CASE REPORT

Edward S. Traisman,[1] *M.D.; Stephanie Young,*[2] *M.D.; Barry D. Lifschultz,*[3] *M.D.; Howard S. Traisman,*[4] *M.D.; Irwin Benuck,*[5] *M.D.; and Ira Chasnoff,*[6] *M.D.*

Sudden Death in a Neonate as a Result of Herpes Simplex Infection

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ABSTRACT: This paper describes a case of a neonate with disseminated herpes simplex born to a 14-year-old asymptomatic mother. The infant's physical examination was normal at birth, and subsequent abnormalities were so subtle that infection was not recognized during life. Postmortem cultures of liver and spleen grew herpes simplex virus, and immunofluorescent direct antibody typing revealed Type 2. A cervical culture of the mother obtained after the infant's death was negative.

KEYWORDS: pathology and biology, herpes simplex virus, death

Genital herpes simplex virus (HSV) infection occurs in 270 000 to 600 000 new patients a year [*1,2*], and in the 1970s reached apparent epidemic proportions in the United States [*3*]. A serious complication of genital herpes is infection of the neonate. Neonatal herpes simplex causes severe neurologic sequelae (seizures, ocular abnormalities, developmental delay) or death in over 75% of infected newborns [*4,5*]. The estimated number of new cases of neonatal herpes simplex virus infection is thought to be between 1 for every 2500 and 1 for every 10 000 deliveries per year, although the number may be increasing [*6*]. Most deaths result from disseminated (visceral) herpetic disease; unfortunately, 30% of neonates with disseminated disease do not have clinically evident infection and are diagnosed postmortem [*5*], and 50 to 70% of neonates with herpes simplex viral disease are born to mothers without a history of HSV at delivery [*7*].

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[1]Clinical instructor of pediatrics, Northwestern University Medical School, Chicago, IL, and Children's Memorial Hospital, Chicago, IL.

[2]Department of Pathology, Children's Memorial Hospital, Chicago, IL.

[3]Deputy medical examiner, Office of the Medical Examiner of Cook County, Chicago, IL.

[4]Professor of pediatrics, Northwestern University Medical School, Chicago, IL, and the Children's Memorial Hospital, Chicago, IL.

[5]Assistant professor of pediatrics, Northwestern University Medical School, Chicago, IL, and the Children's Memorial Hospital, Chicago, IL.

[6]Assistant professor of pediatrics, Northwestern University Medical School, Chicago, IL, and the Children's Memorial Hospital, Chicago, IL.

This paper presents a case of disseminated neonatal herpes simplex infection diagnosed at autopsy. Pathogenesis of the infection is reviewed. The pathologist should be alerted to this disease since it is a cause of sudden death and since proper diagnosis of neonatal herpes simplex infection affects management of future pregnancies.

Case Report

A 2955-g male was born to a 14-year-old gravida 1 para 0 (G_1P_0) female at 40 weeks of gestation. The pregnancy was uncomplicated by apparent venereal infection and the delivery was vaginal. The Apgar score was 8 at 1 min and 9 at 5 min. The newborn had a normal physical examination and was discharged home on Day 3 of life in good health. On Day 6 of life the infant developed a temperature of 39.2°C and was admitted to the Children's Memorial Hospital, Chicago. The infant's physical examination was unremarkable except for irritability. The hemoglobin was 14.8 g/dL with white blood cell (WBC) 21 500, 57% polymorphonuclear (PMN), 11% bands, 27% lymphocytes, and 5% monocytes. The platelet count was 250 000. The cerebrospinal fluid contained 6 red blood cells (RBC), 1 WBC (mononuclear), a protein of 54 mg/dL, and glucose of 72 mg/dL. Bacterial cultures of cerebrospinal fluid (CSF), blood, urine, throat, and stool showed no growth at 72 h. Chest and abdominal radiographs were normal for age. Intravenous ampicillin and amikacin therapy was instituted. Antibiotics were discontinued after 72 h, and the patient discharged home afebrile with a normal physical examination on Day 10 of life. At age 14 days the patient presented to the Children's Memorial Hospital Emergency room cyanotic and without spontaneous heart rate or respirations. Cardiopulmonary resuscitation was unsuccessful.

The mother was examined two weeks after the newborn's death by her gynecologist, and the examination was normal. No herpetic lesions were seen. A culture for herpes simplex virus had no growth. A herpetic culture was not done before delivery. The mother's Papanicolaou smear was read as Class I.

Autopsy Findings

External examination of the body revealed a well-developed 3111-g (25th percentile) black male infant with a crown-heal length of 47 cm (5th percentile). The skin, oral mucosa, and conjunctiva were unremarkable; no vesicular lesions or jaundice were present. The pathology was confined to the liver and adrenal glands.

