Herpes Simplex Virus Hepatitis in Infants: Clinical Outcomes and Correlates of Disease Severity

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Objective To better characterize the clinical outcomes of infants with herpes simplex virus (HSV) infection and identify useful correlates of disease severity.

Study design Infants aged ≤6 months with HSV infection treated between 1999 and 2009 were identified. In patients with concurrent hepatitis, laboratory and clinical variables were examined to identify predictors of specific outcomes, including death or the need for liver transplantation and the need for intensive care.

Results Of the 15 patients enrolled, 4 (27%) had fatal disease and 2 (13%) required liver transplantation. Infants who lacked skin lesions ($P = .04$), had a positive HSV polymerase chain reaction result ($P = .01$), had more severe thrombocytopenia ($P = .001$), or had other organ system dysfunction ($P = .002$) were more likely to require intensive care. A higher International Normalized Ratio value ($P = .001$) and peak total bilirubin level ($P = .0002$) were predictive of death or the need for liver transplantation. Peak direct bilirubin level was predictive of the need for intensive care and of death or the need for liver transplantation ($P = .04$ and .009, respectively).

Conclusions HSV hepatitis represents a broad spectrum of disease from mild aminotransferase elevation to fulminant liver failure and death. HSV DNA detected by polymerase chain reaction, a lack of skin lesions, and the degree of coagulopathy, thrombocytopenia, and cholestasis portend unfavorable outcomes. *(J Pediatr 2011;159:608-11)*.

Approximately 1500 cases of neonatal herpes simplex virus (HSV) infection are reported in the United States annually.[1] Even with acyclovir treatment, the mortality rate for infants with disseminated or central nervous system (CNS) involvement can exceed 50%.[2] Clinical presentations of HSV infection are categorized into (1) skin, eye, and mucous membrane disease; (2) CNS disease; and (3) disseminated disease. Since the use of systemic acyclovir therapy became routine, the proportion of infants with severe disseminated disease has declined.[3] However, given the nonspecific symptoms of HSV infection, a high index of suspicion is needed for early detection and prompt treatment to circumvent neurologic complications and mortality. Although the epidemiology of HSV infection is well known,[2,4,5] the precise incidence of and risk factors for HSV hepatitis are poorly understood. We hypothesized that worse outcome is associated with prematurity, a longer time interval between onset of symptoms and initiation of acyclovir, and a greater number of organ systems involved.

Hepatic involvement, including hepatic necrosis[6-9] and acute liver failure,[6,7,10-13] is common in neonatal HSV infection. Indeed, HSV is considered the most common viral cause of liver failure in neonates.[14] The limited available literature, consisting mostly of small case series, fails to illuminate environmental, maternal, immunologic, or other host factors pertinent to the development of HSV hepatitis and its complications.[6,12] Given that HSV-induced liver failure is associated with high mortality, the elucidation of objective indices of disease progression is vital to guide optimal therapy. Liver transplantation can be life-saving and should be considered early in these patients. Prognostic models bear special significance in neonatal HSV, because the presenting symptoms of HSV infection are often nonspecific, frequently delaying the correct diagnosis. The purpose of the present study was to examine the clinical outcomes of neonatal HSV hepatitis and identify correlates of disease severity.

Methods

This study was approved by the University of Florida's Institutional Review Board. Patients up to age 6 months with HSV infection who were treated at our institution between 1999 and 2009 were identified by computer search using International Classification of Diseases, Ninth Revision codes (054.0 to 054.9, 573.1). Infants with diagnosis of HSV infection and concurrent hepatitis were included. Hepatitis was defined as aspartate aminotransaminse (AST) and alanine aminotransaminse (ALT)

ALT	Alanine aminotransaminase
AST	Aspartate aminotransaminase
CNS	Central nervous system
HSV	Herpes simplex virus
ICU	Intensive care unit
INR	International Normalized Ratio
PCR	Polymerase chain reaction

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levels at least 1.5 times the upper limit of normal. HSV infection was diagnosed by HSV polymerase chain reaction (PCR) of blood or cerebrospinal fluid, direct fluorescent antibody testing of skin lesions, or viral culture. Viral culture specimens were obtained with swabs of mucous membranes, endotracheal tube culture, or stool culture. Demographic, laboratory, and clinical data were obtained by a review of electronic and paper medical records. The data were recorded using Excel 2007 (Microsoft Corp, Redmond, Washington). The clinical variables recorded included length of hospital stay, days from symptom onset to initiation of acyclovir therapy, age at diagnosis, gestational age, involvement of other organ systems, and presence or absence of skin lesions. The laboratory data recorded included complete blood counts, liver function tests, coagulation studies, HSV serotype, and HSV-PCR results. For laboratory values that were evaluated multiple times, the initial, final, and peak values were examined. The main outcomes analyzed for correlation included the need for intensive care, need for liver transplantation, and death. Data analyses were done with the Student *t* test, Fisher exact test, or Pearson correlation coefficient, as appropriate, using GraphPad InStat 3.06 (GraphPad, La Jolla, California). A 2-tailed *P* value $\leq$.05 was considered statistically significant.

