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Case Report

Neonatal herpes simplex virus presenting with isolated liver failure

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ABSTRACT

Disseminated neonatal herpes simplex virus infection usually presents with multi-organ involvement. Untreated, this disease has a mortality rate of approximately 80%. Here, we describe a well-appearing 3-week old infant with isolated compensated hepatic failure caused by HSV-2.

Introduction

Neonatal herpes simplex virus (HSV) infection manifests either as skin, eye, mouth (SEM) disease, central nervous system (CNS) disease, or disseminated disease. Disseminated neonatal HSV infection characteristically presents as a sepsis syndrome with fever, hepatitis, and pneumonia with or without encephalitis. Untreated, the mortality rate for disseminated HSV infection approaches 80% [1]. Prompt diagnosis and early initiation with antiviral therapy can be life-saving, but early recognition of the infection is difficult in infants with non-specific symptoms. We present a 3-week old infant whose clinical presentation of disseminated HSV-2 infection included only compensated hepatic failure.

Case presentation

A 37-week gestation male was born via cesarean section to a 23-year old primigravida mother. The pregnancy was uncomplicated. Serologic screening was negative for human immunodeficiency virus and hepatitis B and showed immunity to rubella. At 30 weeks gestation, as per standard of care at the mother's obstetrics practice, serologic testing for HSV-1 and HSV-2 IgG were obtained and were negative. At 35 weeks, vaginal swabs for Group B streptococcus were negative. The mother had a non-specific febrile illness at 35 weeks gestation that self-resolved, but never had symptomatic genital herpes.

The patient was born at 37 weeks gestation via cesarean section due to failure to progress, with APGAR scores of 8 and 9 at 1 and 5 min, respectively. There was no documentation of prolonged rupture of membranes in the medical records. No fetal scalp monitoring was used during labor or delivery. He had a normal newborn physical exam and was discharged home from the newborn nursery with the mother in good clinical condition.

On day of life 21, he was noted to have poor weight gain and jaundice and was hospitalized for evaluation. He did not have fevers, respiratory symptoms, irritability, lethargy, vomiting, diarrhea, or change in appetite. At the time of hospital admission, he was well-appearing, with jaundice and hepatomegaly being the only remarkable findings on physical exam. Initial laboratory evaluation revealed an aspartate aminotransferase (AST) concentration of 130 U/L, alanine aminotransferase (ALT) concentration of 141 U/L, gamma-glutamyl transpeptidase (GGT) of 141 U/L, total bilirubin of 13.6 mg/dL, direct bilirubin of 10.8 mg/dL, and albumin of 1.9 g/dL. Coagulation studies revealed a prothrombin time (PT) of 18.8 s and an international normalized ratio (INR) of 1.51. A complete blood count was normal. Abdominal ultrasound showed hepatomegaly with extensive punctate calcifications, splenomegaly, and ascites. An infectious work up directed at hepatotropic organisms was then pursued.

Cerebrospinal fluid (CSF) studies demonstrated 77 white blood cells/mm^3, with 24% polymorphonuclear cells and 76% mononuclear cells, 23,500 red blood cells/mm^3, glucose of 32 mg/dl, and protein of 51 mg/dl. Bacterial studies of the blood, cerebrospinal fluid, and urine were negative. Virologic evaluation including serologies for

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hepatitis A, hepatitis B, hepatitis C, toxoplasma and polymerase chain reaction (PCR) for parvovirus from blood as well as adenovirus, cytomegalovirus, Epstein–Barr virus, varicella zoster virus, human herpes virus 6, and enterovirus from the cerebrospinal fluid, and a urine culture for cytomegalovirus were all negative. However, herpes simplex virus (HSV) PCR of oropharynx, conjunctiva, and CSF, and rectal culture were all positive for HSV type 2. Subsequent work-up for disseminated HSV infection with central nervous system involvement included a computed tomography (CT) of the brain, hearing evaluation using auditory brainstem response, and ophthalmologic exam, all of which were within normal limits.

Treatment with intravenous acyclovir was initiated on hospital day 2. Repeat HSV PCR from CSF on day 19 of treatment was negative. During his hospitalization, ursodeoxycholic acid, albumin, and furosemide were given for treatment of hyperbilirubinemia and edema, respectively. The patient's clinical status and laboratory values remained stable during hospitalization and he was discharged home after completion of three weeks of intravenous acyclovir. Upon discharge, he was started on oral acyclovir suppressive therapy.