The liver was enlarged (108 g; normal weight 78 g), and the surface was studded with irregular yellow depressed necrotic areas which varied in size from 2 to 4 mm in diameter. Cut section revealed hemorrhagic red-purple zones alternating with red-brown areas. Numerous depressed yellow lesions were randomly scattered throughout (Fig. 1). Microscopically, at low power, the liver had a diffusely mottled appearance in every section. Only small patches of intact liver parenchyma were identified which alternated with areas of hemorrhage containing foci of eosinophilic necrotic debris (Fig. 2). The hemorrhagic areas consisted of dense clusters of red blood cells with interspersed necrotic cell ghosts. The larger amorphous zones of eosinophilic debris had irregular borders. The liver parenchyma adjacent to the hemorrhagic areas contained numerous scattered cells and some cell clusters with distinct eosinophilic nuclear inclusions as well as clumped chromatin along the nuclear membrane characteristic of Cowdry Type A inclusions (Fig. 3). In addition, other parenchymal cells at the junction of the necrotic zone contained smudged basophilic nuclei characteristic of "ground-glass" inclusions. Occasional multinucleated giant cells are identified in this area. Within the preserved parenchyma, but adjacent to the hemorrhagic zone, a few clusters of fragmented nuclear debris were present; however, no PMN leukocyte infiltrates were present. The intact liver parenchyma consisted of irregular patches of liver cell trabeculae which showed no pattern of preservation; some contained central veins while others con-

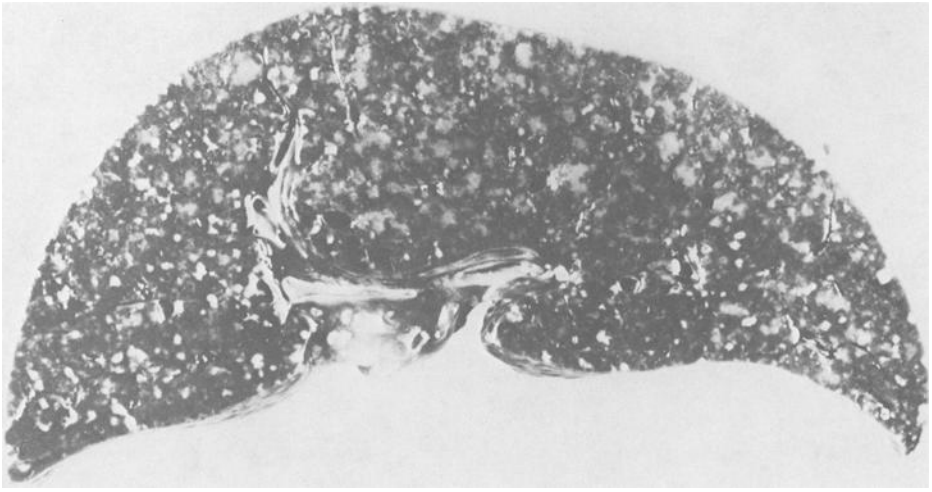

FIG. 1—*Irregular depressed zones of necrosis alternate with areas of red-brown parenchyma.*

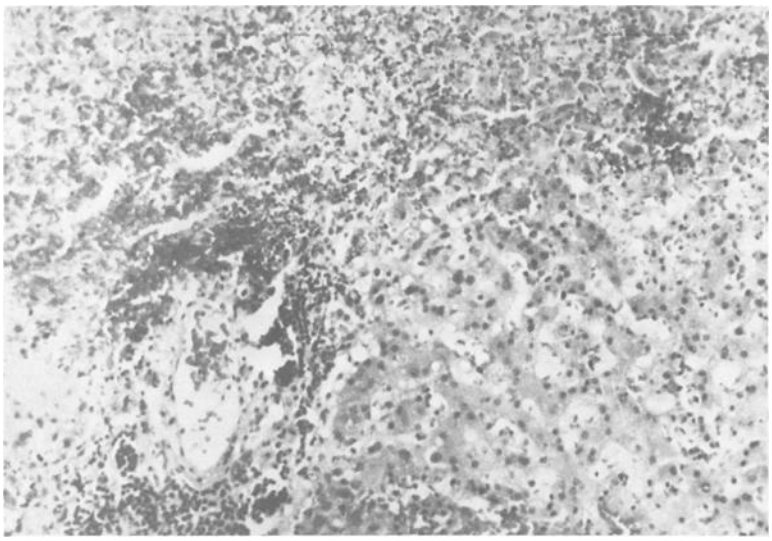

FIG. 2—*Irregular patches of liver parenchyma lie adjacent to larger areas of hemorrhagic necrosis (×75, hematoxylin and eosin [H&E]).*

tained portal fields. The portal fields exhibited a distinct mixed inflammatory infiltrate containing PMN leukocytes and mononuclear cells. Similarly, mixed inflammatory infiltrates surrounded central veins.

