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A Report of Three Cases and Review of Intrauterine Herpes Simplex Virus Infection

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Abstract

Background—Intrauterine herpes simplex virus (HSV) infection often is omitted from descriptions of neonatal HSV disease. Previous characterizations of intrauterine HSV infection limit manifestations to the triad of cutaneous, central nervous system (CNS), and ophthalmologic findings. We report 3 cases of intrauterine HSV infection and provide a contemporary literature review of this disease.

Methods—Cases published between 1963 and January 2009 were identified. Selected cases fit the clinical description of intrauterine HSV infection, had manifestations present at birth, and had virologic confirmation of infection.

Results—This review yielded 64 cases, 3 of which were our own, of intrauterine HSV infection. Less than one-third fit the typical triad. Of the patients with cutaneous findings at birth, 24 (44%) had manifestations other than vesicles or bullae. Confirmation of HSV infection by culture of cutaneous lesions present at birth was delayed beyond 72 hours after birth in 15 patients and occurred at a median of 10 days of age. Nine of these patients had lesions at birth that were neither vesicles nor bullae, and 14 cases were confirmed by culture of new vesicles.

Conclusions—More than two-thirds of reported cases do not present with the typical triad. Cutaneous findings are not limited to vesicles or bullae. A high index of suspicion and recognition of varied cutaneous manifestations is necessary to diagnose infants with intrauterine HSV infection.

Keywords

herpes simplex virus; newborn; infection; congenital abnormalities/anomalies

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Herpes simplex virus (HSV) infection of the newborn can be acquired in utero, intrapartum, or postnatally. Intrapartum infection accounts for 86% of neonatal HSV cases.[1] The National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group suggests that intrauterine transmission represents 4% to 5% of neonatal HSV disease.[2,3]

Prospective data suggest the incidence of neonatal HSV disease to be 1 case in 3200 deliveries, though ranges for incidence span from 1 in 1400 to 1 in 30,000 deliveries.[4] Assuming an incidence of 1 in 5000 deliveries and that intrauterine disease accounts for 5% of all neonatal cases, then intrauterine infection occurs in 1 in 100,000 deliveries. Despite this low incidence, intrauterine HSV infection is important because it can have potentially catastrophic consequences such as death or severe neurodevelopmental disability. The objectives of this study are to report 3 cases of intrauterine HSV infection and to provide a contemporary literature review of this disease.

CASE REPORTS

Case 1

A 34 1/7-week African-American female was born to a 19-year-old primigravida mother by cesarean section due to fetal decelerations. The mother was hospitalized for 8 weeks before delivery because of preterm labor. Hydrocephalus was noted on fetal ultrasound. She had negative prenatal laboratory studies for syphilis, human immunodeficiency virus, hepatitis B, and gonorrhea. She was rubella immune. Early in the second trimester, she had a flu-like illness that resolved after 5 days. The following month, she had “bumps” on her genitalia. No cause for these lesions was found, and they resolved without treatment.

The infant was born limp and apneic with Apgars of 1, 6, and 8 at 1, 5, and 10 minutes, respectively, and was intubated. Physical examination revealed a microcephalic infant with multiple hypopigmented scaling and crusted erosions on the trunk and extremities ranging in size from ½ cm to several centimeters long (Fig., Supplemental Digital Content 1, http://links.lww.com/INF/A590). Both the palms and soles had vesicles several millimeters in size that resolved within 24 hours. The liver was palpable 2 to 3 cm below the costal margin.

Initial white blood cell count (WBC) was 9600/mm^3 with 20% neutrophils, 62% lymphocytes, 10% monocytes, and 6% atypical lymphocytes. Liver function tests and serum electrolyte evaluations were normal. The cerebrospinal fluid (CSF) contained 5 WBC/mm^3, 6000 red blood cells (RBC)/mm^3, protein 189 mg/dL, and glucose 37 mg/dL. No organisms were seen on Gram stained smear. CSF was sent for bacterial culture, viral culture and polymerase chain reaction (PCR) testing for HSV. Viral cultures of vesicles were not obtained. A blood culture was obtained, and therapy with ampicillin, gentamicin, and acyclovir was initiated.

Further laboratory evaluations consisted of a nonreactive serum RPR, negative cytomegalovirus IgM, negative HSV IgM, and negative varicella virus IgM. Toxoplasma and lymphocytic choriomeningitis virus serologies also were negative.

