Neonate with intractable seizures and metabolic acidosis: an unusual case of type-1 herpes simplex encephalitis-diagnostic and management challenges

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ABSTRACT
Neonatal Herpes simplex virus (HSV) infection is usually caused by type 2 virus following maternal peripartum genital HSV infection. Type 1 HSV usually affects infants after 3 months of age. Neonatal HSV infection present as skin, eye and mouth disease (SEM disease); affect the central nervous system (CNS disease) or involve multiple organs (Disseminated disease). Illustrative case: A full term male baby; birth weight of 3.25 kg, born to a primiparous mother with uneventful intrapartum and postpartum period and normal physical examination. At 20 days of life, the neonate presented with lethargy, poor feeding and later developed generalized tonic-clonic seizures. Initial workup showed metabolic acidosis; neuro-sonogram showed diffuse cerebral edema. Seizures were not controlled initially with intravenous phenobarbitone, phenytoin and pyridoxine. On starting intravenous midazolam baby developed poor respiratory efforts and was intubated. Serum ammonia and lactate levels were mildly elevated. Lumbar puncture attempted after seizure control showed 93 WBCs, 90% lymphocytes, normal glucose and mildly elevated proteins. With possibility of viral encephalitis; intravenous acyclovir was started. EEG showed PLEDS and CSF HSV-PCR detected Type 1 HSV. This case illustrates the nonspecific presentation of HSV infection in the neonatal period without history of HSV in the mother and challenges faced during the management. Early initiation of acyclovir reduces HSV associated morbidity and mortality in neonates

Keywords: herpes encephalitis type 1, neonatal period, seizures, acyclovir

INTRODUCTION
Neonatal seizures are caused by several metabolic and neurologic causes; of which herpes simplex encephalitis is one of the rare causes. However delay in treatment could lead to severe long standing complications including epilepsy, mental retardation and mortality.

PURPOSE
We present an unusual case of refractory neonatal seizures in a newborn with no previous antenatal, natal or postnatal history of herpes simplex.

CASE REPORT
A full term male baby; birth weight of 3.25 kg, was born vaginally to a primiparous mother with uneventful antenatal period and no history of HSV infection. Intrapartum and postpartum period were uneventful with normal physical examination. Baby gained weight adequately; was exclusively breast fed during the early neonatal period. At 20 days of life, the neonate presented with lethargy, poor feeding. Initial workup including the septic workup was normal and was presumed to have viral fever in view of low grade fever, cough and rhinorrhea. During the hospital stay baby developed generalized tonic-clonic seizures. Subsequent workup showed metabolic acidosis with normal septic screen, glucose, calcium and electrolytes. Neuro-sonogram showed diffuse cerebral edema without gross structural malformation or intracranial hemorrhage. Seizures were not controlled...
with intravenous phenobarbitone, phenytoin and pyridoxine. On starting intravenous midazolam baby developed poor respiratory efforts and was shifted to the Neonatal Intensive care unit (NICU). Baby was started on cefotaxime and ampicillin after drawing blood for culture. Serum ammonia and lactate levels sent were mildly elevated. Lumbar puncture attempted after seizure control showed 93 WBCs, 90% lymphocytes, normal glucose and mildly elevated proteins. With possibility of viral encephalitis; intravenous acyclovir was started. The remaining CSF sample collected was then sent for PCR and CSF HSV-PCR detected Type 1 HSV. EEG done after 2 weeks showed Periodic Lateralized Epileptiform Discharges (PLEDs). The seizures were controlled and sensorium improved following introduction of Acyclovir within 72 hours; child received Intravenous acyclovir for 21 days. Follow-up of the patient after 6 months showed mild motor delay with no seizures.

**DISCUSSION**

Herpes Simplex encephalitis is one of the rare causes of neonatal seizures. Herpes simplex virus (HSV) encephalitis has a fulminant course with very high mortality (80%) and morbidity if there is a delay in introduction of proper antiviral medication and in adequate dose and duration. Most infants who survive may have severe morbidity such as mental retardation, hypertonia and seizures1,2.