At his follow-up visit, four months after discharge, the patient was thriving, with resolving hepatomegaly, normal laboratory evaluation, including transaminases, hepatic function, and coagulation studies, and normal neurodevelopment. Repeat maternal serologic testing for HSV type 2 IgG was also positive. Upon further questioning, the mother disclosed having sexual contact with a partner known to have HSV during the last two months of her pregnancy.

Discussion

Neonatal HSV infection, a potentially devastating disease with a high rate of morbidity and mortality, occurs between 1/12,500 and 1/1700 live births in the United States [2]. Neonatal HSV infection is divided into three general classifications: SEM disease, CNS disease, and disseminated disease.

SEM disease accounts for 45% of neonatal HSV cases, with infection limited to skin vesicles, involvement of the eye, and/or oral mucosa. CNS disease accounts for 30% of neonatal HSV cases. Approximately two thirds of these babies will also have skin lesions, although these lesions may not be present early in disease process. While neonates with SEM disease most often present between the first and second week of life, those with CNS disease present between the second and third weeks of life [3].

Disseminated HSV infection, typically presenting during the first two weeks of life, accounts for approximately 25% of neonatal HSV cases and is the most lethal of the disease classifications. Disseminated infection most commonly involves the liver, adrenal glands, respiratory tract, and central nervous system. Thus, neonates with disseminated infection may present with fever, hypothermia, hepatitis, respiratory distress, disseminated intravascular coagulation (DIC), shock, seizures, and/or encephalitis [2,4,5]. Almost half of these babies will not have any skin lesions present, making early diagnosis of HSV infection more elusive. Without antiviral therapy, mortality from disseminated HSV infection is approximately 80% [1]. Here, we describe an unusual case of a 3 week old baby whose presenting symptoms of disseminated neonatal HSV-2 infection with central nervous system involvement included only jaundice and poor weight gain. Despite the biochemical findings of meningitis, the infant never demonstrated overt neurologic symptoms. Absence of neurologic signs and symptoms, and normal neuroimaging with the excellent developmental outcome also suggest absence of encephalitis.

Previously published cases have also described disseminated neonatal HSV infection presenting with fulminant liver failure. White presented a febrile 10-day old infant born to a mother with no history of HSV who was found to have transaminitis, CSF pleocytosis, and HSV 2 detected by CSF PCR. He received 4 weeks of intravenous acyclovir with clinical and laboratory improvement [6]. Abuhasna describes a 4-day old baby boy born to a mother with no history of HSV who presented with fever, lethargy, respiratory distress and was found to have fulminant hepatic failure and HSV-2 detected by CSF PCR. He was treated with 6 weeks of intravenous acyclovir, due to herpetic relapses after discontinuation of the antiviral medication, with ultimate clinical and laboratory improvement [7]. Similarly, Greenes presented a case of disseminated HSV-2 infection in a full term 6-day old female infant born to a mother with no history of HSV who was ill-appearing with fever, vomiting, and hepatomegaly. She went on to develop fulminant hepatic failure and respiratory arrest on day of life 35 [8]. Contrary to the febrile, lethargic, ill appearing neonates described in these previously published reports, our patient with disseminated HSV infection was afebrile, well-appearing, with isolated compensated liver failure.

Neonatal HSV infection is typically acquired through exposure to infected maternal genital secretions during delivery. The risk of acquiring neonatal infection is influenced by several factors, including the type of maternal infection and maternal antibody status, as well as prolonged rupture of membranes and the use of fetal scalp monitoring [9,10]. Infants born to women who have a first episode genital HSV infection near term are at a much greater risk of developing neonatal HSV infection when compared to mothers with a history of recurrent HSV infection [11]. Similar to the cases mentioned, our patient was also born to a mother with no history of HSV infection. Maternal serologic testing at 30 weeks gestation were negative for HSV and repeat testing 4 weeks post-partum were positive for HSV-2, findings consistent with a primary HSV infection near term.

Treatment for neonatal HSV infection requires intravenous acyclovir (60 mg/kg/day in three divided doses) for 14 days for SEM disease, and for a minimum of 21 days for CNS disease or disseminated disease [3]. Early initiation of appropriate antiviral therapy has significantly reduced mortality from disseminated HSV infection to approximately 30% [1].

Conclusion

Early administration of antiviral therapy is effective in reducing morbidity and mortality. It is therefore important to maintain a high level of suspicion of HSV infection in neonates with evidence of liver injury, regardless of maternal history of HSV, even in the absence of other symptoms.

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