A chest radiograph demonstrated no abnormalities. A computerized tomographic (CT) scan of the brain revealed microcephaly, ventricular enlargement, and diffuse porencephalic changes. Intracranial calcifications were noted adjacent to the third ventricle bilaterally. Ophthalmologic examination revealed chorioretinitis and optic atrophy.

The infant was extubated 48 hours after delivery and remained stable. Intravenous acyclovir was discontinued on day 10 when the CSF HSV PCR was negative. Ten days after stopping

acyclovir, new vesicles several millimeters in size appeared on the hands, feet, fingers, and toes. Direct fluorescence antibody testing of tissue from the base of the lesions for HSV was negative, and a Tzanck smear failed to identify multinucleated giant cells. Culture of the vesicular material was obtained and grew HSV type 1 within 24 to 48 hours. Therapy with acyclovir was resumed to complete an additional 14-day course. Repeat CSF analysis was unremarkable, including HSV CSF PCR.

Case 2

A 36-week, 2305-g Latin-American male was born to a 31-year-old primigravida mother by vaginal delivery. The labor was induced because of pregnancy-induced hypertension of 3 weeks' duration. Otherwise, the maternal history and laboratory studies were unremarkable. Prenatal ultrasound 2 days before delivery was normal.

Rupture of membranes occurred 6½ hours before delivery with clear amniotic fluid. Apgar scores were 9 and 9 at 1 and 5 minutes, respectively. Physical examination revealed vesicles measuring 2 to 4 mm in size over the left lower quadrant of the abdomen and on the fourth and fifth digits of the left hand. No oral or mucous membrane lesions were identified. The remainder of the infant's examination and gross inspection of the placenta were normal.

The immediate neonatal course was complicated by multiple episodes of apnea and hypoglycemia. A sepsis evaluation was performed. The leukocyte count was 12,500/mm^3 with 44% neutrophils, 54% lymphocytes, and 2% monocytes. There were no other hematologic or electrolyte abnormalities. CSF analysis revealed 51 WBC/mm^3, 69 RBC/mm^3, protein 59 mg/dL, glucose 63 mg/dL. No organisms were seen on Gram stain, and the CSF VDRL test was nonreactive. The infant received empiric ampicillin, gentamicin, vancomycin, and acyclovir therapy. Antiviral ophthalmic solution was initiated for prophylaxis. Bacterial cultures of the skin lesions, blood, and CSF were negative. Tzanck smear from a vesicle was negative.

Five days after delivery, viral eye cultures obtained at birth grew HSV type 2. Ophthalmologic examination identified an anterior stromal infiltrate and an epithelial defect consistent with herpetic keratitis. CT scan of the brain demonstrated a hemorrhagic infarct in the right cerebral hemisphere. The vesicles crusted and resolved without scarring. A repeat lumbar puncture performed following 21 days of acyclovir therapy was unremarkable.

Case 3

A 32-week, 1600-g white female was born to a healthy 28-year-old gravida 2 para 1 female with an unremarkable prenatal history until 3 days before delivery when she was admitted for preterm labor. Ultrasound examination revealed severe hydrocephalus with presumed Dandy-Walker malformation and agenesis of the corpus callosum.

Artificial rupture of membranes occurred 2½ hours before delivery and revealed clear amniotic fluid. Apgar scores were 7 and 9 at 1 and 5 minutes, respectively. Physical examination revealed bulging fontanelles with split cranial sutures, generalized hypotonia, and missing or incomplete primitive reflexes. No skin lesions were present.

Initial laboratory evaluation showed 16,210 WBC/mm^3 with 50% neutrophils, 34% lymphocytes, and 14% monocytes. Serum electrolytes and transaminases were normal. CSF analysis revealed 178 WBC/mm^3 with 25% neutrophils and 75% mononuclear cells, 790 RBC/mm^3, protein 1458 mg/dL, and glucose of 20 mg/dL. No organisms were observed on Gram stain.

Transcranial ultrasound of the head showed hydrocephalus ex vacuo and extreme bilateral encephalomalacia and CT of the brain revealed absent cerebellar hemispheres and hypoplastic cerebral hemispheres. Curvilinear calcifications were identified on skull films and skeletal radiographs demonstrated a uniform pat tern of diminished mineralization in the metaphyses of the long bones. Severe bilateral chorioretinitis with vitreal hemorrhages was noted on ophthalmologic examination.

