

## BRIEF REPORT

# Neonatal Herpes Infection: Case Report and Discussion

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**Neonatal herpes simplex virus (HSV) infections are often life-threatening. Although sometimes difficult to diagnose, most infections can be treatable when found early. Infection with HSV should be kept high on the differential diagnosis of a febrile newborn younger than 1 month old, and treatment should be strongly considered for infants with certain risk factors, even before definitive culture or polymerase chain reaction results are available. The case presented here exemplifies the benefits of maintaining a high suspicion of and empirically treating for HSV in a 10-day-old febrile infant. (J Am Board Fam Med 2011;24:758–762.)**

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A 10-day-old boy was brought to his primary care doctor's office by his mother, who had been concerned that he felt warm and discovered an axillary temperature of 101.2°F a few hours earlier. The mother reported no cough, no runny nose, and no vomiting or diarrhea. The baby was alert and had been bottle-feeding as expected since his discharge from the hospital after birth. The patient was not given any medications for his fever before arrival.

His medical history reveals that he weighed 3540 g at birth, and he was born via spontaneous vaginal delivery to a 20-year-old woman, for whom this was her first pregnancy, at 39 5/7 weeks. The mother's prenatal course was significant for chlamydia infection discovered early in the pregnancy and treated with azithromycin. A test of cure to ensure adequate treatment was completed and was negative. She was intermittently taking sertraline

during her pregnancy to treat her depression. Her blood type was A+ with a negative antibody screen, and her vaginal/rectal group B streptococcal screen was positive. The mother denied any significant febrile illnesses during her pregnancy and denied having any history of or known exposure to herpes. To her knowledge, she had never had a vaginal vesicular lesion.

She presented in active labor. She received an epidural at 4 centimeters and Pitocin augmentation at 6 centimeters when her labor stalled. Her membranes ruptured spontaneously, and they were ruptured for 12 hours before delivery. At 1.5 hours before delivery, she had a temperature of 100.8°F and was started on ampicillin, gentamicin, and clindamycin for presumed chorioamnionitis. She also received a total of four doses of penicillin to prevent transmission of group B streptococcus to the neonate.

The fetal heart tracing was reassuring throughout the labor. The patient delivered vaginally over an intact perineum. The neonate was brought skin-to-skin after a spontaneous cry, and he received no resuscitation. Apgar scores were 8 and 8 (−1 color, −1 tone). The initial newborn examination was significant for a temperature of 100.8°F, retractions, and tachypnea, with an oxygen saturation of 97%.

Initial laboratory data of the neonate revealed a white blood cell (WBC) count of 34.6 (normal

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range, 5.0–20.0 cells/ $\mu$ L) with 73% neutrophils (normal range, 25.0–45.0%), 1+ toxic granules, and occasional bands. His blood glucose level was normal. He was started on ampicillin and gentamicin, which were discontinued after blood cultures were negative for 48 hours. Circumcision was done without complication and the patient was discharged from the hospital.

His mother reports an uncomplicated postnatal course, but he did miss the first two scheduled appointments with his primary care doctor. He presented to care on his 10th day of life with the above-mentioned fever. His examination at that point was notable for a rectal temperature of 101°F. A detailed examination, including a neurologic examination, was otherwise unremarkable.

He was admitted to the hospital for a work-up of his febrile illness. Laboratory data at admission included a WBC count of 17.2 (normal range, 5.0–20.0 cells/ $\mu$ L) with a differential of 63.1% lymphocytes, 24.8% neutrophils, occasional bands, and occasional atypical lymphocytes. Hemoglobin, platelets, electrolytes, blood urea nitrogen, and creatinine levels and a urinalysis were within normal limits. Urine and blood cultures were sent. A lumbar puncture was done, and all tubes were bloody in appearance. Tube 4 had 116,000 red blood cells (normal range, <1000 cells/ $\mu$ L) and 114 WBCs (normal range, 0–5 cells/ $\mu$ L) for a ratio of 1000:1 (normal, 500:1). The differential showed 30% neutrophils, 2% stabs, 62% lymphocytes, and 6% monocytes. Protein was 120 mg/dL (normal range, 15–45 mg/dL) and glucose was 52 mg/dL (normal range, 40–70 mg/dL). A gram stain showed scant polymorphonuclear leukocytes and no bacteria. Cerebrospinal fluid (CSF) culture, herpes simplex virus (HSV) 1 and 2 polymerase chain reaction (PCR), and enterovirus PCR were ordered. Because of concern about HSV, liver function tests (LFTs) were ordered and revealed marked transaminitis (aspartate transaminase, 2879 U/L [normal range, 15–35 U/L]; alanine transaminase, 1108 U/L [normal range, 13–45 U/L]). Bilirubin was slightly elevated at 1.6 mg/dL (normal range, 0.3–1.2 mg/dL). The patient's acetaminophen level was less than 10  $\mu$ g/dL (normal range, <30  $\mu$ g/dL), and a hepatitis panel was negative. Coagulation studies were drawn, but were unable to be analyzed because of laboratory error.

