Initial Presentation of Neonatal Herpes Simplex Virus Infection

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Objective To inform the decision to test and empirically treat for herpes simplex virus (HSV) by describing the initial clinical presentation and laboratory findings of infants with a confirmed diagnosis of neonatal HSV.

Study design This is a retrospective case series performed at 2 pediatric tertiary care centers. Infants who developed symptoms prior to 42 days of age with laboratory confirmed HSV from 2002 through 2012 were included. We excluded infants <34 weeks gestation, those who developed illness before discharge from their birth hospital, and those who developed symptoms after 42 days of age.

Results We identified 49 infants with HSV meeting these criteria. Most infants (43/49, 88%) came to medical attention at ≤28 days. Of 49 infants, 22 (45%) had disseminated, 16 (33%) central nervous system, and 10 (20%) skin, eye, mouth HSV disease. Eight infants (16%) had nonspecific presentations without the classic signs of seizure, vesicular rash, or critical illness (intensive care admission). All infants with nonspecific presentation were ≤14 days, had cerebrospinal fluid pleocytosis, or both.

Conclusions The majority of infants with HSV (84%) presented with seizure, vesicular rash, or critical illness. A subset of patients (16%) lacked classic signs at hospitalization; most manifested signs suggestive of HSV within 24 hours. Further studies are needed to validate the risk factors identified in this study including age <14 days and cerebrospinal fluid pleocytosis at presentation. *(J Pediatr 2016;172:121-6)*.

Neonatal herpes simplex virus (HSV) is an uncommon but potentially devastating infection that is classically defined as HSV infection in infants less than 42 days of age.[1-7] The incidence of neonatal HSV was 9.6 per 100 000 births in 2006,[8] and annual prevalence has been estimated at 1500 cases.[9] Several previous studies have demonstrated that neonates with HSV infection may not have classic symptoms of seizures or mucocutaneous vesicular lesions, and that some can come to medical attention with nonspecific symptoms including fever, poor feeding, or decreased activity.[6,10-12] Various strategies have been proposed to determine which neonates require HSV evaluation and empiric acyclovir therapy, with some experts testing all febrile infants younger than 21 days,[6] and others limiting testing to those with the more classic signs such as seizures or mucocutaneous lesions.[13] Delay in acyclovir initiation results in worse outcomes in neonatal HSV,[14-18] therefore, acyclovir should be initiated as soon as HSV is suspected. However, HSV testing has been increasing in infants 30-60 days of age,[19] and testing for HSV can prolong hospital stay in infants ultimately shown not to have HSV.[20] Validated risk stratification tools are needed to help clinicians determine which neonates without classic signs of HSV need HSV testing and empiric treatment with acyclovir.

The purpose of our study was to describe the clinical and laboratory presentation of patients with neonatal HSV at their initial medical evaluation. In addition, we sought to describe infants with HSV lacking classic signs of the disease.

Methods

We conducted a retrospective case series study at 2 large pediatric tertiary care hospitals: St. Louis Children's Hospital (SLCH) in St. Louis, Missouri and Primary Children's Hospital (PCH) in Salt Lake City, Utah. SLCH is a 300-bed hospital with approximately 50 000 emergency department visits per year. PCH is a 289-bed hospital, with approximately 40 000 emergency department visits per year. HSV testing was performed in-house at both institutions, but HSV

ALT	Alanine aminotransferase
CNS	Central nervous system
CSF	Cerebrospinal fluid
HSV	Herpes simplex virus
PCR	Polymerase chain reaction
PCH	Primary Children's Hospital
SEM	Skin, eye, mouth
SLCH	St. Louis Children's Hospital

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typing was not routinely performed. At PCH, a guideline for evaluation of the febrile infant was present during the entire study period which recommended testing and treatment for HSV for certain infants less than 42 days of age. At SLCH, no HSV-related clinical pathway existed during the study period. The institutional review boards of Washington University in St. Louis School of Medicine and the University of Utah and Intermountain Healthcare (Salt Lake City, Utah) approved this study and granted waiver of informed consent.

We identified all infants ≤60 days of age with documented HSV infection between January 1, 2002 and December 31, 2012. This age window was chosen to capture infants whose symptoms began before 42 days of age but presented for evaluation at some point between 42 and 60 days of age.

