Chattagram Maa-O-Shishu Hospital Medical College Journal
Volume 23, Issue 1, January 2024

Case Report

A Case of Fulminant Hepatic Failure with Neonatal Cholestasis Caused by Disseminated Herpes Simplex Virus (HSV) Infection

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Abstract

Background: *Disseminated herpes simplex virus infection is an life threatening infection which may initially present as cholestasis, but eventually lead to multiple organ failure with a high mortality rate. But the good news is that the introduction of antiviral agent like acyclovir for the treatment of neonatal herpes has significantly improved the outcome of this potentially devastating infection. The early initiation of acyclovir highly depends on clinician's suspicion, especially when overt signs of the infection are absent. So the objective of our case report was to raise awareness among the physicians to consider herpes virus infection in the differential when a patient present with features of cholestasis and hepatic failure.*

Case Presentation: *Our case is aone month old male infant who got admitted in Chittagong Medical Hospital on 7th January, 2023 with the complaints of lethargy, blood mixed vomiting and black stool for 1 day with a history of jaundice and pale stool from 3rd week of life. His bleeding manifestations exacerbated and developed features of hepatic failure with coagulopathy. He was treated with plasma transfusion, viamin k, injectable antibiotics and other supportive care. A TORCH panel was sent. HSV Ig G came positive with 12 folds increased titre. Observing his deteriorating consciousness level intravenous acyclovir 60 mg/kg/day was initiated on 16th January, 2023. Within 3-4 days his overall general condition improved. The baby was discharged after getting 21 days of acyclovir therapy.*

Conclusion: *Neonatal herpes virus infection can be a life threatening condition. An early diagnosis and effective treatment with antiviral agent can reduce morbidity and mortality.*

Key words: Acyclovir; Disseminated herpes simplex virus infection; Neonate.

INTRODUCTION

Neonatal herpes, although relatively rare, has a high mortality and morbidity.[1] Herpes simplex viruses are large, enveloped viruses with double stranded DNA core.[2] Two neurological subtypes can be distinguished: HSV 1 & HSV2. HSV 1 affects face and skin above waist and HSV 2 affects genitalia and skin below waist.[3] After primary infection with or without clinical signs, the virus resides in the local sensory ganglion, especially in the trigeminal and sacral ganglion and can be reactivated frequently. It is regarded as a common viral pathogen which produces a wide variety of diseases. Clinical manifestations categorized as i) Infection localized to Skin, Eye, Mouth (SEM) ii) Encephalitis with or without localized mucocutaneous disease iii) Disseminated infection with multiple organ involvement.[4]

i) SEM disease : 45% cases are of this type.Without treatment, there is high risk of progression to encephalitis or disseminated disease.

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Date of Submission : 13.10.2023
Date of Acceptance : 19.11.2023

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ii) Encephalitis with or without mucocutaneous disease:It accounts for 30% of neonatal herpes infection with or without SEM lesion.[3]

iii) Disseminated disease: Infants with disseminated herpes accounts for 25% of all neonatal herpes. Patients present with fever, lethargy, apnea, septic shock, liver failure, neutropenia, thrombocytopenia and DIC. 60-75% of infants have CNS involvement and >20% may not develop cutaneous manifestations.

Approximately 20% infants present between 5 and 9 week of age. Infants with SEM disease present at 5-11 day of life, infants with encephalitis present at 8-17 days of life and infants with disseminated disease generally become ill at 5-11 days of life. More than 20% infants with disseminated disease and 30-40% infants with encephalitis never have skin vesicles.[3,5]

HSV infection should be considered in the differential diagnosis of all ill neonates with CNS abnormalities, fever, shock, DIC and/or hepatitis. It should also be considered in infants with respiratory distress without an obvious bacterial cause or a clinical course. Viral isolation or PCR detection of viral DNA remains critical to diagnosis.[6]

The introduction of acyclovir therapy for the treatment of neonatal herpes has had a profound impact on the management and outcome of this potentially devastating infection. Acyclovir must be initiated before widespread viral dissemination throughout the body or to a significant replication within Central Nervous System (CNS).[7]

The diagnosis of neonatal disseminated herpes simplex infection can be difficult, because a documented history of perinatal or postnatal HSV exposure is often lacking and even a known history of HSV exposure is of little predictive value. In addition, presenting symptoms can be non-specific. We report a case of neonatal herpes infection presenting as fulminant hepatic failure which was rapidly improved after getting acyclovir therapy.