The patient was started on ampicillin, gentamicin, and acyclovir. He was watched closely overnight for signs of bleeding or neurologic impair-

ment. Because of his transaminitis, he was transferred to the pediatric gastroenterology service the next morning. His urine culture was negative, and his blood culture grew a presumed contaminant, *Streptococcus salivarius*. The CSF PCR subsequently was positive for HSV2.

Overall, the patient remained clinically stable. Acyclovir was continued, and his LFTs trended down. A magnetic resonance image of his head was normal. A repeat lumbar puncture on hospital day 20 remained positive for HSV2, so he continued on acyclovir. A third lumbar puncture on hospital day 27 was negative for HSV, so acyclovir was discontinued at that point. After his treatment course was completed, he was discharged from the hospital. Although at this point he has been lost to follow-up, there were no developmental or neurologic concerns noted at his 1-year well-child check-up.

## Discussion

Fever (defined as temperature higher than 100.4°F) with an unidentifiable source is a common problem encountered in pediatric primary care. Myriad algorithms exist to aid the clinician in diagnostic and treatment options when a child presents with fever. The primary aim of these algorithms is to determine which children are at risk for serious bacterial infection. Most algorithms suggest that a newborn younger than 29 days of age should be admitted to the hospital for workup and observation. Suggested workup includes a complete blood count with differential, a urinalysis with culture, blood cultures, CSF analysis and cultures, intravenous antibiotics (usually ampicillin and gentamicin), and observation for 48 hours or until a source of fever is found.<sup>1</sup>

The prevalence of HSV infection in hospitalized 0- to 28-day-old infants is thought to be about 0.2%, not statistically different from that of bacterial meningitis at 0.4%. HSV infection is thought to account for illness in 0.3% to 0.9% of febrile neonates.<sup>2,3</sup> An estimated 25% of US women are seropositive for HSV2 (positive immunoglobulin G), and though the number is similar for pregnant women, only 5% of pregnant women report a history of symptomatic infection.<sup>4</sup> Two percent to 3% of women seroconvert during pregnancy. During a primary HSV outbreak, there is a 33% risk of vertical transmission from mother to newborn; this number drops to 3% during a secondary reactivation. Perinatal transmission of HSV occurs in three

ways: antenatal (5%), intrapartum (85%), and postnatal (10%, primarily HSV1). HSV2 accounts for 50% to 70% of neonatal HSV infection, mainly antenatal and intrapartum infections, although 75% of neonatal HSV1 infections are transmitted not postnatally but from recently acquired maternal genital infections.<sup>4–6</sup>

Given that the majority of women with HSV seropositivity do not report a history of symptoms consistent with HSV, that antenatally acquired infections are likely to result in a spectrum of findings such as microcephaly and hydrocephalus, and that postnatal infections are most likely to be HSV1, our patient was probably infected with HSV2 during the intrapartum period.

Neonatal HSV infection manifests in three forms, which are not always discrete. Approximately 45% of cases have mucocutaneous infection, which presents with only skin, eye, or mucosal findings—lesions begin as erythematous macules, which develop into vesiculopustules, crusts, or erosions. There is no evidence of systemic or central nervous system involvement: CSF, chest radiograph, and LFTs are normal, and mortality is highly unlikely. There is minimal morbidity, as well (only 5% may develop neurologic abnormalities).<sup>6</sup>

Central nervous system HSV, which accounts for approximately 30% of cases, may present with lethargy, poor feeding, irritability, or seizures, though neonates may appear to have completely normal behavior. Diagnosis is made by abnormal brain magnetic resonance imaging or abnormal CSF findings such as pleocytosis (defined as CSF WBC count  $>25$  cells/ $\mu$ L in infants younger than 28 days old and  $>10$  cells/ $\mu$ L in patients aged 29–90 days; the CSF WBC count should be corrected for the number of red blood cells using a ratio of 500:1)<sup>7</sup> in conjunction with positive surface cultures and/or a finding of HSV DNA in the CSF. Sixty-eight percent of these patients also have skin involvement. Even with treatment, there is a 4% to 14% mortality rate and the majority of survivors will have long-term neurologic sequelae.<sup>6,8</sup>

