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Herpes Simplex Testing in Neonates in the Emergency Department

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Abstract

Objectives—To determine the prevalence of central nervous system (CNS) herpes simplex virus (HSV) infection in neonates evaluated in the emergency department (ED) and to identify factors associated with cerebrospinal fluid (CSF) HSV polymerase chain reaction (PCR) testing. An existing testing paradigm was then applied to determine its potential impact on testing frequency.

Methods—This nested case-control study included infants 0-28 days of age that had lumbar puncture in the ED. Multivariate logistic regression was used to identify factors associated with CSF HSV PCR testing.

Results—CSF HSV PCR testing was performed in 266 (47%) of 570 neonates. The prevalence of CNS HSV infection was 0.5% compared with 1.6% for bacterial meningitis. Performance of CSF HSV PCR testing was not associated with known HSV risk factors. Application of a known HSV testing paradigm would have reduced the proportion of infants tested by 21% without missing any of the cases of CNS HSV infection.

Conclusions—HSV testing remains common despite the low prevalence of HSV infection. CSF HSV PCR testing is not well aligned with known risk factors. Future testing strategies should incorporate community HSV prevalence, known neonatal risk factors, and clinical judgment.

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Keywords

herpes simplex virus; neonates; cerebrospinal fluid; PCR

INTRODUCTION

Herpes simplex virus (HSV) is a rare but serious cause of neonatal central nervous system (CNS) infection [1, 2]. Prompt diagnosis is difficult because neonates often do not exhibit classic signs and symptoms of HSV disease early in the infection. For example, vesicles, the most common clinical feature, are absent in over one-third of infants with CNS or disseminated disease[3, 4], and fever is not associated with a higher likelihood of neonatal HSV[4]. Other findings in HSV CNS disease, such as lethargy and temperature instability are nonspecific, and the resulting clinical picture may resemble that of other illnesses, including bacterial or enteroviral infection[4-6].

CSF HSV testing by polymerase chain reaction (PCR) is currently the method of choice for diagnosing HSV CNS infection[7]. However, there is no consensus on how to best utilize this test in neonates to detect all cases of HSV infection while avoiding excess testing. Testing for HSV CNS infection in all neonates evaluated by lumbar puncture (LP) in the emergency department (ED) would carry substantial financial cost as well as increase the likelihood of exposure to unnecessary medications and other risks of hospitalization (e.g., medication errors, hospital-acquired infections) since patients are usually admitted to the hospital and empirically treated until the PCR testing results are available. Few studies have examined the prevalence of HSV in neonates undergoing LP in the emergency department [8], but of all infants undergoing HSV testing, CSF HSV PCR tests are positive in <2% [9, 10]. Therefore, a strategy of routine PCR testing could potentially cause more harm than benefit. Caviness et al[11] suggested that it would be cost-effective to order CSF HSV PCR and empirically treat all febrile neonates with CSF pleocytosis if PCR results were available quickly and neonates required 3 or fewer days of hospitalization. Tang et al[12] showed that eliminating CSF HSV PCR testing for samples with normal CSF protein (≤45mg/dL) and leukocytes (≤5 nucleated cells/mm^3) reduced cost by one-third without decreasing sensitivity, though this study was not limited to neonates.

The objective of the current study was to determine the prevalence of CNS HSV infection in neonates evaluated by LP in the ED and to better identify factors associated with performing CSF HSV PCR. Two cost-effective paradigms proposed by Caviness et al[11] and Tang et al[12] were then applied to this study population to determine whether such protocols would have reduced testing frequency in this population. A better understanding of clinical and laboratory features associated with CSF HSV PCR testing, as well as available testing paradigms will help focus educational efforts to minimize unnecessary testing and the associated morbidity and cost.

MATERIALS AND METHODS

Study Design and Setting

This retrospective nested case-control study was conducted at The Children's Hospital of Philadelphia (Philadelphia, Pennsylvania), an academic tertiary care children's hospital, among a cohort of neonates undergoing lumbar puncture. The Committees for the Protection of Human Subjects of The Children's Hospital of Philadelphia approved this study with a waiver of informed consent.

