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Effectiveness of Early Antiviral Therapy in Disseminated Neonatal Herpes Simplex Virus 2 (HSV-2) with Fulminant Hepatic Failure

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Male, 11-day-old
Final Diagnosis: Disseminated neonatal herpes simplex virus-2
Symptoms: Feeding problems • lethargy • rash
Medication: —
Clinical Procedure: —
Specialty: Pediatrics and Neonatology





Objective: Unusual clinical course
Background: Liver failure in the neonatal population is a life-threatening complication and has a wide array of etiologies, including infectious, immune-mediated, metabolic, or drug-induced. Although neonatal herpes simplex virus (HSV) hepatitis only accounts for 1% of all acute liver failures, it has an extremely aggressive clinical course that carries a mortality rate of 85%.

Case Report: We report a rare case of disseminated neonatal HSV-2 with late presentation associated with fulminant liver failure. The patient recovered without obvious neurologic deficits or need for liver transplant.

Conclusions: This case study emphasizes and promotes awareness of early recognition and appropriate clinical management of neonatal HSV infection, and its positive outcome.

MeSH Keywords: Herpes Simplex • Infant, Newborn • Liver Failure, Acute

Full-text PDF: <http://www.amjcaserep.com/abstract/index/idArt/902418>

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Background

Despite advances in treatment and diagnosis, herpes simplex virus (HSV) carries a high morbidity and mortality in neonates [1–9]. An estimated 1 in every 3200 live births have an occurrence of neonatal HSV infection, and approximately 1500 cases of neonatal HSV infections are reported annually in the United States [1]. Globally, according to the World Health Organization, there are 536 million people aged 15–49 years living with HSV-2 [2]. HSV infections can be transmitted through asymptomatic cervical shedding of the virus after an initial event of genital HSV in the third trimester [3]. Antibodies to HSV-2 are detected in 20% of pregnant women, while only 5% of pregnant women report a history of symptomatic infection [4]. Mothers who have a primary episode of genital HSV infection near term are at much greater risk of transmitting the infection to the neonate, compared to mothers who have had recurrent genital HSV [5].

Neonatal HSV can have various presentations, including isolated fever, rash, CNS infection, or fulminant or disseminated infection involving multi-organ systems [1,6,7]. A high degree of clinical suspicion is required to make a diagnosis, as symptoms are often vague and nonspecific. Untreated cases of neonatal disseminated HSV infection carry an estimated 85% risk of mortality, and patients with CNS disease have a 50% mortality risk [1,7,8]. Of all infants with neonatal HSV, 30% have CNS disease and about 25% have disseminated disease [9]. Approximately 60–75% of infants with disseminated disease will have CNS involvement [9].

In neonates, disseminated or SEM HSV typically presents at 10–12 days of life, and CNS involvement is detected in the second or third week of life [1]. HSV encephalitis due to disseminated disease is spread via a hematogenous route, whereas isolated encephalitis is caused by retrograde intraneuronal transport of the virus [9]. Disseminated disease presents earlier, causing diffuse brain involvement, whereas CNS disease presents later and causes focal brain involvement [9].

High-dose acyclovir (60 mg/kg/day) is required immediately upon clinical suspicion to avoid disseminated disease, as vesicles or other signs of HSV may be absent in 40% of

cases [10,11]. With the use of Acyclovir, mortality has been reduced to 29% in disseminated HSV infection and to 4% in patients with CNS involvement [1]. We present the case of a neonate with disseminated disease associated with acute liver failure. The patient successfully survived his course of illness without need for a liver transplant and without any neurological deficits. This case highlights the importance of early recognition of herpes simplex virus infection in neonates and demonstrates that prompt management and treatment results in favorable outcome.

Case Report

An 11-day-old male presented to the Emergency Department with worsening rash, fever, and poor feeding. The patient was born full-term to a G2P1 mother via normal spontaneous vaginal delivery and had regular prenatal follow-up, with no prenatal or postnatal complications, and was discharged home on day 2 of life. Birth weight was 3575g and birth length was 21 inches. According to the mother, the patient started developing a rash on the lower eyelid on day 4 of life and developed a similar rash in the left axilla, as well as around the umbilicus. Subsequently, the baby had 2 days of lethargy and poor feeding. There was no history in either parent of past or current HSV outbreaks, and the mother's HSV titers were never checked. The mother was not on any medication throughout the pregnancy, and she never reported a history of genital lesions or sexually transmitted infections. In addition, the patient had no known sick contacts.

Upon arrival to the Emergency Department, the patient was found to be febrile (101.3°F [38.3°C]) with stable vitals. A full sepsis work-up was completed and the initial lab results showed an ALT of 2862 U/L (7–55 U/L) and AST >1000 U/L (8–60 U/L) (Table 1). The PT was >100 s (10.3–12.8 s), PTT 35 s (26–36 s), and the INR was indeterminate (Table 2). The initial CSF results showed a glucose level of 45 mg/dL (70–140 mg/dL), protein level of 82 g/L (62–80 g/L), WBC 50.0 cells ×10³/μL (5.0–20.0 cells ×10³/μL), and RBC 2 million/mm³ (4.3–5.9 million/mm³) (Table 3). CSF culture and HSV PCR were sent, and ceftriaxone, ampicillin, and acyclovir were started. The patient was admitted to the PICU for further management of suspected

Table 1. Liver function test measurements throughout the patient's stay at the hospital.