On the second day after birth, multiple erythematous erosions were noted on trunk and buttocks, and vesicles appeared on the hands and feet. A Tzanck smear showed multinucleated giant cells, and viral culture of the vesicular material grew HSV type 2. Acyclovir was initiated on the third day after birth, and antiviral ophthalmic solution was added. Vesicles continued to appear on the hands, feet, genitalia and buttocks over the next several days. Because of the severity of the central nervous system abnormalities, the mother directed the physicians to withhold aggressive medical therapy and the infant expired on the 10th day after birth.

MATERIALS AND METHODS

We conducted a Medline bibliographic database search of cases from 1963 (first case in reviewed literature) through January 2009 using the following keywords: newborn, neonatal, intrauterine, congenital, prenatal, and herpes simplex virus. The search was limited to the English language and human references. Each reference was reviewed for single case reports and case series. Reference lists from relevant articles were used to identify additional cases.

Criteria for Inclusion of Cases

There were 3 diagnostic criteria necessary for inclusion:

1. Clinical manifestations consistent with previously described intrauterine HSV cases.[5] In the absence of cutaneous disease, involvement of at least 2 of the following organs or organ systems: (1) central nervous system (CNS), (2) eyes, and (3) viscera. Involvement of viscera, which includes adrenal glands, liver, and lungs, refers to hepatomegaly, transaminitis, organ necrosis, and calcifications.
2. Involvement of at least 1 organ system (skin, CNS, eyes, or viscera) at birth.
3. HSV infection confirmed through identification of virus in culture, immunohistochemistry, or PCR.

Due to limited reporting of exclusion of other congenital infections, this was not included in the criteria.

Database Development

Microsoft Office Excel 2003 for Windows was used to develop a database of categorical variables. The variables included year the case was published, the principal author of publication, birth weight, gestational age of infant, herpes simplex serotype, means of diagnosis and timing of specimen collection, clinical manifestations, time of rupture of membranes, method of delivery, history of maternal or paternal HSV disease and antiviral therapy, and outcome.

RESULTS

Sixty-four cases met the study inclusion criteria (Table, Supplemental Digital Content 2, http://links.lww.com/INF/A591). Three cases seen by the authors and not previously

published were included in the analysis. Nine cases were excluded due to failure to meet study inclusion criteria.

Clinical Manifestations

Cutaneous lesions were the most common clinical manifestation (Table 1). The triad of cutaneous, CNS, and ophthalmologic disease occurred in 19 (30%) cases. Cutaneous and CNS manifestations without ophthalmologic disease occurred in 22 (34%) infants while cutaneous and ophthalmologic disease without CNS involvement was uncommon (6 [9%] cases). Isolated cutaneous manifestations occurred in 14 (22%) cases. Two (3%) infants had CNS disease alone.[6,7]

Of the 61 cases with cutaneous manifestations, 55 had lesions present at birth or within 12 hours of life. Vesiculobullous lesions were the most common initial skin finding (Table 1). Three of 10 cases with erosions and 4 of 6 with erythematous macules and plaques at initial presentation progressed to form vesicles or pustules.[8–13] Three had scalp ulcerations clinically consistent with cutis aplasia.[9,14,15] Four infants had absence of the nail plate of several digits.[11,16–18]

Forty-three (67%) patients had CNS manifestations of intrauterine HSV infection (Table 1), of which 29 had more than 1 neurologic finding. Twenty-five (39%) patients had ocular findings, 18 of which had retinal disease. There were 4 cases of microphthalmia and cataracts, respectively. Two patients had keratitis and 1 had conjunctivitis. Visceral involvement occurred in about one-third of patients. Findings included hepatomegaly, elevated transaminases, or postmortem examination revealing necrosis of the liver, adrenals, or lungs. Liver disease occurred in 18 of 23 visceral cases. Dystrophic calcification was found in the brain, adrenals, and liver on postmortem examinations. One patient had diffuse hepatic calcifications that were detected on plain radiography[19] while another had cutaneous calcinosis.[20]

Limb and bone anomalies also were observed. Five infants had lucencies and irregularities near the metaphyses of long bones, principally the femur.[19–22] One infant had a hypoplastic leg with osseous changes[23] and 2 had truncated digits.[11,16] Synechiae in the popliteal and inguinal regions occurred in 2 patients.[15,23]

Diagnosis

Culture grew HSV in 54 (84%) cases; 4 specimens were obtained postmortem and 7 cases did not report the timing of the culture. Nine were obtained from sites other than skin, including the eye, blood, urine, CSF, and various organs on postmortem examination. HSV 2 was isolated from 36 infants and HSV 1 from 10.