CASE PRESENTATION

A one month old male baby, 1st issue of a non-consanguineous parent, was apparently in good health till 3 weeks of postnatal age. Mother's antenatal period was uneventful with no complaints of fever, rash or perineal itching. He was born at 37 weeks of pregnancy by normal vaginal delivery at home with a birth weight 3000 gram. There were no postnatal complications.

From the 3rd week of life, the baby developed jaundice, intermittent pale stool and dark urine for which they consulted with a local physician. But the jaundice was not resolving, in addition, the baby developed poor activity, poor feeding, blood mixed vomiting and black stool at his one month of age. He was immediately admitted to Chittagong Medical College Hospital on 7th January, 2023. On admission, he was lethargic, moderately pale, deeply icteric, fontanelle was open and not bulged, hemo-dynamically unstable, blood pressure-60/30, cold periphery, respiratory rate-48 breath/min, heart rate-160 beats/min, spo2-96%, capillary blood glucose-3.6 mmol/l, no bleeding spots or vesicular lesions in the skin were noted. Abdomen was not distended, liver was palpable 5 cm from right costal margin along mid-clavicular line which was firm, non-tender, smooth surface; spleen was just palpable. But after a day of admission, his bleeding manifestations increased. Large echymotic spots developed over both limbs, fresh and clotted blood passed through vomiting, stool was black tarry in color. Patient's general condition deteriorated and developed shock. He was immediately shifted to Pediatric Intensive Care Unit (PICU) on 8th January, 2023. In PICU, he was managed with normal saline, packed red cell, fresh frozen plasma, vitamin k, broad spectrum antibiotics and ionotropic agents. Afterwards, the patient developed convulsion several times which were managed by injectable anticonvulsants.

Laboratory evaluation revealed, Hemoglobin 5.2 g/dl, total count-22, 260/cmm, platelet count-normal, neutrophil-60%, lymphocyte-36%, prothrombin time-60 sec, partial thromboplastintime-120 sec, INR-5.08, alkaline phosphatse-492 IU/L, SGPT-16 u/l, total bilirubin-10.75 mg/dl, direct bilirubin-6.55 mg/dl, indirect bilirubin- 4.2 mg/dl, HBsAg negative, coombs test negative, no growth on blood or urine culture, no urinary reducing substance, thyroid function-normal, ophthalmoscopy examination-normal, ultrasonography finding of abdomen was normal, ammonia and lactate was normal, maternal HSV 1 & 2 Ig G was positive. On 7th day of admission, a TORCH panel was sent. His HSV 1& 2 IgG came positive with 12 folds raised from the cut off value.We could not send Cerebrospinal Fluid (CSF) study for HSV DNA PCR at that moment for financial problem of the father and also due to non-availability of this investigation in Chattogram. Observing his deteriorating condition i/v acyclovir at 60 mg/kg/day was initiated on 16th January, 2023. Patient's clinical status significantly improved after 3-4 days of acyclovir administration. After 14 days of acyclovir therapy, a Cerebrospinal Fluid (CSF) study for HSV DNA PCR was sent to abroad and the result came negative. In the meantime, baby's feeding was established and he was shifted to general ward. The baby was discharged after getting 21 days of acyclovir therapy.

