CASE REPORTS

SERENDIPITOUS DISCOVERY OF DISSEMINATED NEONATAL HERPES SIMPLEX VIRUS INFECTION

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Abstract

A five day old full term girl presented with fever. Prenatal course was remarkable for fever during labor. Baby was noted to have jaundice, but was otherwise well appearing. Patient was subsequently found to have Herpes simplex virus (HSV) viremia as well as central nervous system (CNS) HSV disease, despite a lack of pleocytosis in the CSF. Repeat laboratory investigation at the completion of 21 days of therapy revealed that the infection had cleared. Thus, disseminated HSV could present without outward signs of infection as well as without CSF pleocytosis.

Introduction

Herpes Simplex Virus (HSV) infections of the neonate occur in about 1 per 3200 live births in the USA. (1) Recent estimates from the Centers for Disease Control and Prevention (CDC) suggest that 20% of women of child bearing age are infected with HSV-2 and that 81% of those infected are undiagnosed. (2) As a result, congenital HSV infection is likely to remain an important diagnosis to consider when caring for ill neonates. Neonatal HSV presents in three different ways, with reasonably predictable timing: skin/eye/mouth (SEM) infection at 5-10 days of life, central nervous system (CNS) infection at 14-21 days, and disseminated infection at 5-10 days. (3) The clinical presentation of disseminated HSV infection may have no clinical features to set it apart from bacterial sepsis, making it generally the hardest presentation to identify. (3) With the advent of acyclovir therapy, there has been a reduction in mortality and morbidity rates associated with this disease, although these numbers are still significant. Recent reports suggest that 12 month mortality in patients treated with acyclovir is 29% for disseminated neonatal disease and 4% for CNS disease. (4) In patients who receive acyclovir, normal neurological outcome occurs in 83% of those with disseminated HSV, compared with 50% in the preantiviral era. (4) Therefore early recognition and treatment of the disease is essential to prevent devastating long term complications.

Case Report

A five day old full term girl presented to the emergency department because of fever and jaundice. Mother had received prenatal care and all routine screening had been negative. She denied having had vaginal lesions at delivery or following delivery. She had been treated for Chlamydia trachomatis infection 2 years prior, and had since then had no known sexually transmitted infections. The baby had been delivered via vaginal delivery with a birth weight of 2545 grams. Maternal history was significant for fever during labor and presumed chorioamnionitis. She had received intrapartum ampicillin and the neonate had a complete blood count and blood culture obtained as a screen for sepsis. The infant was treated with ampicillin and gentamicin for 48 hours in the nursery before discharge home, after the blood culture remained negative.

Upon presentation, the infant?s vital signs included a temperature of 39.2 0 C measured rectally, heart rate of 172/min, and respiratory rate of 68/min, and she was jaundiced. She appeared alert and active, without abnormal movements. Her skin was without lesions. Her anterior fontanel was soft and flat, and systemic examination was normal apart from hepatomegaly. Investigations are depicted in Table 1. She was treated with ampicillin and cefotaxime. Due to the elevated transaminase levels, the possibility of disseminated HSV infection was considered, and acyclovir (60 mg/kg/day, in three divided doses) therapy was initiated 24 hours after admission. After 48 hours, blood, urine, and cerebrospinal fluid (CSF) cultures were negative and the patient was afebrile. Antibacterial therapy was discontinued. Also at 48 hours, the CSF

Table 1: Laboratory results of the patient

	At admission	After 24 hours	Reference range
Aspartate amino transferase (IU/L)	16	970	10-42
Alanine amino transferase (IU/L)	13	201	14-54
Total bilirubin (mg/dL)	0.7	11.9	0.3-12
Direct bilirubin (mg/dL)	0.3	0.6	0-0.3
White blood cell count (cells/cumm)	16800	-	9000-30000
Hemoglobin (g/dL)	21.9	-	14.0-24.0
Platelet count (cells/cumm)	297000	-	150000-400000
Cerebrospinal fluid (CSF) white cells	0	-	0-20
CSF red blood cell (cells/cumm)	540	-	0
CSF glucose (mg/dL)	43	-	30-70
CSF protein (mg/dL)	73	-	40-170

HSV PCR and the blood PCR were found to be positive for HSV-2. Surface cultures of the eye, mouth, and anus were negative for HSV. Acyclovir therapy was continued intravenously for a total of 21 days. A repeat lumbar puncture was obtained on hospital day 18 and was normal. Repeat CSF HSV PCR was negative. Transaminases normalized after 3 days of therapy, and the absolute neutrophil count (ANC) was monitored routinely without observed neutropenia. The patient completed her therapy without any adverse event.

Discussion

In this case of a neonate with fever, the patient presented without many of the typical external signs of HSV infection. These include lethargy, skin vesicles, fever, and seizure, with the latter two characteristics being the most suggestive of HSV disease. (3) In this patient, due to the lack of visible outward signs and without CSF pleocytosis, acyclovir therapy was not begun initially. Previous reports suggest that a small percentage (3% to 5%) of patients with severe CNS infection with HSV may have normal CSF analysis. (5,6) The diagnosis of disseminated HSV infection was suspected due to the elevated transaminase levels, and confirmed with a positive serum HSV PCR. Encephalitis was diagnosed based on the positive CSF HSV PCR. Elevated hepatic enzymes have been previously reported to be associated with disseminated HSV infection, with significant elevation (>1000 IU/L) in as high as 30% of infected patients. (7,8) One study found that in neonates presenting with fever admitted to the hospital with concern for serious bacterial infection (SBI), the incidence of disseminated HSV infection of 0.2% was not statistically different than that of bacterial meningitis of 0.4%. (8) The debate continues about whether acyclovir should be initiated empirically for all febrile neonates, or just in the subset of those who have CSF pleocytosis. (9,10) While experts may disagree on this subject, most would agree that acyclovir therapy should be initiated if hepatic aminotransaminases are elevated. (9,10) For this reason transaminase levels should be measured in all febrile or septic appearing infants less than 28 days of age as an additional screening tool for HSV infection.

Conclusion

CNS HSV may be present in the absence of CSF pleocytosis. We recommend that transaminase levels be tested in all febrile neonates less than 28 days of age, and that if they are elevated, testing for HSV be performed, and empiric antiviral therapy be instituted immediately.

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