LFT	Admission day	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 10	Day 12	Day 14	Day 16	Discharge day	Reference range
ALT (SGPT)	2498	1014	819	619	537	456	428	321	210	141	81	40	30	7–55 U/L
AST (SGOT)	8718	2206	1621	993	758	482	308	206	101	66	43	33	37	8–60 U/L

Table 2. Coagulation studies.

Coagulation	Day of admission	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Reference range
APTT	32.0	31.5	31.4	30.7	33.0	31.6	36.4	47.0	41.0	36.2	35.4	31.9	40.9	26–36
D-Dimer										12.27			8.93	≤250 ng/mL
Fibrinogen							39			59			47	15–400 mg/dL
INR	IND	1.1	1.2	1.2	1.5	1.5	2.0	1.8	1.7	1.7	1.5	1.4	2.0	0.9–1.2
PRO time	11.9	14.6	15.3	15.8	18.4	18.4	22.7	20.9	19.9	20.3	18.7	18.8	22.6	10.3–12.8 sec

Table 3. CSF analysis.

	Patient	Normal	Units
Glucose	45	70–140	mg/dL
Protein	82	62–80	g/L
WBC	50.0	5.0–20.0	cells ×10 ³ /μL
RBC	2	4.3–5.9	million/mm ³

disseminated HSV with hepatic failure. While in the PICU, the patient began desaturating and required 2 liters of oxygen via nasal cannula. The patient was then transferred to a higher-level facility for further management. During the PICU course, the patient was hemodynamically stable. The patient had increasing abdominal distention, moderate hepatomegaly, mild splenomegaly, and ascites confirmed by ultrasound. Transaminases were trended throughout the hospital stay, with the highest AST 8718 U/L and ALT 2498 U/L (Table 1). The patient continued to require 2 liters of oxygen via nasal cannula; however, due to increased respiratory distress, he was started on nasal intermittent mechanical ventilation, and thereafter was intubated and placed on synchronized intermittent mechanical ventilation (SIMV) after developing bilateral HSV pneumonitis. A skin viral culture was done and was positive for HSV 2. The video electroencephalogram and a brain MRI were normal. The patient was weaned off of SIMV after resolution of pneumonitis and was then stable on room air. After 19 days of acyclovir, a CSF HSV PCR was still positive for HSV 2. Acyclovir was then continued for a total of 28 days. On day 26, a third CSF HSV PCR was sent and was still positive for HSV 2. The fourth CSF HSV PCR was negative and the patient completed a 35-day course. The discharge AST was 37 U/L and ALT was 30 U/L. On discharge, the patient was tolerating full feeds, with good suck and swallow, and at 4 months of age has no neurological deficits and did not need a liver transplant. Currently, he is on oral suppressive antiviral therapy for a total of 6 months.

Discussion

We present a case of fulminant hepatic failure with disseminated neonatal HSV, including CNS, blood, and skin involvement. To the best of our knowledge, this is only the second documented case of neonatal HSV with fulminant hepatic failure in the U.S., with no neurological complications and a successful outcome [12].

In the adult population, 1.5 million new cases are diagnosed each year [13]. Around 5% of all women of childbearing age report a history of HSV-2 infection, and approximately 30% have antibodies to HSV-2 and 2% of the women acquire HSV 2 infection during pregnancy [13,14]. About 75–90% of patients with HSV-2 are not aware of the presence of the infection [5,6,13]. Similarly, in most cases of neonatal HSV there has been no known history or report of maternal external genital lesions [5,6,13]. The typically asymptomatic nature of this disease facilitates the transmission to the population and the fetus while the mother is infected. The prevalence of maternal genital herpes simplex infection while giving birth has increased by 30% [14]. HSV infection raises concerns about increased risk of viral transmission during childbirth.

Although intrapartum transmission is the most common route of transmission in the neonate, HSV can be transmitted to the neonate before or after delivery [13,14]. Approximately 85% of HSV transmission in the neonate is during vaginal delivery, via an infected birth canal [1,6,13,14]. Approximately 5% of all cases of neonatal HSV infections are a result of *in utero*

transmission [13,14]. In neonates, there are 3 different disease presentations in the setting of HSV: SEM (skin, eyes, and mucous membranes), CNS, and disseminated infections [13]. Neonates may or may not have the classic vesicular rash associated with most HSV infections; therefore, treatment in the setting of disseminated and CNS disease is often delayed [15].

