Clinical and Laboratory Characteristics of Disseminated Herpes Simplex Virus Infection in Neonates

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KEY WORDS
acyclovir, clinical characteristics, disseminated herpes simplex infection in neonates, herpes simplex infection, laboratory characteristics, retrospective case series

ABBREVIATIONS
ALT: alanine aminotransferase
AST: aspartate aminotransferase
CNS: central nervous system
CRP: C-reactive protein
CSF: cerebrospinal fluid
DIC: disseminated intravascular coagulation
HSV: herpes simplex virus
PCR: polymerase chain reaction
ROM: rupture of membranes
SEM: skin/eye/mouth

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abstract

BACKGROUND AND OBJECTIVES: Disseminated herpes simplex virus (HSV) infection is the most fulminant type of neonatal HSV infection and has the highest mortality. Early diagnosis and treatment are essential for patient survival. We describe the clinical presentation, laboratory characteristics, and outcomes of neonates with disseminated HSV infection at our institution.

METHODS: A retrospective review of electronic medical records from 2006 to 2013 was performed. Only neonates with disseminated HSV infection, confirmed by using polymerase chain reaction or viral culture results, were included.

RESULTS: Twenty-two cases were identified; the age range was 1 to 14 days. The majority of patients did not have a maternal history of HSV or a history of maternal fever at delivery. Eleven of the patients were delivered by cesarean delivery, and 3 of these patients did not have prolonged rupture of membranes. Neonatal fever, the most common historical characteristic, was present in only one-half of the patients. Pneumonia and respiratory distress were present in one-half of the patients. Serum aspartate aminotransferase and alanine aminotransferase levels were elevated in most, but not all, patients. The blood HSV polymerase chain reaction was positive in all patients tested. Of the 22 study patients, 16 survived and 6 died. The majority of the patients who died had respiratory disease and a delay in the initiation of acyclovir therapy.

CONCLUSIONS: Disseminated HSV infection in neonates can be challenging to diagnose and is associated with high mortality. Clinicians must strongly consider this diagnosis, test the blood for HSV polymerase chain reaction, and initiate early treatment in the appropriate clinical scenarios.

Neonatal herpes simplex virus (HSV) infection has significant morbidity and mortality and is estimated to occur in 1 of every 3200 to 10 000 live births.[1–4] Three forms of this disease have been well described. The skin/eye/mouth (SEM) form is most common and represents ~45% of cases. The central nervous system (CNS) form is found in ~30% of cases. The third and least frequent type is the disseminated disease, which occurs in 25%. Disseminated disease is defined according to organ involvement other than the CNS and SEM alone. The blood, lungs, and liver are most often affected.[5]

The disseminated form often has a fulminant course, with a mortality of ~80% to 90% if not treated.[6] When early diagnosis and acyclovir therapy are initiated, however, mortality drops to ~29%.[5] At initial presentation, neonates with disseminated disease sometimes have only nonspecific complaints and no skin abnormalities.[6]

For these reasons, early identification of neonates with disseminated HSV can be difficult.

In this report, we describe presenting symptoms, physical examination findings, and laboratory test results of 22 neonates with disseminated HSV. We also examined the relationship between these patient characteristics, the timing of acyclovir initiation, and mortality. We hope that a better understanding of the presenting signs and symptoms of disseminated neonatal HSV infection may lead to earlier diagnosis, earlier treatment, and improved patient outcomes.

METHODS

We conducted a retrospective review of electronic medical records from 2006 to 2013 at Children's Healthcare of Atlanta at Scottish Rite and Egleston, two free-standing children's hospitals. The medical records were searched according to diagnosis of HSV (*International Classification of Diseases, Ninth Revision*, codes 054 and 771) in patients aged <2 months. To be included, patients must have had HSV infection documented by using polymerase chain reaction (PCR) from the blood or cerebrospinal fluid (CSF) or a viral culture from another site. At our institution, a qualitative PCR test is used, and this test does not distinguish between HSV-1 and HSV-2 infection. In addition, the patients were required to have organ involvement of the blood, lungs, and/or liver; those with only CNS or SEM disease were excluded from study. The patients in this study were either admitted from the emergency department or were transferred from outside hospitals.

History and physical examination findings were reviewed by the primary author. For cases in which historical components such as maternal fever and maternal HSV were omitted, the data were recorded as "not documented." The laboratory values reported in this article are the first set of laboratory tests drawn on each patient, typically within 24 hours of admission. Prematurity was defined as <37 weeks' gestation. Fever was defined as ≥38°C, and hypothermia was defined as <36°C.[7] Respiratory disease was defined as increased work of breathing noted by the clinician and respiratory support in the form of oxygen or positive pressure ventilation.

The following upper limits of normal for laboratory values were used: C-reactive protein (CRP), >1.58 mg/dL; aspartate aminotransferase (AST), >100 U/L for age 0 to 7 days and >71 U/L for age 8 to 30 days; alanine aminotransferase (ALT), >40 U/L; CSF white blood cell count, >20 cells/mm^3; and CSF protein, >100 mg/dL.[8] Disseminated intravascular coagulation (DIC) was defined as decreased platelet count and fibrinogen levels, together with elevations in prothrombin time and partial thromboplastin time. Delay in acyclovir therapy was measured from the day of admission to any hospital to the day of initiation of acyclovir. In some of the cases reviewed, the delay in initiation of therapy occurred at outside hospitals before patient transfer.