Disseminated HSV is responsible for 25% of cases. Disseminated disease often starts with systemic symptoms that may progress rapidly to jaundice, hypotension, disseminated intravascular coagulation (DIC), and shock. The lung, liver, and adrenal glands are the most commonly affected sites outside of the CNS. Disseminated HSV car-

ries a 20% to 60% mortality rate, usually related to coagulopathy (secondary to hepatic failure) or pulmonary involvement. Fifteen percent to 25% of survivors will have neurologic sequelae.<sup>8,9</sup> Fortunately for our patient, despite his disseminated disease, his clinical course remained relatively benign; at one point, the team questioned whether the initial PCR result could have been a false positive. As noted above, he has not developed known neurologic problems.

Despite these numbers and potentially poor outcomes, it is not routinely recommended to treat neonates with fever empirically for HSV; it is instead recommended that evaluation for HSV is considered when risk factors for or symptoms of HSV are present.<sup>1</sup> The most important risk factor is maternal infection at time of delivery, though this is often unknown. Other risk factors that increase the risk of intrapartum transmission if the mother is infected include the use of fetal scalp electrodes; vaginal delivery; prolonged rupture of membranes; CSF pleocytosis; and skin, eye, or mouth lesions.<sup>1</sup> HSV infection should also be considered in any infant who presents during the first month of life with lethargy, poor feeding, irritability, or seizures.<sup>2,4</sup> Some sources recommend that if a neonate is not improving while taking antibiotics, treatment for HSV should be considered (Table 1).<sup>1</sup> In our case, the patient was treated empirically with acyclovir because of his elevated LFTs, CSF pleocytosis, and age.

In terms of diagnosis of HSV, the sensitivity of PCR is only 70% early in the disease process.<sup>10</sup> Some sources recommend that serial evaluations of the CSF should be done during the first week of illness if it is thought that HSV encephalitis is likely and initial PCR was negative.<sup>11</sup> Skin lesions or conjunctival cultures consistently provide the greatest yields, with  $>90\%$  of cultures positive within 4 days in an affected infant).<sup>11</sup> Once diagnosed, HSV is treated with intravenous acyclovir (60 mg/kg/d divided three times daily for 21 days in patients with CNS or disseminated disease, 14 days if only mucocutaneous infection).<sup>9</sup> A repeat lumbar puncture should be completed at the end of antibiotic therapy to ensure that HSV PCR is negative. Because our patient's PCR remained positive, acyclovir was continued another week until it was negative. Some centers repeat lumbar punctures after treatment in the case of any fever, neurologic impairment, or skin lesion because recurrence of CNS disease is quite common. Studies of the effects of long-term suppressive therapy are ongo-

**Table 1. Risk Factors That Increase the Likelihood of Neonatal Herpes Simplex Virus Infection**

	Risk Factors
If maternal infection is present at time of delivery	<ul style="list-style-type: none"> <li>• Use of fetal scalp electrode</li> <li>• Prolonged rupture of membranes (longer than 6 hours)</li> <li>• Vaginal delivery</li> <li>• Presence of cervical lesions</li> <li>• Primary infection with HSV</li> </ul>
In a neonate undergoing evaluation and/or treatment	<ul style="list-style-type: none"> <li>• Presence of CSF pleocytosis</li> <li>• Skin, eye, or mouth lesions</li> <li>• Symptoms of lethargy, seizure, poor feeding, or irritability during the first month of life</li> <li>• Has been receiving antibiotics for fever without clinical improvement</li> </ul>

HSV, herpes simplex virus; CSF, cerebrospinal fluid.

ing; some centers consider oral acyclovir after intravenous treatment is completed.<sup>11</sup>

Acyclovir has been shown to improve mortality; Corey and Wald<sup>6</sup> report a reduction from 85% to 31% in patients with disseminated disease and from 50% to 6% in patients with CNS disease. However, acyclovir therapy has had less impact on morbidity, which includes mental retardation, blindness, seizures, spasticity, and paralysis. Of untreated patients with disseminated disease, for example, it is very rare to find normal neurologic status at 1 year of age. This number decreases to 83% in patients with disseminated disease who have been treated.<sup>6</sup> Risk factors for significant morbidity include aspartate transaminase >10 times normal, disseminated disease, DIC, encephalitis, pneumonia, HSV2, lethargy, coma, persistent positive PCR after acyclovir, prematurity, and seizures.<sup>9</sup> Some studies do show that early institution of acyclovir is extremely beneficial to the outcome of HSV disease and that, as the interval between the onset of symptoms and the initiation of therapy is shortened, morbidity is lessened.<sup>8,9</sup> This may explain the positive outcome seen in our patient despite his risk factors for significant morbidity.