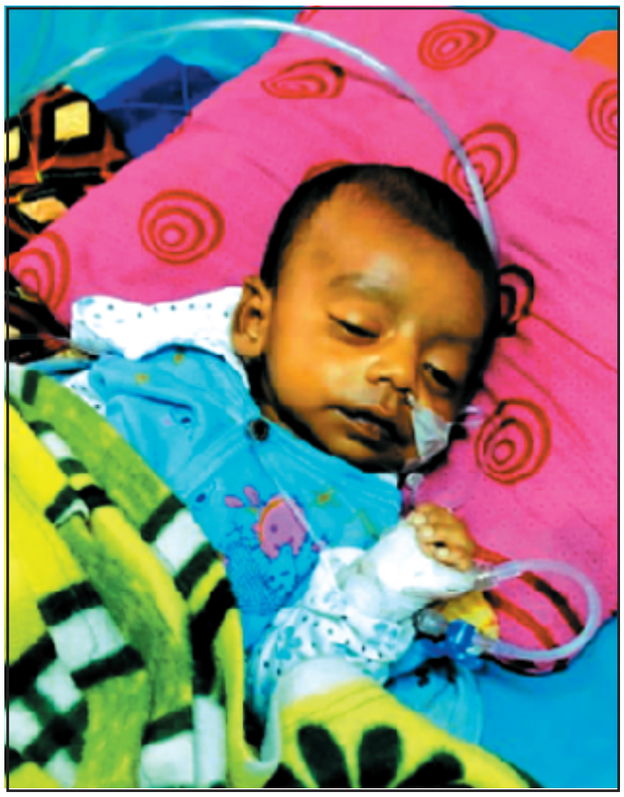

Image 1 Criticall ill, deeply icteric & lethargic while in PICU

Image 2 Pale stool

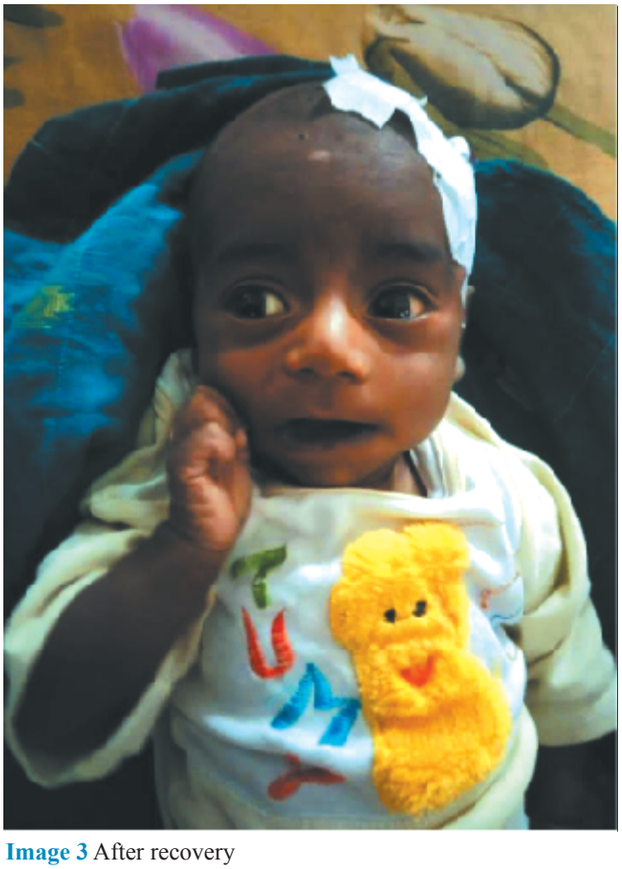

Image 3 After recovery

DISCUSSION

HSV infection is a significant contributor to morbidity and mortality in newborn. It is estimated that 1 neonate in 3200 live births has HSV infection.[1] Neonatal HSV can be acquired in utero (5%), in the peri-partum period (85%) or in the postnatal period (10%).[2] Postpartum transmission may occur from the mother or another adult with a non-genital (Typically HSV-1) infection such as herpes labialis. 60-80% of the mothers of infected neonates are asymptomatic. The risk for infection is higher in infants born to mothers with primary genital herpes than with recurrent genital herpes.[2,8]