Abuhasna et al. described a case of a 4-day old infant born to a mother with no prior history of HSV, who presented with fever, lethargy, and respiratory distress [16]. The case report was the first documented case featuring a neonate with fulminant liver failure surviving following medical treatment. The infant was found to have fulminant hepatic failure with HSV-2 detected by viral PCR. The infant was treated with 6 weeks of acyclovir therapy and recovered without developing CNS dysfunction [16]. Yamada et al. presented a case of a 4-day-old neonate with fever and increased transaminases and lactate dehydrogenase. The patient developed disseminated HSV infection, which resulted in acute liver failure and hemophagocytic lymphohistiocytosis [17]. With the use of high-dose acyclovir and anti-cytokine therapy, this patient recovered without the need for a liver transplant and showed no neurological deficit [17]. Similarly, Pilorget et al. published a case report of an 8-day-old infant presenting with fever, seizures, vomiting, and liver dysfunction. This patient was treated with high-dose acyclovir and survived with complete recovery from neonatal HSV hepatitis [18]. Contrary to the neonates presenting earlier in their illness in the previously published cases, our patient presented late, on day 11, with disseminated HSV. Our case clearly demonstrates that early initiation of appropriate therapy and clinical management can result in a favorable outcome. Although the patient had abnormal laboratory findings signifying neonatal HSV infection with hepatic failure, he did not require a liver transplant and survived without any focal abnormalities.

An increase in liver transaminases is associated with increased mortality and morbidity in neonates [8]. Depending on the degree of severity of liver involvement, liver transplantation is a treatment option often utilized in the pediatric population [8]. Furthermore, the presence of vesicles in patients with hepatic disease may suggest a less severe course of illness [8]. Our patient presented to our institution with vesicles and rash. Although the liver transplant team was consulted, correction of liver transaminases followed a medical course of acyclovir.

Disseminated HSV infection has also been known to trigger neonatal hemophagocytic lymphohistiocytosis (HLH) [19]. HLH is characterized by fever, hepatosplenomegaly, CNS symptoms, cytopenias, coagulopathy, lipid changes, and elevated ferritin levels exceeding 10 000 µg/L (20–250 µg/L) [17,19]. Our case did not have the hallmark feature of a massively elevated ferritin level and no hemophagocytes were seen in the peripheral

blood smear. The patient was improving with antiviral therapy and there was no suspicion of HLH.

Guidelines for the treatment of neonatal fulminant liver failure state that treatment with acyclovir should be initiated when a diagnosis of HSV infection is suspected, as early administration is associated with decreased mortality and morbidity [6,10,18]. Early detection with PCR provided the opportunity for prompt and adequate treatment [1].

The International Herpes Management Forum (IHMF) guidelines outline the diagnosis, prevention, and effective management of neonatal herpes [7]. Neonates with suspected disseminated HSV infection or HSV encephalitis should be immediately treated with intravenous acyclovir (60 mg/kg/day) for at least 21 days. Guidelines should be established to recheck PCR for the virus, and treatment should be continued until the PCR result is negative [5,7,10,15]. Rechecking the PCR consistently and discontinuing acyclovir treatment only after CSF PCR is negative should be the standard of care in neonates presenting with neonatal HSV encephalitis [5,7,15,19]. The therapy should be followed with oral suppression therapy with 300 mg of acyclovir per square meter per dose administered 3 times daily for 6 months after initial treatment of neonatal HSV disease [6,16,20]. Follow-up treatment with oral acyclovir is shown to reduce recurrence of skin lesions in neonates and to reduce CNS complications [6,16,20].

According to American College of Obstetricians and Gynecologists' guidelines, the risk of transmission of HSV in neonates can be reduced by performing Cesarean delivery in cases of active maternal genital lesions or prodromal symptoms [16]. In addition, it is common practice to provide suppressive therapy with acyclovir or valacyclovir near the end of pregnancy [16]. Despite preventive measures with suppressive therapy, viral shedding is still known to occur; therefore, neonatal infection is still possible [16]. Physicians and residents alike should be on high alert to diagnose and treat HSV infection in neonates, as early detection and treatment are associated with lower morbidity and mortality [5,9,17].

Conclusions

To the best of our knowledge, this is only the second documented case of disseminated HSV infection with fulminant hepatic failure in the United States that presented late and achieved recovery with no obvious sequela. Due to early recognition and immediate treatment, the case had a positive outcome without the need for a liver transplant. HSV is difficult to recognize in a clinical setting and a high degree of clinical suspicion is required. Neonates presenting with lethargy, poor feeding, somnolence, and other nonspecific symptoms in absence of a

clear diagnosis should be tested for HSV. Mandating HSV testing via PCR in neonates, may lead to early diagnosis and prevention of more severe sequela of herpes infection. Another recommendation is starting acyclovir immediately upon presentation, before the diagnosis has been confirmed. A CSF PCR should be performed multiple times beyond 21 days of therapy with acyclovir to check for persistence of the virus, and the treatment regimen should be extended beyond the standard 21 days to ensure resolution. This case report emphasizes and promotes awareness of early recognition and appropriate clinical management of neonatal HSV infection, and its positive outcome.

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Conflict of interest

All authors have indicated they have no potential conflicts of interest to disclose.