Participants, Study Protocol, and Data Collection

All neonates 0-28 days of age who had lumbar puncture performed in the emergency department between January 1, 2005 and December 31, 2007 were eligible for inclusion. Subjects were identified using two data sources, Emergency Department billing records and Clinical Virology Laboratory records. Cases were defined as those neonates for whom CSF HSV PCR was performed and controls were those for whom CSF HSV PCR was not performed. Patient data, including demographics, epidemiologic information, clinical findings, and laboratory and radiologic study results were recorded onto a standardized data collection form. The procedural details of the HSV PCR are described in Appendix A.

Study Definitions

All data were obtained by review of medical records from the initial evaluation in the Emergency Department at our institution. Fever was defined as a temperature ≥ 38.0°C on examination or history. Hypothermia was defined as rectal temperature less than 36.5°C. Hypoxia was defined as a percutaneous oxygen saturation less than 90% or receipt of supplemental oxygen.

Hepatic transaminases were considered abnormal if the value was 50% greater than the upper limit of normal as defined by our laboratory. Thrombocytopenia was defined as a platelet count less than 150,000/mm^3. CSF glucose values <40 mg/dL were considered low and CSF protein values >170mg/dL were considered elevated. CSF pleocytosis was defined as >22 white blood cells (WBC)/mm^3 [13]. Traumatic lumbar puncture was defined as lumbar puncture with >500 red blood cells (RBC)/mm^3[14].

Serious bacterial infection was defined by the diagnosis of urinary tract infection, bacteremia, or bacterial meningitis. Urinary tract infection was defined as growth of a single known pathogen meeting one of three criteria: (1) ≥1000 colony-forming units (cfu)/mL for urine cultures obtained by suprapubic aspiration, (2) ≥50,000 cfu/mL from a catheterized specimen, or (3) ≥10,000 cfu/mL from a catheterized specimen in association with a positive urinalysis[15-17]. Bacterial meningitis was defined as either the isolation of a bacterial pathogen from the CSF or, in patients who received antibiotics prior to evaluation, the combination of CSF pleocytosis and bacteria detectable on Gram stain of the CSF. Bacteremia was defined as isolation of a known bacterial pathogen (excluding commensal skin flora) from blood culture. Bacteremia in isolation was defined as bacteremia in the absence of meningitis or urinary tract infection.

Enterovirus season was defined as June 1 through October 31 of each year.

Data Analysis

Data were analyzed using STATA version 11.0 (Stata Corp., College Station, TX). Continuous variables were described using median and intraquartile range (IQR) or range values and compared using the Wilcoxon rank sum test. Categorical variables were described using counts and frequencies and were compared using the Chi-square test or Fisher exact test. An odds ratio (OR) and 95% confidence interval (CI) were calculated to evaluate the strength of any association, as well as the precision of the estimate of effect. Stratified analyses were conducted to elucidate where confounding and effect modification were likely to exist. Multivariate logistic regression was used to identify factors independently associated with the performance of CSF HSV PCR testing in our study population. The initial multivariate model included CSF white blood cell counts, and performance of enterovirus PCR based on our *a priori* hypotheses. Variables were subsequently considered for inclusion in the multivariate model if they were associated with CSF HSV testing on bivariable analysis ($P \leq 0.20$). These variables remained in the final multivariate model if they were statistically significant after adjusting for other covariates or if their inclusion in the model resulted in a 15% or greater change in the effect size of any known confounders. Statistical significance was determined a priori as a two-tailed P-value <0.05. All analyses were clustered by season.

Existing HSV CNS infection testing paradigms were then applied to the current study population to determine their impact on testing frequency and sensitivity in this cohort. Per Caviness et al[11], the effect of testing all febrile neonates in the study cohort with pleocytosis (and not testing the remaining febrile neonates without pleocytosis unless otherwise specifically indicated) was determined, assuming HSV PCR results were available within 3 days of testing. In addition, per Tang et al[12], the effect of eliminating testing of neonates in the study cohort with normal CSF WBC and protein was determined.

