Global Pediatric Health
January-December 2015: 1–3

DOI: 10.1177/2333794X15574089
gph.sagepub.com
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Electroencephalography as an Adjunct in the Diagnosis of HSV Encephalitis in Preterm Twins

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Introduction

Neonatal herpes simplex virus (HSV) infections are rare, with an estimated 1500 cases diagnosed annually in the United States.[1] Intrapartum exposure to HSV in vaginal secretions leads to 85% of neonatal HSV infections, while intrauterine and postpartum infection accounts for 5% and 10% of infections, respectively.[2] Irrespective of the route of exposure, neonatal HSV infection can cause devastating disease if not recognized and treated early.[3]

Primary maternal HSV infections carry a considerably higher risk of vertical transmission compared with reactivated latent infection or asymptomatic viral shedding because of the higher titer of virus found in the maternal genital track and the lack of transplacental transfer of protective IgG to the fetus.[2] Other important risk factors for transmission include prolonged rupture of membranes, which increases the likelihood of ascending infection, and the use of intrapartum fetal scalp monitoring.[2]

Neonatal disease is classified as cutaneous/mucosal, central nervous system (CNS; with an encephalitic presentation), or disseminated disease involving multiple organs with or without CNS involvement.[3] CNS and disseminated disease have the highest risk of morbidity and mortality, and favorable clinical outcomes are more likely if intravenous acyclovir is started promptly.[2,3] However, treatment is frequently delayed because the presenting symptoms of neonatal HSV infection are often nonspecific. Despite decades of research there has not been a significant shortening of the time to institution of therapy.[3]

Because of the potentially devastating consequences of neonatal HSV infection, many researchers have evaluated screening of pregnant women for HSV infection and third trimester prophylaxis of HSV-positive women. Unfortunately, serological screening of pregnant women is of little use in preventing neonatal HSV infection because seropositivity does not predict the presence of infectious virus in the genital secretions of pregnant women at the time of parturition.[4] Likewise, antenatal surveillance cultures to detect HSV in maternal genital secretions had poor correlation with the presence of infectious virus at the time of delivery.[5] Third trimester prophylaxis has been demonstrated to reduce the incidence of genital lesions in pregnant women at delivery, the detection of HSV in genital secretions, and the rate of Caesarean delivery; however, the evidence is insufficient to support a recommendation for prophylaxis of pregnant women.[6] It should be kept in mind as well that Caesarean delivery does not eliminate the risk of neonatal HSV infection, and in the setting of premature or prolonged rupture of membranes may provide little benefit.[7] Because of the diagnostic uncertainty and the lack of effective preventive measures, some researchers support the use of acyclovir along with empiric broad-spectrum antibiotics for infants undergoing a rule out sepsis workup, though to date no standard of care has been defined.[1]

The cases described here illustrate the diagnostic uncertainty posed by neonatal HSV encephalitis. We propose an evidence-based application of routine electroencephalography (EEG) to aid in the workup of equivocal cases.

Case Report

Thirty-two and 5/7 week twin males were born to a 23-year-old woman who initiated prenatal care at 28 weeks. The mother had a history of illicit substance use, including marijuana and cocaine, and had been incarcerated early in her pregnancy. Additionally, she had a history of appropriately treated gonococcal infection. Prenatal serologies demonstrated that she was not infected with HIV, *Treponema pallidum*, or hepatitis B virus, and she was immune to Rubella. An uneventful

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Cesarean delivery was performed because of premature and prolonged rupture of membranes, and the infants required only blow by oxygen during resuscitation. APGAR scores were 7 and 8 for twin A and 8 and 9 for twin B at 1 and 5 minutes, respectively. Both infants were small for gestational age and were tachypneic with mild retractions. The physical exams were otherwise unremarkable, and the infants were transferred to the neonatal intensive care unit for further evaluation and management where they were started on continuous positive pressure ventilation. On the day following delivery, the patients' mother was noted to have an ulcerated vaginal lesion suspicious for HSV. The mother denied a history of herpetic outbreaks, and primary genital herpes was subsequently confirmed by a positive viral culture for HSV-1 but negative IgM and IgG serologies.

The infants were started empirically on intravenous acyclovir at 60 mg/kg/day administered every 8 hours.[8] Initial workup of the infants for neonatal herpesvirus infection included surface viral cultures; lumbar puncture with cell counts, glucose, protein, and polymerase chain reaction (PCR) analysis for HSV DNA; complete metabolic panel; and a complete blood count. All laboratory values for both infants were within normal limits for gestational age, and the HSV PCR and surface viral cultures were subsequently reported as negative. Because of the high-risk clinical scenario, however, routine EEG was conducted on day of life 7 to evaluate for signs of encephalitis. EEG results for both infants were abnormal, with temporal slowing with spikes bilaterally in twin A and unilaterally in twin B, concerning for HSV encephalitis.

Despite negative PCR for HSV in cerebrospinal fluid obtained on the second day of life, the twins were administered acyclovir for a full 21-day course based on the EEG results. The infants tolerated acyclovir without adverse reactions, and at the time of discharge home they both had normal neurological exams.

Discussion

The most important factor affecting the outcome of neonatal HSV infection is the timing of initiation of acyclovir. Despite decades of research, however, the timing of acyclovir initiation has not changed significantly.[3]

PCR analysis of cerebrospinal fluid (CSF) has supplanted viral culture in the diagnosis of neonatal HSV encephalitis because of more rapid turnaround, increased sensitivity, and reduced interference by prior antiviral treatment. However, the sensitivity of PCR is dependent on the timing of sample acquisition relative to symptom onset, such that in neonates the sensitivity early in the course of disease is thought to be only ~70%.[9] This is likely due to the initial involvement of a restricted area of brain tissue following retrograde axonal transport of viral particles. Subsequent spread of the infection within the brain results in sufficient release of HSV nucleic acid into the CSF allowing for detection by PCR.[10] To circumvent this source of false-negative PCR results, many experts recommend serial sampling of CSF following initiation of acyclovir.[9]

An alternative to serial lumbar puncture is the use of EEG as in the cases above. Previous studies have demonstrated EEG abnormalities in 75% to 100% of neonates with HSV encephalitis.[3,11-14] Given the frequency with which EEG abnormalities are associated with neonatal HSV encephalitis and the noninvasive nature of the test, we recommend considering EEG as part of the diagnostic workup of equivocal cases.

Author Contributions

SCM contributed to conception and design; contributed to analysis; drafted the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. CAB contributed to conception and design; contributed to analysis; drafted the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported partly by the National Institute of Child Health and Human Development (K12 HD068322).

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