Diagnosis of neonatal herpes can be challenging and is often delayed. Early manifestations are subtle and non-specific. The maternal history is often not helpful.[3] In this case, the first clinical diagnosis was septicemia with disseminated intravascular coagulation, as it was very difficult to distinguish from bacterial sepsis to herpes infection. In our case, mother had no symptoms herpes infection. She was never tested for HSV infection before delivery. There were no characteristic vesicular skin lesions. But the one thing that led the suspicion that patient may have HSV infection was the presence of features of neonatal cholestasis. Patient had jaundice and pale stool from the 3rd week of life which was overlooked by the parents, but later, during history taking, it was revealed. As TORCH infection comprises almost 15.7% cases of neonatal cholestasis, we felt the necessity to rule out TORCH infection.[9]

After getting 12 folds raised HSV IgGtitre, antiviral acyclovir was added promptly. His response to acyclovir was instant. Within 3 days, his consciousness level improved and features of coagulopathy demolished. Enteral feeding and subsequently breastfeeding was initiated. Astrid, on his study, revealed a case of HSV 1 induced liver failure, where HSV 1 was not diagnosed when the patient was alive. HSV 1 was found to be the causative agent of the disease at the postmortem liver biopsy report.[4] In a study described by Marwan, prompt initiation and three weeks course of acyclovir treatment of a neonate, who presented with isolated liver failure, was lifesaving.[10] The application of PCR to CSF samples has revolutionized the diagnosis of CNS neonatal herpes disease. The overall sensitivities of CSF PCR in neonatal HSV disease have ranged from 75% to 100%, with overall specificities ranging from 71% to 100%. A negative PCR result from the CSF does not rule out neonatal HSV disease, as tests may be negative in very early stages of infection.[2] In our patient, sample of CSF DNA PCR was sent after 14th day of initiating injectable acyclovir. We could not send the investigation at the right time due to non-availability and patient's poor financial condition. Though the report came negative, we believed administration of acyclovir for 14 days might have cleared off the remaining DNA of HSV present in the CSF sample.

Abu Hasna describes a 4 day old baby 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 intravenous acyclovir for 6 weeks due to herpetic relapses, with ultimate clinical and laboratory improvement.[1,11] Greenes presented a case of disseminated HSV 2 infection in a 6 day old neonate born to a mother with no history of HSV infection who was ill appearing with fever, vomiting and hepatomegaly. She went on to develop hepatic failure and respiratory arrest on 35th day of life.[12] Benador described three cases of neonatal herpes virus infection presenting as fulminant hepatitis where acyclovir therapy was initiated late. All three of the patients died.[11] Similar to both the case mentioned, our patient was febrile, ill appearing and presented with features of cholestasis, DIC and liver failure, but unlike Greenes and Benador's study our patient recovered successfully.

There is clear evidence that intravenous administration ofacyclovir at 20 mg/kg of body weight every 8 hour for 21 days significantly reduces mortality for babies with either encephalitis or disseminated disease. Antiviral treatment must be introduced before an irreversible damage of liver tissue was present.[2] Acyclovir has been shown to improve mortality. There is a reduction from 85% 31% in patients with disseminated disease and from 50% to 6% in patients with CNS disease.[13] In our case, an empiric treatment with acyclovir was started and potential fatal outcome of the disease were successfully avoided.

LIMITATIONS

Our study has several limitations including difficulties in proving HSV infection due to limited finance. Our patient could not afford some valuable investigations that were needed for the case. There is also lack of long term follow up to assess the morbidities.

CONCLUSION

Neonatal HSV disease should be suspected in case of any neonate who has features of liver dysfunction, as appropriate diagnosis, aggressive intensive therapy and timely administration of acyclovir can save a life.

RECOMMENDATIONS

We recommend that neonates with onset of a febrile or other illness, who would be admitted, tested or treated with empirical antibiotics for possible serious bacterial infections, should also be tested to rule out HSV infection.

DISCLOSURE

All the authors declared no competing interest.

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