RESULTS

Of the 570 neonates from 0-28 days of age (median age 14 days, IQR 7-22) who received lumbar puncture in the ED, 3 neonates (0.5%) ranging from 6 to 19 days of age were diagnosed with HSV CNS infection by CSF HSV PCR. Of these 3 neonates, 1 was hypothermic without CSF pleocytosis, and the other 2 were normothermic with CSF pleocytosis. None had rash or evidence of CNS hemorrhage. Clinical characteristics of these 3 neonates are presented in detail in Appendix B. HSV CNS infection was not subsequently diagnosed in any neonate who tested negative or who did not undergo initial CSF HSV PCR testing in the ED. The prevalence proportions of HSV and serious bacterial infections for the entire study population are shown in Table 1.

CSF HSV PCR was performed in 266 (47%) of the 570 neonates. HSV infection was diagnosed in 3 (1.1%) of the neonates tested for HSV. Neonates tested for HSV (median, 9 days; IQR: 4-16 days) were younger than neonates not tested (median, 19 days; IQR 13-25 days, $p < 0.001$, Wilcoxon rank sum test). CSF HSV PCR testing was more common with concurrent enterovirus testing; 136 (51%) of the 266 neonates who underwent CSF HSV

PCR also had CSF enterovirus PCR performed, while only 58 (19%) of the 304 neonates not tested for HSV CNS infection had CSF enterovirus PCR performed ($p < 0.001$). Vesicular rash was uncommon in both tested and not tested groups. Other demographic and clinical characteristics of all patients tested and not tested are shown in Table 2. CSF pleocytosis was present in 32% of neonates with CSF RBC >500/mm^3 and in 9% of those with CSF RBC≤500/mm^3. CSF WBC counts were not available in 10%.

The results of bivariate analysis are presented in Appendix C. In multivariate analysis, CSF HSV PCR testing was independently associated with transport from an outside hospital, concurrent enterovirus testing, hypothermia, seizures, tachypnea, hypotension, and vesicular rash (Table 3). Testing was not associated with CSF mononuclear pleocytosis or method of delivery.

Application of the testing strategy proposed by Caviness et al[11] to empirically test and treat febrile neonates only if they had pleocytosis would have reduced testing by 57 neonates: a 17% reduction in that febrile subpopulation, and an 10% reduction in the total population of this study. This single intervention would have resulted in a 21% reduction in testing (from 47% to 37% of the total cohort that received LP) without missing any cases of CNS HSV. Application of the testing strategy proposed by Tang et al [12] to eliminate testing for samples with normal CSF protein and without pleocytosis would have reduced testing by 154 neonates: a 27% reduction in the total population of this study. This intervention would have resulted in a 58% reduction in testing (from 47% to 20% of the total cohort that received LP), but it would have missed one case of neonatal HSV CNS infection.

DISCUSSION

HSV CNS infection was uncommon in this study, with a prevalence of just 0.5%, compared with 1.6% for bacterial meningitis, and 8.4% for any serious bacterial infection. CSF HSV PCR testing, however, was commonly performed in the absence of known risk factors (CSF pleocytosis or vaginal delivery) or clinical features suggestive of HSV CNS infection. Implementing a testing strategy based on fever and the presence of CSF pleocytosis[11] would have decreased testing from 47% of the total cohort to 37%, or a relative decrease of 21% without missing any cases of neonatal HSV.

The prevalence of bacterial meningitis (and therefore any serious bacterial infection) in this study is higher (Table 1) than a previous report by Caviness et al [8], which considered all neonates ≤28 days of age hospitalized from the ED at Texas Children's Hospital. They found bacterial meningitis (classified as positive CSF bacterial culture and confirmed by review of medical records) in 0.4% compared with HSV CNS infection in 0.2%. In both studies, however, the confidence intervals overlap between the HSV CNS infection and bacterial meningitis groups, and the confidence interval for HSV CNS infection prevalence in the present study does include the 0.2% prevalence of HSV CNS infection found by Caviness et al. If, instead, we compared febrile neonates with a mononuclear pleocytosis, our study showed no cases of either bacterial meningitis or HSV CNS infection. In contrast, Caviness et al reported a higher prevalence of HSV infection (1.6%) compared to bacterial meningitis (0.8%) in this subgroup. One explanation for this difference may be that the