Results

A total of 15 patients were identified for this study (Table I). Five of the patients (33%) were born preterm (gestational age $\leq$37 weeks). The mean age at diagnosis of HSV infection was 15 days. In only 3 patients was the mode of transmission known; 1 mother had an oral herpetic lesion, and 2 mothers had genital lesions. Ten patients had HSV serotype 2, 1 patient had serotype 1, and 4 patients had an unknown serotype. Twelve patients (80%) required intensive care in either the pediatric or neonatal intensive care unit (ICU). All patients were treated with intravenous acyclovir therapy. The mean interval from onset of symptoms to initiation of acyclovir therapy was 2 days. Four patients had fatal disease (27%), with a mean age at death of 23 days.

The factors significantly associated with the examined outcomes are listed in Tables II and III. The need for liver transplantation and death separately were not associated with any demographic, clinical, or laboratory factor analyzed. However, when patients who required liver transplantation or died were grouped, higher International Normalized Ratio (INR; $P = .001$), peak total bilirubin level ($P = .0002$), and peak direct bilirubin level ($P = .009$) were predictive of these dire outcomes. Younger age at diagnosis, preterm birth, and degree of liver enzyme elevation were not associated with worse outcomes.

Only two of our patients were listed for transplantation and both underwent liver replacement, one at age 4 weeks and the other at age 7 weeks. Both of these patients did well without significant complications.

Discussion

We found clinical and laboratory factors that correlated with outcomes that serve as markers of disease severity. Although these observations are novel, neonatal HSV is a relatively rare disease, and multicenter studies are needed to test the reproducibility of our correlations and their strength with larger sample sizes. Interestingly, infants who presented to an outside institution did not have worse outcomes than those who were first seen at the University of Florida, a tertiary academic

Table I. Patient characteristics

				AST, U/L		ALT, U/L		Total bilirubin, mg/dL		INR		Albumin, g/dL			
Patient	Race	Sex	Preterm	Initial	Peak	Initial	Peak	Initial	Peak	Initial	Peak	Initial	Nadir	Other organ systems involved	Outcome
1	Caucasian	F	No	330	726	54	266	7	7	NA	NA	2.8	2.7	None	Discharge
2	Caucasian	F	Yes	3878	4998	453	535	6.7	6.7	2.6	7.6	1.6	1.2	Respiratory, renal, CV, CNS	Death
3	Caucasian	F	No	151	196	47	63	1.5	1.5	NA	NA	3.7	3.1	None	Discharge
4	Caucasian	M	Yes	106	242	22	290	3.9	6	1.7	1.7	2.2	1.9	Respiratory	Discharge
5	Hispanic	F	Yes	259	259	291	351	0.4	0.4	1.6	1.6	3.0	2.7	Respiratory, CNS	Discharge
6	Caucasian	F	No	563	563	534	534	16.5	22.5	5.9	8.3	2.9	2.4	Respiratory	Transplantation
7	African American	M	No	2195	2195	545	545	3	5.3	1.7	1.9	1.7	1.1	CNS	Discharge
8	African American	F	No	10 136	10 136	1340	1340	4.5	7.4	1.3	1.4	1.5	1.3	Respiratory, CV, CNS	Discharge
9	African American	M	No	8935	8935	1808	1808	8	8	2.9	2.9	2.5	2.0	Respiratory, CV, CNS	Discharge
10	Caucasian	M	No	290	290	209	209	1.7	2.3	NA	NA	3.3	3.0	None	Discharge
11	African American	M	Yes	>8500	>8500	1080	1080	5	13.7	2.3	4.2	2.3	1.4	Respiratory, renal, CV	Death
12	Caucasian	F	No	5840	5840	627	627	2.9	18	1.5	5.1	3.6	2.5	Respiratory, CNS	Death
13	African American	M	No	6743	13 383	2111	3396	1.8	15.5	2.8	5	2.8	1.8	Respiratory, renal	Transplantation
14	Hispanic	F	Yes	10 216	10 315	2478	2478	2.7	14.1	3.3	3.3	3.1	1.0	Respiratory, CV	Death
15	African American	F	No	19	241	38	183	0.4	0.8	1.2	1.2	2.4	2.4	Respiratory, CNS	Discharge

CV, cardiovascular; *NA*, not available.