The most common adverse event associated with acyclovir is transient neutropenia. The absolute neutrophil count should be monitored twice weekly while receiving therapy, and if it remains <500 for a prolonged period, the acyclovir dose can be decreased or granulocyte colony-stimulating factor can be administered.<sup>12</sup> Nephrotoxicity is the other concern; in one study, incidence was 6%, but all patients with nephrotoxicity had disseminated infection, which alone could explain elevated creatinine.<sup>12</sup>

Prenatal prevention of HSV may include screening and education (Table 2). It has been shown that routine serologic screening of asymptomatic women does not reduce transmission to newborns, mostly because women at the highest risk are serologically negative at the time of screening.<sup>13</sup> There is also no evidence that treating seronegative women decreases neonatal infection.<sup>13</sup> Screening by way of checking cervical viral cultures during pregnancy does not predict viral shedding during labor and delivery, nor does a negative culture preclude the possibility of subsequent neonatal disease.<sup>5</sup> Therefore, the American College of Obstetricians and Gynecologists (ACOG) does not currently recommend screening— either serologically

**Table 2. Prevention of Neonatal Herpes Simplex Virus Infection**

Obtain a history of HSV infection in a woman and her sexual partner at the first prenatal visit.
Counsel pregnant women with no history of HSV about prevention methods.
Encourage condom use by partners with HSV if there is no history of HSV in the pregnant woman.
Consider prophylactic acyclovir at 36 weeks for pregnant women with a history of HSV infection.
Ask women presenting in labor about symptoms of HSV infection.
Women in labor who have active genital HSV infection should be delivered by Caesarian section.
Keep newborns with known or suspected HSV in isolation with contact precautions. Skin lesions should be covered.
Healthcare providers with lesions should not have contact with newborns. Parents with active herpetic lesions on any part of the body should pay careful attention to the handling of their neonate.

HSV, herpes simplex virus.

or by cervical culture—of pregnant women for HSV.<sup>5</sup> Instead, the clinician must determine whether there has been any history of HSV infection in the patient and/or her sexual partner, followed by information about consistent condom use and information about symptoms of HSV.<sup>4,14</sup>

ACOG recommends that pregnant women with known HSV be treated with suppressive therapy starting at 36 weeks.<sup>5</sup> The US Preventive Services Task Force, however, states that there is limited evidence that this prevents neonatal infection.<sup>13</sup> Guidelines for Cesarean delivery also differ. ACOG recommends that a Cesarean delivery be performed for women with primary and recurrent infection who have active genital lesions or a herpes prodrome, because some studies show that Cesarean delivery within 4 hours of membrane rupture in these women can reduce the risk of transmission to neonates.<sup>5</sup> However, the US Preventive Services Task Force again states that there is limited evidence that this prevents neonatal infection, and the number needed to treat with such an invasive procedure is high: 1580 Cesarean deliveries must be performed before one case of neonatal herpes is prevented.<sup>13</sup> One recent study found that a rapid test for HSV PCR in laboring women had high sensitivity (99.6%) and specificity (96.7%).<sup>15</sup> If further studies in the clinical setting support these results, this test may allow us to more appropriately manage women in labor. Postnatally, newborns with known or suspected HSV should remain in isolation with contact precautions, and skin lesions should be covered. Health care providers with lesions should have no direct patient contact with newborns.<sup>4</sup>

## Conclusions

HSV infections in the neonate have the potential to cause significant morbidity and mortality, and recognition of this disease can be difficult. The clinician should keep HSV infection high on his/her differential when evaluating a febrile neonate without other obvious source for fever, especially an infant younger than 1 month old, even if the mother reports no history of genital HSV lesions. Rapid diagnosis and early initiation of treatment is

essential to preventing significant morbidity and mortality in the neonate.

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