prevalence of HSV infection depends heavily on the underlying source population [18, 19]. In both studies the population of neonates examined was limited to those presenting to the ED from home. Both thereby excluded those neonates transferred to the neonatal intensive care unit due to severe illness immediately following birth. Therefore, strategies for testing should account for HSV CNS infection prevalence in the source population and the specific medical and exposure history of the neonate.

Factors associated with testing were not consistent with commonly identified HSV risk factors. There was a peak in CSF enterovirus and HSV PCR testing in the summer months coincident with known seasonal epidemiology of enterovirus, but there is no known seasonality to HSV infection to justify this increase. In this study, mononuclear pleocytosis was not an independent risk factor for HSV CNS infection testing, and thus did not drive testing. Instead, this seasonality may be related to the fact that many physicians, especially early in their training, order multiple PCR tests simultaneously, disregarding clinical indications for individual tests[12]. This problem is magnified during the summer and fall when most cases of aseptic meningitis in young infants are caused by enterovirus rather than HSV[20]. In addition, in this study population an elevated CSF RBC count was not significantly associated with CSF HSV PCR testing. While an elevated CSF RBC may be due to a traumatic LP, this is difficult to distinguish from a CNS hemorrhage (a recognized result of HSV CNS infection[22]), based on a single cell count.

Data in this study differ from a prior study by Cohen et al [10] who examined the rationale for performing CSF HSV PCR in a case control study of 478 infants from birth to 90 days of age who underwent concurrent enterovirus PCR testing during enterovirus season. This prior study was limited both by absence of data on HSV prevalence and the population restriction of those infants undergoing concurrent enterovirus PCR. Here, we were able to show a significant association with enterovirus testing. Davis et al [21], in a matched case control study of 171 infants less than 60 days of age who received an LP in the ED throughout the year, also found an association of increased use of CSF HSV PCR with enterovirus PCR testing and lack of association with mononuclear pleocytosis. However that study was limited by small sample size and also by absence of data on HSV prevalence.

Because CSF HSV PCR tests are positive in fewer than 2% of infants and are associated with a significantly longer length of stay and higher hospital charges per infant[23], why are so many tests ordered? Most hypothesize this is related to concern about delayed diagnosis and treatment, which may lead to worse outcomes. This practice is compounded by the lack of a national consensus or practice parameter to significantly help guide testing[23]. Few prior studies have examined this question. The American Academy of Pediatrics recommends CNS HSV infection be considered with vesicular rash, or if fever, irritability, and abnormal CSF findings are present, especially with concurrent seizure activity or during the time of year when enterovirus is not endemic [24]. However, we would have missed all 3 cases of HSV CNS infection in our study if we had followed these criteria, as none of them presented with fever. If we instead considered the Caviness et al[11] subpopulation of febrile neonates in our study and followed their model to empirically test only those with CSF pleocytosis, we would have reduced testing by 57 neonates, resulting in a 21% reduction in testing without missing any cases of HSV CNS infection. However this criteria does not help guide us for

afebrile or hypothermic neonates. If we had used the Tang model we would have missed 1 case of HSV CNS infection, though this model was not developed specifically for neonates.

Of the three neonates in our study that tested positive for HSV CNS infection, none were febrile. Two of the three had seizures and CSF pleocytosis, and the third presented with unexplained lethargy. Therefore, all three had clinical and/or laboratory features concerning for HSV infection: two with isolated CNS disease, and one with disseminated disease with concomitant CNS involvement. While experts differ in their recommendations about routine testing[25-27], most agree that clinical findings be incorporated into the decision to test and treat infants for CNS HSV outside of a reflex protocol, however this is a difficult concept to concretely put into a formal guideline.

