenting with symptomatic disease.TORCHS has been expanded to be more inclusive **SCRATCHEZ,** where s stands for **S**yphilis, C for **C**MV, R for **r**ubella, A for **A**cquired immunodeficiency syndrome (AIDS or HIV infection, **T** for toxoplasmosis, **C** for chickenpox or varicella, **H** for herpes, ES for **E**nterovirus infections, and **Z** for Zika virus.

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Diagnosis:

Isolation of virus is definitive diagnostically. Swabs of mouth, nasopharynx, conjunctivae, and rectum should be tested for HSV surface cultures and/or polymerase chain reaction (PCR), but should be delayed to 24-48 hours after birth to differentiate viral replication in the newborn from transient colonization of the newborn at birth. Specimens of skin vesicles should be tested for culture or PCR. Cerebrospinal fluid (CSF) specimens should be tested for HSV PCR. An early sampling of CSF may not detect HSV; therefore, repeating an LP should be considered when the diagnosis is suspected but not confirmed on an earlier sample. The CSF in HSV cases exhibits findings of meningoencephalitis (i.e., pleocytosis and elevated protein content). In the past,

the presence of red blood cells in CSF was suggestive of HSV CNS infection, likely due to relatively advanced disease due to diagnostic limitations. However, with the development of more advanced imaging and diagnostic capabilities, hemorrhagic HSV encephalitis is less commonly seen now, and as such, most HSV CNS do not have red blood cells. Whole blood samples should be tested for HSV PCR. Alanine aminotransferase should be measured as an indicator of hepatic involvement. Serologic testing is not helpful in neonatal disease because transplacentally transferred maternal antibody confounds the interpretation. PCR testing has become invaluable, especially for CSF, which has a very low recovery rate for HSV cultures.

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Therapy:

Acyclovir is the only drug recommended for use in neonates with neonatal HSV disease. The recommended dose is 60 mg/kg/day in three divided doses for 21 days for disseminated or CNS disease and 14 days for disease localized to the skin, eyes, or mouth. Infants with an abnormal creatinine clearance need to have the acyclovir dose adjusted, and all infants need to be monitored for neutropenia. All neonates should have ophthalmologic and MRI examinations. CT and ultrasonography may be used alternatively but are not as sensitive to abnormalities. Infants with CNS disease need to have a repeat lumbar puncture at the end of treatment. Treatment should be continued until the CSF's PCR is negative. Infants who continue to have detectable HSV DNA in CSF by PCR at the end of therapy are more likely to die or have moderate to severe impairment. Oral acyclovir suppressive therapy for six months after parenteral treatment is recommended.

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Prevention:

In 1999, the American College of Obstetrics and Gynecology recommended that cesarean delivery be performed if a mother has HSV genital lesions or prodromal symptoms at the time of delivery. Seventy percent of mothers of infants with the neonatal disease do not have a history or symptoms of HSV infection; however, their partners do not have a history of HSV infection, and neonatal infection may still occur even if a cesarean delivery is performed. Repetitive cervical cultures do not predict whether a mother will be shedding virus at delivery. Mothers should be counseled regarding the signs and symptoms of disease, and some may then recognize the infection. If rupture of membranes has been present longer than 6 hours, some experts still recommend cesarean delivery in the face of genital lesions, but data are lacking, and controversy exists. Scalp electrodes should be avoided. There is also no consensus about treatment when a mother has genital lesions and ruptured membranes, except in the case of a very immature fetus. If an infant is delivered vaginally to a mother with recurrent genital lesions (5% risk of infection), most experts do not recommend treating the Infant. The Infant does not need contact precautions. Cultures and PCR of the neonate should be obtained at 24 hours of life, and the Infant should be observed. Circumcision should be delayed until cultures are known to be negative. Hand washing should be emphasized. The Infant should be managed with contact precautions. If the mother has an active labialis or stomatitis, she should wear a disposable surgical mask while handling her Infant until the lesions have crusted and dried. She should not kiss the Infant. Breastfeeding may be allowed if there are no lesions on the breast. The mother needs to be taught the signs and symptoms of the neonatal disease because culture does not always detect neonatal disease.

"The initial presentation of HSV disease is indistinguishable from other causes of neonatal sepsis, meningitis, or encephalitis. Delays in treatment for HSV can be devastating. Therefore, HSV should be considered in the differential diagnosis of sick neonates. While in a NICU, babies' vital signs should be monitored closely for clinical changes. Any time temperature instability or the development of poor feeding appears for a previously stable baby requires a workup that includes testing for HSV."

Conclusion:

The initial presentation of HSV disease is indistinguishable from other causes of neonatal sepsis, meningitis, or encephalitis. Delays in treatment for HSV can be devastating. Therefore, HSV should be considered in the differential diagnosis of sick neonates. While in a NICU, babies' vital signs should be monitored closely for clinical changes. Any time temperature instability or the development of poor feeding appears for a previously stable baby requires a workup that includes testing for HSV. The case presented above was unique because he was still hospitalized, not arriving in the Emergency Room with a vague history. Nevertheless, despite the

multitude of signals with temperature instability, poor feeding, and the development of lethargy and hypotonia despite initially having been a vigorous baby, the signals were ignored. Because most mothers with HSV do not have active genital HSV lesions at the time of birth, a high vigilance is necessary to screen ill infants for HSV infection.

Suggested Reading:

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