Herpes infection in the neonates can be caused either of the two strains: HSV-1 or -2. Majority of the cases of HSV is caused by genital herpes which is predominantly caused by HSV-2. HSV-2 infection is responsible for approximately 85% of cases resulting in genital herpes, which is then perinatally transmitted to the neonate resulting in 70% of neonatal herpes6,7. HSV-1 is usually noted in older infants following community acquired infections while HSV-2 encephalitis is more common in neonates following genital infection in the mother. The case in view was noted to be caused by HSV-1 type that resulted in encephalitis and refractory seizures. The metabolic acidosis noted in the case was probably following intractable seizures.

Neonatal HSV infection can be divided according to the organs involved into the following categories: Skin Eye Mouth disease (SEM disease), CNS disease and disseminated disease8,9,10.

SEM Disease usually has an incubation period of approximately 10–11 days.11 SEM disease usually presents with discrete vesicles over the trunk and extremities also involving the area around the mouth, within the oral cavity also involving the eyes leading to keratoconjunctivitis. Keratoconjunctivitis may rarely lead to blindness; however mortality in neonates with SEM disease is low. 30–40% of cases with SEM disease may develop CNS disease or disseminated disease if they do not receive timely antiviral therapy12.

CNS Disease (ENCEPHALITIS): The signs and symptoms of CNS disease include drowsiness, poor feeding, irritability, seizures, tremors, temperature instability, poor perfusion, bulging fontanelle and pyramidal tract signs including rigidity, hypertonia and exaggerated reflexes13.

35% of HSV-infected infants present with CNS disease and seizures are the presenting feature in nearly half these cases. The characteristic electroencephalographic (EEG) changes noted are Periodic Lateralized Epileptiform Discharges (PLEDs). Untreated children have high mortality (50%), usually due to brain-stem involvement. Early introduction of Antiviral therapy results in good response, however CNS sequelae is evident in approximately 70% of surviving neonates12.

Infants with Disseminated disease have multiple organs involved such as liver, lung, and adrenal gland, with or without involvement of the CNS. The clinical presentation may be varied ranging from vesicular skin eruptions, lethargy, irritability, convulsions,
petechiae, purpura, bleeding diathesis, tachypnea, jaundice and shock. Disseminated disease may be the initial presentation in 22% of neonatal HSV infection; the prognosis is poor with high mortality noted in the absence of early treatment (85%)\textsuperscript{1,12,14}. The case in review had predominately CNS disease with progressive dissemination; however due to early introduction of antiviral therapy the recovery was faster.

Neonatal HSV caused by Type-1 strain is noted to have a better prognosis than those caused by Type-2 strain.\textsuperscript{11} Early suspicion of HSV infection in patients with neonatal seizures with early introduction of Acyclovir in suspected cases of viral encephalitis before confirmatory PCR results is useful in reducing mortality and neurological morbidity in surviving neonates\textsuperscript{1}.

The gold standard for diagnosis of HSV infection in neonates is virus culture of the body fluids, although Polymerase Chain Reaction (PCR) is an alternative with faster results as compared to culture. Further PCR assay for HSV DNA from CSF is more sensitive than culture especially in CNS infections\textsuperscript{15}. PCR assay of CSF turns negative following completion of antiviral therapy and should be strongly considered at the end of therapy for CNS and disseminated disease. Antiviral therapy should be continued or medication changed if the patient remains PCR positive at this site.

The antiviral used for treatment include acyclovir and vidarabine; early introduction of these drugs have significantly reduced the morbidity and mortality of neonatal HSV infection\textsuperscript{9,11}. A comparative study between acyclovir (10 mg/kg every 8 h for 12 days) versus vidarabine (10 mg/kg every 8 h for 12 days) demonstrated that both drugs were effective in reducing both mortality and morbidity following various HSV infection\textsuperscript{16}.

Duration of therapy: Neonatal HSV infection needs to be treated early in the course with antiviral therapy including intravenous acyclovir. Among neonates with disease localized to SEM, intravenous acyclovir is usually administered for 14 days.\textsuperscript{17} Cases with disseminated or CNS disease need to be treated for at least 21 days with intravenous acyclovir. If a CSF analysis is not available or not done, the longer duration of treatment is advised even in neonates with HSV localized to SEM.

CONCLUSION
Herpes simplex encephalitis type-1 is an uncommon cause of neonatal seizures that one should consider in the differential diagnosis. Early treatment results in significant reduction in mortality and morbidity. HSV-PCR has become the gold standard in early diagnosis of this condition and also helps in monitoring the antiviral therapy.

REFERENCE