Statistical analyses included the calculation of means, medians, ranges, and percentiles as appropriate. The Wilcoxon rank sum test was used to analyze continuous variables for an association with mortality. This nonparametric test was used because of our small sample size and because a normal distribution was not observed with any of the continuous variables. Fisher's exact test was used to analyze binary variables for an association with mortality.

This study was approved by the Children's Healthcare of Atlanta institutional review board.

RESULTS

A total of 22 neonates were found to have disseminated HSV. The age range of their presentation was day of life 1 to day of life 14, with a median age of 6 days. Historical characteristics of the patients are summarized in Table 1. A history of maternal HSV was positive in only 4 patients. None of the 4 cases with maternal HSV lesions at delivery had a documented history of previous maternal HSV infection; thus, it is likely that these were primary maternal infections. Cesarean delivery was noted in 11 patients. Rupture of

TABLE 1 Historical and Examination Characteristics

Patient and Maternal Characteristics	*n/N* (%) of Patients
Prematurity	7/22 (32)
Cesarean delivery	11/18 (61), 4 not documented
Prolonged ROM for cesarean delivery	6/9 (67), 2 not documented
Maternal fever	9/21 (43), 1 not documented
Maternal history of HSV	4/18 (22), 4 not documented
Lethargy	9/22 (41)
Fever	11/22 (50)
Apnea	7/22 (32)
Skin lesions	8/22 (36)
Emesis	5/22 (23)
Hypothermia	1/22 (5)
Respiratory distress	11/22 (50)

membranes (ROM) was not prolonged in 3 of the 11 cesarean deliveries. In 2 of the 3 patients delivered by cesarean delivery without prolonged ROM, the ROM occurred at the time of delivery.

The most common neonatal complaint was fever (11 patients). Two patients presented with fever alone with no other complaints. Although none of the patients were described in the medical records as sick- or ill-appearing, 14 of the 22 were initially admitted to the ICU.

Of the 22 neonates in this study, 11 had respiratory distress as the primary manifestation of disease. These patients had a documented increase in work of breathing and/or respiratory rate together with a requirement of oxygen or positive pressure ventilatory support. All 11 also had abnormalities on chest radiograph consistent with HSV pneumonia. These abnormalities were described by the radiologist as bilateral interstitial disease, diffuse opacities, patchy bilateral opacities, bilateral air space consolidation, or diffuse haziness.

Skin lesions were noted on physical examination in 8 patients, and eye infection was evident in 1 patient. One patient had a lesion at the site of a scalp monitor.

Laboratory findings on the 22 neonates are presented in Table 2. The blood HSV PCR was tested in 20 patients, and results were positive in all 20 patients. The 2 remaining patients were diagnosed by using nasal wash culture plus skin direct fluorescent antibody in 1 case and by using CSF PCR in the other case. Viral culture results revealed HSV-1 in 6 cases, HSV-2 in 7 cases, and all negative culture results in 6 cases. No cultures were sent for 3 of the patients. Detailed results of culture sites are shown in Table 3.

TABLE 2 Laboratory Characteristics

Laboratory Value	Range	No. of Patients With Elevated Value
AST, U/L	35–13 240	18/21
ALT, U/L	13–3130	15/22
CRP, mg/dL	1–6.6	14/17
PLT, 10^3/uL	16–272	0/22 (9 patients with low PLT <150)
WBC, 10^3/uL	6–19	4/22
CSF WBC, cells/mm^3	0–110	1/16
CSF RBC, cells/mm^3	0–70 000	6/16
CSF glucose, mg/dL	35–57	0/16
CSF protein, mg/dL	43–125	2/16

PLT, platelet count; RBC, red blood cell count; WBC, white blood cell count.

CSF produced a positive HSV PCR result in 9 patients and a negative PCR result in 7 cases; CSF was not tested in 6 cases. An elevation in CSF white blood cell count was found in only 1 case. The CSF red blood cell count was elevated in 6 cases. Trauma during the lumbar puncture procedure was not documented in 5 of the 6 cases with red blood cell count elevation.

Serum AST levels were elevated in 18 of the 21 patients tested. ALT levels were elevated in 15 of 22 patients. All 3 patients with a normal AST finding also had a normal ALT finding. Of the 3 patients with normal AST and ALT levels, all except 1 patient had respiratory disease. This 1 patient presented with lethargy, apnea, and vomiting and had skin lesions noted on examination.

The CRP level was elevated to >1.58 mg/dL in 14 of the 17 patients in whom it was tested. Of these 17 patients, the CRP level was >5 mg/dL in only 2 patients.

Thrombocytopenia was found in 9 patients on the day of admission. The white blood cell count was elevated >15 000/uL in 4 patients. A predominance of neutrophils and bands was found in 14 of the 22 patients. One patient presented with a band percentage of 31%. DIC was found in 13 patients, either at the time of presentation or as their illness progressed.