There were several limitations to our study. First, as with any retrospective study, there may have been undocumented factors that contributed to the decision to perform CSF HSV PCR. Second, it is unclear from our data if CSF cell counts and differentials were available when the decision to perform CSF HSV PCR was made. If not, it is understandable why CSF mononuclear pleocytosis was not an associated factor with testing. However, this raises the larger question of whether clinicians are making the decision to order CSF HSV PCR in a logical timeline with available data, or if the decision is made at the same time they decide to perform lumbar puncture. Third, we did not have data regarding possible maternal primary or latent infection during pregnancy. While it is possible that lack of such information by the treating clinicians contributed to the decision to send a CSF HSV PCR, the lack of this data is conceptually unlikely to confound the other objective variables examined in this study. Fourth, only 62 neonates in this study had fever and CSF pleocytosis, limiting the power to detect HSV infection in that population. In addition, only 3 infants had positive CSF HSV PCR tests. While a larger population would have been ideal, HSV CNS disease is not common. In a discussion of testing practices in the ED with applicability in to an individual patient, these data remain informative and should instigate further discussion. Finally, given differences in HSV CNS infection prevalence depending on different source populations, this data may not be completely generalizable to all tertiary care pediatric hospitals. However, the discussion these findings raise should be applicable in any setting.

In summary, CSF HSV PCR testing of neonates in the emergency department is common, while HSV infection is not. In fact, HSV prevalence in this study population is lower both independently and with respect to bacterial meningitis than prior studies. In this study, the decision to send CSF HSV PCR testing was not associated with known risk factors, likely resulting in unnecessary hospital stays and cost. The decision to order HSV PCR is not simple or straightforward and therefore requires a nuanced approach, incorporating community prevalence of HSV infection, known neonatal risk factors including CSF pleocytosis and probably hypothermia, and clinical judgment based on the individual neonate.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Prevalence proportions of herpes simplex virus and serious bacterial infections by temperature and cerebrospinal fluid findings

Characteristic	N (% of total)	HSV % (95% CI)	Serious Bacterial Infection			
			Any SBI % (95% CI)	Meningitis % (95% CI)	UTI % (95% CI)	Bacteremia[a] % (95% CI)
All	570	0.5 (0-1.1)	8.4 (6.1-10.7)	1.6 (0.6-2.6)	5.1 (3.3-6.9)	1.8 (0.8-3.2)
Temperature						
<36.5° C	41 (7)	2.4 (0-7.4)	4.9 (0-11.8)	0 (0-8.6)	4.9 (0-11.8)	0 (0-8.6)
36.5-37.9° C	194 (34)	1.0 (0-2.5)	5.2 (2.0-8.3)	1.0 (0-2.5)	2.6 (0.3-4.8)	1.5 (0.3-4.5)
>38.0° C	335 (59)	0 (0-1.1)	10.7 (7.4-14.1)	2.1 (0.6-3.6)	6.6 (3.9-9.2)	2.1 (0.8-4.3)
CSF Pleocytosis						
No	421 (74)	0.2 (0-0.7)	7.8 (5.3-10.4)	1.2 (0.1-2.2)	4.8 (2.7-6.8)	1.9 (0.8-3.7)
Yes	91 (16)	2.2 (0-5.3)	6.6 (1.4-11.8)	3.3 (0-7.0)	3.3 (0-7.0)	0 (0-4.0)
≤50% monos	42 (7)	0 (0-8.4)	9.5 (0.3-18.8)	7.1 (0-15.3)	2.4 (0-7.2)	0 (0-8.4)
>50% monos	49 (9)	4.1 (0-9.8)	4.1 (0-9.8)	0 (0-7.3)	4.1 (0-9.8)	0 (0-7.3)
Variable Combinations						
Fever and CSF Pleocytosis	62 (11)	0 (0-5.8)	8.1 (1.1-15.0)	3.2 (0-7.7)	4.8 (0-10.3)	3.2 (0.4-11.2)
Fever, CSF Pleocytosis and >50% monos	35 (6)	0 (0-10.0)	5.7 (0-13.8)	0 (0-10.0)	5.7 (0-13.8)	0 (0-10.0)

N = number, HSV = herpes simplex virus, SBI = serious bacterial infection, UTI = urinary tract infection, CI = confidence interval, monos = mononuclear cells, CSF = cerebrospinal fluid.