Viral growth was delayed beyond the first few days after birth in 15 patients (Table, Supplemental Digital Content 3, http://links.lww.com/INF/A592). All cases had skin lesions at birth but required recurrence of vesicles for isolation of virus in culture. Six of these patients had cultures obtained on at least 1 other occasion that failed to grow HSV (false negatives). In one case, culture and electron microscopy from vesicles were negative on day of life 1, 13, and 16 but grew on day 29.[24] Three cases were biopsy and culture negative on day of life 1 but cultures grew on days 4, 10, and 16, respectively.[10,29] Another 2 cases had confirmation of herpes infection through histopathology on days 2 and 5, respectively, but virus was not isolated in culture until days 10 and 120, respectively.[12,26] In these cases, culture confirmation occurred at a median of 10 days (range, 4 days to 14 months).

Diagnosis of intrauterine HSV infection was made using PCR alone, immunohistochemistry alone, and immunohistochemistry and PCR in 3, 3, and 4 patients, respectively. Fifteen

cases had multinucleated giant cells and 19 had intranuclear inclusions, most of which were seen at autopsy.

Maternal and Birth History

Vesicles, some culture-confirmed as HSV, occurred in 23 (36%) mothers during pregnancy. All had genital or oral lesions except one with a vesicular eruption on the knee.[27] Two other mothers had a history of herpetic lesions before pregnancy. Nonspecific illnesses without a vesicular eruption including fever, vaginal discharge, and dysuria occurred in 10 mothers. Partners had oral or genital lesions in 5 cases.[8,25,26,28]

Twenty-four infants were delivered by cesarean section and 21 vaginally (method of delivery not reported in 19). Intact membranes at the time of delivery occurred in 15 cases while 23 were ruptured before delivery (8 > 24 hours, 4 at 8–24 hours, and 11 < 8 hours). The timing of rupture of membranes was not reported in 26 cases.

Outcomes

Death occurred in 29 (45%) infants, including 4 cases of intrauterine demise.[7,30–32] Of the 25 nonintrauterine deaths, 20 (80%) occurred in the first month of life. One pregnancy was terminated at 27 weeks due to fetal anomalies (not included in case fatalities).[15] HSV 2 was isolated in 19 (66%) fatalities and type 1 in 2 (7%). Serotyping was not performed in 8 fatal cases. All cases (6) of hydrops were fatal; 1 was associated with intrauterine demise,[32] 4 died in the first 2 days of life,[33–36] and 1 died outside of the neonatal period.[22] Of the survivors for whom outcome was reported, 13 patients had developmental delay and 8 were well at 6 months of age.[9–11,14,24,37,38]

DISCUSSION

Some investigators have questioned the importance of intrauterine HSV disease.[26] Avgil and Ornoy[4] stated that “in utero infection by HSV bears relatively little danger for significant fetal damage ... and has weak teratogenic potential.” While not a common entity, the cases of intrauterine HSV infection reviewed in this work demonstrate HSV is clearly a teratogen.

A case definition of intrauterine HSV infection has been attempted previously. Baldwin and Whitley[3] described a case as having: (1) evidence of infection in the first 48 hours of life, (2) virologic confirmation, and (3) exclusion of other illnesses. Fagnant's[39] group asserted that a case includes: (1) evidence of an effect on embryogenesis, (2) virologically or histologically demonstrated herpetic infection within 24 hours of rupture of membranes, and (3) evidence of viral placentitis. Lastly, Monif[40] required evidence of disease within 48 hours of rupture of membranes and a lesion older than what could be accounted for by ascending infection.

Our case definition did not include exclusion of other illnesses because this information was not available in the literature. While conformation of HSV disease was a prerequisite, some patients had delayed identification of virus raising the possibility of inclusion of cases of acquired disease.

There are deficiencies in published reports of intrauterine HSV; single case reports or small case series are limited by inconsistent definitions of intrauterine disease and misclassification of intrapartum cases as intrauterine. To date, there is no extensive review of reported cases of intrauterine HSV infection.

Our review significantly expands the limited literature on the disease. The largest published series by Hutto et al[41] in 1987 described 13 infants with intrauterine HSV infection. It did

not include descriptions of individual cases, rendering it impossible to analyze within our database. However, we found similarities in cutaneous involvement (95% vs. 92%), visceral involvement (34% vs. 31%), and prematurity (64% vs. 69%), but lower rates of CNS (67% vs. 92%) and ophthalmologic (39% vs. 69%) involvement.