At SLCH, the virology laboratory database was queried for positive HSV polymerase chain reaction (PCR) or viral culture, and the hospital's internal data warehouse was queried for HSV-related International Classification of Diseases, Ninth Revision codes. At PCH, the Intermountain Healthcare Enterprise Data Warehouse was queried for infants with a positive HSV PCR or culture. No autopsy data were reviewed. We collected demographic features and reviewed the clinical history, vital signs, physical examination, and laboratory findings at presentation, as well as the subsequent hospital course. To estimate the incidence of HSV disease in hospitalized infants, we also obtained hospital registration data on the total number of infants ≤60 days who were admitted after discharge from a birth hospital to both centers during the study.

At PCH, febrile infants 1-90 days of age have been identified in the electronic health record since 2004, and a large cohort is available for analysis.[21] We used this cohort of febrile infants to provide context for infants with HSV, many of whom also present with fever. We calculated the proportion of infants with HSV of all febrile infants ≤14 days or <60 days of age who were evaluated at PCH with and without cerebrospinal fluid (CSF) pleocytosis.

Inclusion and Exclusion Criteria

Study population included infants whose symptoms began prior to 42 days of age and presented to the hospital in the first 60 days of life who had a positive HSV PCR test or viral culture from skin, conjunctiva, mouth, blood, or CSF. Infants had to be discharged from a birth hospital and later admitted to be included. Infants were excluded from analysis if their initial presentation was at an outside hospital and the medical records describing this presentation were not available. Consistent with our primary objective to describe the initial clinical presentation of otherwise healthy patients with neonatal HSV, we excluded subjects born before 34 weeks gestation, those previously diagnosed with HSV, and those with a significant comorbid medical condition that could affect the clinical presentation.

Definitions

We defined initial presentation as the first health care encounter after HSV-related symptoms began. When referring to "symptom onset," we are indicating the age at which the patient's symptoms began prior to presentation to the hospital. If laboratory tests were repeated in the first 24 hours, the first value was used. Two study authors categorized each subject and discordant classifications were adjudicated by all authors and resolved by consensus.

Certain signs should prompt clinicians to consider HSV in a neonate, such as mucocutaneous lesions, seizures, or critical illness.[6,7] We defined nonspecific presentation as fever, poor feeding, or decreased activity in the absence of mucocutaneous lesions, seizures, or critical illness. All patients who were admitted to an intensive care unit were defined as critically ill.

Based on overall clinical course, we classified patients to 3 common HSV groupings.[22]

Group 1: Disseminated Disease. Disseminated disease is characterized by end organ involvement defined by hepatitis (alanine aminotransferase [ALT] ≥×1.5 normal),[23] HSV pneumonitis (severe respiratory distress or failure with radiographic evidence of opacities in the setting of HSV disease), or disseminated intravascular coagulation (defined as decreased platelets and clotting factors as evidenced by platelets <150 000/μL or prothrombin time, international normalized ratio, or partial thromboplastin time above normal range). The presence of a positive blood HSV PCR alone was not sufficient to define disseminated disease. Patients classified with disseminated disease may also meet criteria for central nervous system (CNS) and/or skin, eye, mouth (SEM) disease.

Group 2: CNS Disease. Patients with CNS disease have either (1) positive HSV CSF PCR or viral culture, with or without CSF or neurologic abnormalities; or (2) positive HSV PCR of blood or skin lesion accompanied by neurologic abnormality and CSF pleocytosis. CSF pleocytosis was defined as ≥18 white blood cells/mm^3 in the 1- to 28-day age group and ≥9 white blood cells/mm^3 in the 29- to 60-day age group.[24] Neurologic abnormalities included clinical findings of hypotonia, seizures, abnormal neuroimaging, or electroencephalograms. Patients classified with CNS disease may also meet criteria for SEM disease.

Group 3: SEM Disease. SEM disease is characterized by PCR or viral culture positive for HSV from the skin, conjunctiva, and/or mouth, with or without a positive blood HSV PCR, and no evidence of other end organ involvement.

Outcomes and Statistical Analyses

Descriptive statistics were used to determine the proportion of subjects with specific clinical and laboratory findings. Continuous data were described using medians and IQRs for non-normally distributed data. Categorical data are reported as proportions and CIs. χ^2 analyses were performed using JMP Pro 10 (SAS Institute, Cary, North Carolina).