[a] refers to bacteremia occurring in the absence of concomitant bacterial meningitis or urinary tract infection. There were no infants with both meningitis and a urinary tract infection.

Table 2

Characteristics of infants receiving lumbar puncture in the Emergency Department).

	All (% of total infants in study) N=570	Tested (% of infants tested) N=266[a]	Not Tested (% of infants not tested) N=304	P value
Demographic Characteristics				
Male sex	319 (56)	153 (58)	166 (55)	0.485
Black race	249 (44)	97 (36)	152 (50)	0.001
Preterm[b]	82 (14)	37 (14)	45 (15)	0.762
Transport from OSH	111 (19)	92 (35)	19 (6)	<0.001
Age				<0.001
0-7 days	148 (26)	110 (41)	38 (13)	
8-15 days	139 (24)	78 (29)	61 (20)	
16-21 days	132 (23)	46 (17)	86 (28)	
22-28 days	151 (26)	32 (12)	119 (39)	
Historical Characteristics				
Cesarean delivery	173 (30)	81 (30)	92 (30)	0.961
LP during enterovirus season	284 (50)	149 (56)	135 (44)	0.006
Enterovirus PCR sent	194 (34)	136 (51)	58 (19)	<0.001
Clinical Characteristics				
Temperature				<0.001
Hypothermic	41 (7)	27 (10)	14 (5)	
Normothermic	194 (34)	117 (44)	77 (25)	
Fever	335 (59)	122 (46)	213 (70)	
Lethargy	104 (18)	38 (14)	66 (22)	0.022
CSF pleocytosis				
No	421 (74)	173 (65)	248 (82)	<0.001
Yes	91 (16)	61 (23)	30 (10)	
Yes without mononuclear predominance	42 (7)	30 (11)	12 (4)	<0.001
Yes with mononuclear predominance	49 (9)	31 (12)	18 (6)	
CSF RBC > 500/mm^3 [c]	200 (39)	110 (47)	90 (32)	0.001
Seizures	73 (13)	66 (25)	7 (2)	<0.001
Tachypnea[d]	28 (5)	20 (8)	8 (3)	0.007
Vesicular Rash	12 (2)	11 (4)	1 (0)	0.010
Hypotension[e]	34 (6)	28 (11)	6 (2)	<0.001
Hypoxia	30 (5)	18 (7)	12 (4)	0.113

OSH = Outside hospital

[a] Percentages within columns may not add up to 100% due to rounding.

[b] Prematurity defined as gestational age <37 weeks.

[c] CSF RBC data not available for 57 patients

[d] Tachypnea defined as a respiratory rate greater than 70 breaths per minute[28].

[e] Hypotension defined as a systolic blood pressure less than 63 mmHg based on the 5th percentile values published for this age group[29].

Table 3

Multivariate analysis of factors associated with herpes simplex virus testing.

	Adjusted Odds Ratio	95% Confidence Interval	p-value
All patients			
Transport from OSH	3.91	3.09-4.95	<0.001
Cesarean delivery	0.79	0.60-1.05	0.110
Enterovirus PCR sent	7.27	5.30-9.98	<0.001
Temperature			
Normothermic	Reference		
Hypothermia	1.46	1.17-1.83	0.001
Fever	0.48	0.23-0.99	0.048
CSF pleocytosis			
No	Reference		
Yes without mononuclear predominance	3.03	1.98-4.63	<0.001
Yes with mononuclear predominance	2.63	0.31-22.17	0.375
CSF RBC > 500/mm^3	1.60	0.99-2.61	0.057
Seizure	13.75	5.60-33.76	<0.001
Tachypnea	3.67	2.32-5.80	<0.001
Rash			
No Rash	Reference		
Vesicular Rash	18.70	1.28-273.68	0.032
Non-vesicular Rash	1.12	0.76-1.64	0.568
Hypotension	6.89	5.68-8.37	<0.001