HSV 2 accounts for 75% of all cases of intrapartum and postnatal disease.[2] Overall[42] suggested HSV 2 may account for 90% of cases of intrauterine HSV infection. Of the 64 cases presented and reviewed in this report, 46 reported HSV serotype; 36 (78%) were HSV 2, similar to what is seen in intrapartum and postnatal HSV disease.

In our review, more deaths occurred with HSV 2. Prematurity occurred in 64% of infants compared with 40% to 50% previously reported in the literature.[2] It is unclear whether prematurity is a consequence of maternal or fetal disease.

Baldwin and Whitley[3] reported that 50% of cases of intrauterine HSV infection had CNS, cutaneous and ophthalmologic involvement. Johansson[23] reported the triad in 39% of cases, similar to our figure of 30%. We report that intrauterine infection is not limited to the typical clinical triad. Prematurity, visceral involvement, limb and bone abnormalities, altered fetal growth, hydrops, and intrauterine demise are part of the clinical spectrum of intrauterine HSV infection.

Several factors could lead to under recognition of intrauterine HSV, including variations in or absence of cutaneous disease. The expected natural progression of herpetic lesions is to evolve from vesicle to ulcer, crust and then heal. Infants with intrauterine infection have a variety of cutaneous presentations, depending on the stage of the eruption at the time of birth. Secondary skin findings such as erosions or scarring, likely evidence of earlier vesicles, are important to recognize as potential signs of intrauterine disease. Additionally, HSV can mimic other diseases such as epidermolysis bullosa, aplasia cutis congenita, and incontinentia pigmenti. Confirming HSV disease by viral culture can be difficult. In 15 cases where lesions were present at birth, culture confirmation was delayed beyond 72 hours of life. Contributing factors included: (1) false-negative cultures, (2) deferral of culture despite the presence of vesicles, and (3) lesions such as plaques or scars that were not amenable to culture. Older lesions and poor quality specimens result in low culture yield. Several cases required more than 1 culture for confirmation; detecting the virus in culture was facilitated by a recurrence of skin disease, which is anticipated in intrauterine HSV infection. If the index of suspicion for intrauterine HSV infection is high, isolation of virus can be optimized by culturing other sites, such as conjunctiva, nasopharynx, and rectum.

Initiation of antiviral therapy should not be delayed if there is clinical suspicion of HSV disease. In addition, caution should be exercised in discontinuing antiviral therapy in the setting of negative cultures. Treatment will not reverse the organ injury sustained in utero. However, it may prevent progression of disease in a subset of patients with intrauterine HSV infection who do not have neurologic involvement at the time of birth. Thus, treatment aims to prevent CNS and possibly disseminated disease.

Our data are consistent with prior reports where 60% to 80% of mothers with infants who develop neonatal HSV disease have no symptoms at the time of delivery nor a history of genital herpes.[2] An infant is at highest risk for neonatal HSV disease if the mother has primary disease during the pregnancy. However, reports of intrauterine disease in mothers with past herpes infection exist, and this series includes 2 mothers who had primary herpetic lesions prior to their pregnancy. Intrauterine infection is thought to occur via 2 routes—transplacental infection and ascending infection, even in the absence of rupture of membranes.

Data from the early 1980s suggest that intrauterine HSV accounts for nearly 5% of all neonatal disease.[41] New data are needed to determine if that figure prevails today. The incidence of intrauterine HSV infection cannot be inferred from the cases we have reviewed. However, we confirm that maternal HSV infection can result in significant neonatal morbidity and mortality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Clinical Spectrum of Intrauterine Herpes Simplex Virus Infection

Clinical Manifestation	Number (%)
Cutaneous	61 (95)
Initial skin lesion	
Vesiculobullous	35
Erosion/ulceration	10
Pustular	7
Erythematous	6
Plaque or hypopigmented scar	3
Central nervous system	43 (67)
Calcifications	19
Porencephaly/encephalomalacia	16
Ventriculomegaly	13
Microcephaly	10
Hemorrhage	8
Seizures	7
Meningoencephalitis	4
Hypertonia/spasticity	3
Preterm	41 (64)
Ophthalmologic	25 (39)
Visceral (liver, adrenal, lungs)	23 (36)
Limb and bone abnormalities	11 (17)
Altered fetal growth	7 (11)
Hydrops	6 (9)
Intrauterine demise	4 (6)
Total cases	64