Table II. Factors associated with need for intensive care

Variables	Patients requiring ICU	Patients not requiring ICU	*P* value
Positive HSV-PCR (n = 10)*	10	0	.01
Negative HSV-PCR (n = 4)	1	3	
Positive skin lesions (n = 6)	3	3	.04
No skin lesions (n = 9)	9	0	
Organ involvement outside the liver (n = 12)	12	0	.002
No other organ involvement (n = 3)	0	3	

*Fourteen patients underwent HSV-PCR testing.

medical center. Our data showing similar outcomes in preterm and full-term infants argues against our hypothesis that prematurity would portend a more ominous outcome. Two infants were preterm and were already in the neonatal ICU when diagnosed with HSV infection, and so their need for intensive care was not due solely to HSV hepatitis.

We hypothesized that an increased time between onset of symptoms and initiation of acyclovir therapy would be associated with worse outcomes, but this was not the case. However, our small sample size might have limited these analyses. In this series, the degree of serum ALT/AST elevation was not associated with worse outcome. This is in contrast to a previous study showing increased mortality in patients with AST elevation ≥10 times the upper limit of normal.[2] However, that study examined neonates with HSV infection, whereas ours only examined infants with liver involvement. It is not surprising that a greater degree of thrombocytopenia was associated with the need for intensive care. In these patients, thrombocytopenia could be related to viral sepsis, portal hypertension, or decreased thrombopoeitin production related to significant liver dysfunction. It is interesting to note that infants with skin lesions were less likely to require intensive care. We found no significant difference in time between symptom onset and diagnosis or initiation of acyclovir therapy in infants with or without skin lesions. This suggests that skin manifestations may signify less severe disease, even in infants with hepatic involvement.

The are several potential limitations in this study, related to its retrospective nature. First, our patients were all hospitalized in a tertiary medical center, and many had detectable HSV-PCR (71%) and CNS involvement (47%); thus, our cohort is biased to represent sicker infants. Second, quantitative serum (or cerebrospinal fluid) HSV DNA levels, another potential clinically influential outcome factor, were unknown in our patients. Finally, evolving literature in newborns with HSV suggests that acyclovir dose influences outcome,[15] particularly in HSV encephalitis, but many of our patients had received acyclovir before being transferred to our institution. The acyclovir dosing information was not reliably documented in charts and thus was not available for accurate analysis.

Table III. Factors associated with clinical outcomes

	Outcome		
Variables	Patients requiring ICU	Patients not requiring ICU	*P* value
Platelet nadir ($\times 10^3/mm^3$)	48 (50)	276 (177)	.001
Peak direct bilirubin, mg/dL	4.0 (2.8)	0.1 (0.1)	.04
	Death/liver transplantation	**No death/liver transplantation**	
Peak INR*	5.6 (2.0)	1.8 (0.6)	.001
Peak total bilirubin, mg/dL	15.1 (5.2)	4.3 (3.0)	.0002
Peak direct bilirubin, mg/dL	5.5 (2.8)	1.7 (2.1)	.009

Values are reported as mean (SD).
*Twelve patients had INR tested.

Given the rising seroprevalence of HSV-2 infection, the incidence of neonatal HSV infection likely will increase as well.[16] The suspicion for HSV disease must be high in infants undergoing evaluation for sepsis or liver dysfunction, because many infants exhibit no skin lesions at the time of presentation[2] and the majority of their mothers have a negative history of herpes.[10] It is important that AST/ALT testing be completed in all infants with a diagnosis of HSV infection to specifically evaluate for hepatitis. All patients who are diagnosed with HSV hepatitis should be evaluated expeditiously to assess the degree of liver dysfunction. In this regard, despite their prime relevance, 3 infants with HSV hepatitis in our study did not have coagulation studies performed during the course of disease.

Acute liver failure due to HSV carries a poor prognosis.[17,18] As reported previously, infants with HSV-induced acute liver failure can successfully undergo liver transplantation[7,19-21]; thus, these infants should be promptly referred to a pediatric transplantation center. Both of the infants in the present study who underwent liver transplantation had a positive HSV-PCR at the time of transplantation. Despite obvious concerns for posttransplantation worsening of HSV infection with required immunosuppression, our findings suggest that successful outcomes are possible even in infants with active viremia. Similarly, there are reports of adult patients with disseminated HSV who have successfully undergone liver transplantation.[22,23] These patients require long-term treatment with acyclovir after transplantation and remain at risk for subsequent reactivation of HSV. However, because HSV-induced liver failure has such a poor prognosis, liver transplantation may be the only life-saving treatment option in these patients. ■

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