Of the 22 patients in this study, 16 survived and 6 died. Some characteristics of the deceased patients are shown in Table 4. The majority of the patients who died had respiratory distress as the primary disease manifestation. Four of the 6 deceased patients had a delay in acyclovir treatment of ≥3 days, compared with 3 of 16 survivors who had delay in treatment of ≥3 days. Thus, although most of the deceased patients had respiratory disease and a delay in acyclovir therapy, these results were not statistically significant. All of the patients who had skin lesions on physical examination at presentation were survivors, although this result did not achieve statistical significance.

DISCUSSION

In this study, we describe the clinical and laboratory characteristics of neonates with disseminated HSV

TABLE 3 Culture Results

HSV-1 positive culture results (6 patients)
Skin (4 cases)
Nose (2 cases)
Eye (1 case)
Rectum (1 case)
HSV-2 positive culture results (7 patients)
Skin (2 cases)
Nose (3 cases)
Trachea (3 cases)
Viral culture negative results (6 patients)
Skin (4 cases)
Eyes (4 cases)
Mouth (2 cases)
Nose (1 case)
Rectum (1 case)

TABLE 4 Comparison of Deceased Patients and Survivors

Variable	Deceased Patients ($n = 6$)	Surviving Patients ($n = 16$)	*P*
Delay in initiation of acyclovir therapy, d	0–8 (median: 3)	0–7 (median: 0)	.116
Respiratory disease	4 patients (67%)	7 patients (44%)	.635
HSV-2 infection	3 patients (50%)	4 patients (25%)	.192
HSV-1 infection	0 patients	6 patients (38%)	.192
Skin lesions at presentation	0 patients	8 patients (50%)	.051

infection. This case series involves the largest number of patients with disseminated HSV since the study of Kimberlin et al[4] in 2001 and is the largest study to focus only on the disseminated form of the disease. Compared with the CNS and SEM forms of neonatal HSV, the disseminated form presents most acutely, at a younger age, and with different findings from the history, on physical examination, and in laboratory results. Seizures and CSF pleocytosis, which are the hallmarks of the CNS form, are often not present. In addition, the disseminated form has the highest mortality. We believe that our detailed case series emphasize the findings of this disease and can assist clinicians in making the diagnosis.

All patients with disseminated HSV in this study were between the ages of 1 and 14 days. Fever, difficulty breathing, lethargy/poor feeding, apnea/cyanosis, and skin lesions were the most common chief symptoms; however, even the most common complaint of fever was present in only one-half of the patients.

Similar to findings in other retrospective clinical studies,[4,6] maternal history of HSV was negative in the majority of patients in this study. In addition, as has been reported elsewhere,[9,10] our experience showed that neonates born by cesarean delivery can acquire HSV infection even without prolonged ROM. This finding suggests that neonates may acquire HSV from intrauterine infection. Alternatively, these patients may have been exposed from another caregiver after the perinatal period.

Pneumonia, which occurred as the primary manifestation in 50% of the study patients, is perhaps an underappreciated presentation of disseminated disease. In this study, all 6 patients who had a delay in acyclovir initiation of >3 days had pneumonia. Three of these 6 patients eventually developed DIC and died.

Laboratory markers such as CRP, AST, and ALT can be helpful in diagnosis but were not elevated in all cases, and in some patients, they were only mildly elevated. CRP was slightly elevated to >1.58 mg/dL in most patients; however, CRP was >5 mg/dL in only 2 patients and thus may not be as elevated as many clinicians would expect.

CSF pleocytosis was not a frequent finding in this study. Despite this lack of pleocytosis, the CSF HSV PCR was positive in 9 of the 16 patients tested and thus could still be useful in diagnosis. Although CSF HSV PCR has been well established in the diagnosis of CNS HSV disease, blood HSV PCR has not been studied extensively.[4,11] In our series, results of the blood HSV PCR were positive in all patients tested, and it was therefore the single most diagnostic test in this study.

With the exception of 1 case, all of the patients in our study had either respiratory disease or evidence of liver disease with at least mild elevation of AST and/or ALT levels. This 1 patient presented with the combination of skin lesions on examination, lethargy, apnea, and vomiting.

The majority of the patients who died in our study had a delay in initiation of acyclovir of ≥3 days. The importance of early acyclovir treatment of neonatal HSV infection has been shown elsewhere.[12–14]

Our study is limited in that it was a retrospective review of medical records; was dependent on a search of electronic records according to *International Classification of Diseases, Ninth Revision,* diagnosis codes; and involved a single institution. In addition, our sample size of 22 patients was relatively small due to the rarity of this disease.

CONCLUSIONS

We recognize that testing and treating all sick neonates for HSV is controversial.[15,16] However, we believe that this study illustrates that neonatal disseminated HSV can be a challenging diagnosis with a variable presentation and a high mortality rate. We hope that, based on the information presented here, clinicians will strongly consider the diagnosis of disseminated HSV in neonates during the first 2 weeks of life, particularly when respiratory disease, elevation of AST/ALT levels, skin vesicles, fever, lethargy, or apnea are present.

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