Sections of adrenals showed irregular foci of hemorrhage and necrosis alternating with areas of intact cortex. Some of the cells in the parenchymal areas adjacent to the hemorrhage contained hyperchromatic, somewhat smudged nuclei, but definite inclusions could not be

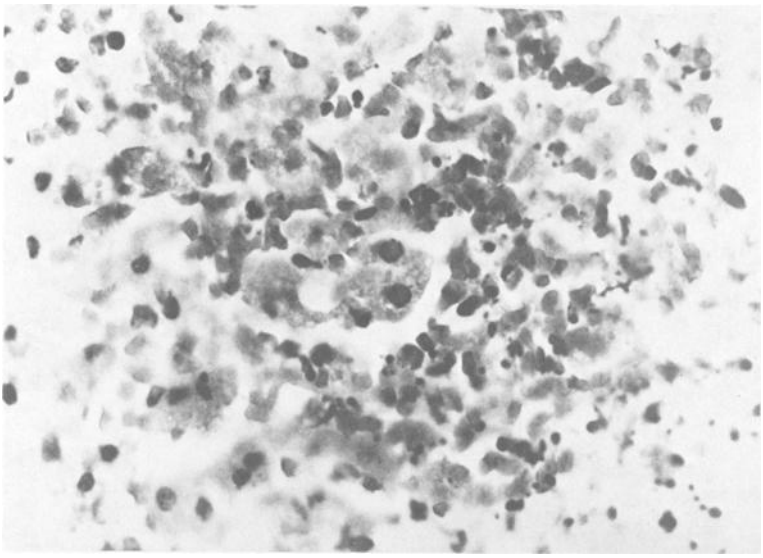

FIG. 3—*Hepatocytes lying adjacent to the hemorrhagic necrotic zones contain discrete nuclear inclusions (×300, H&E).*

recognized. The brain and leptomeninges were unremarkable. Cultures of the liver and spleen grew herpes simplex, and immunofluorescent direct antibody typing revealed Type 2.

Discussion

Genital herpes simplex infection is at epidemic proportions in the United States [*3*]. We have presented one case of fatal disseminated neonatal herpes simplex infection diagnosed postmortem. Pathological findings were remarkable for hepatoadrenal necrosis (consistent with disseminated herpes simplex infection) [*8,9*]. A source of the patient's infection could not be determined, but is likely to be intrapartum. Pathologic findings and date of onset (six days postpartum) support this conclusion. Intrapartum transmission occurs from contact with herpes simplex virus in the vagina at time of delivery [*5*] or after prolonged rupture of the amniotic membranes for greater than 4 to 6 h (ascending infection). Chorioamnionitis has been associated with ascending herpetic infection [*10*]. The mother of our patient did not have chorioamnionitis, and any undetected herpetic lesion at delivery may have cleared by the time vaginal cultures were done four weeks postpartum. Also, viral shedding can occur without recognizable lesions present [*4*] and not be detected by antepartem cultures for herpes simplex [*7*].

Other routes of infection are possible. Antepartum transmission [*11,12*] results from maternal viremia infecting the placenta [*5*]. Transplacental passage of the virus then results in fetal infection. High rates of spontaneous abortion, prematurity [*13*], or congenital anomalies (microcephaly, microphthalmia and chorioretinitis) [*4,11,12*] result. While the mother's placenta was not examined pathologically, this route appears unlikely in our patient. Postpartum contact with an active case of herpes simplex infection may result in neonatal disease [*4,10*]. This appears unlikely in our patient because the patient succumbed to HSV-II. Postpartum acquired disease is associated with HSV-I [*10*], and no known exposure existed in this case. Postpartum HSV-II acquired infection has not been reported [*10*].

The specific microscopic changes in the liver as a result of Cytomegalovirus, herpes sim-

plex virus, Listeria, Varicella-zoster, tuberculosis, and syphilis can be recognized when present; however, a biopsy may be obtained during a period when specific changes are not present. Often, the only findings present in some congenital infections are nonspecific and nondiagnostic. These include cholestasis, portal fibrosis, lymphocytic infiltrates of portal fields, and giant cell transformation [*14*]. Thus, the pediatrician and pathologist must be alert to send viral cultures at time of biopsy or autopsy and process tissue for electron microscopy and immunohistochemical stains in order that a specific diagnosis may be obtained with certainty [*15*]. Proper diagnosis may be the only way to enable appropriate management of future pregnancies, and avoid possible sudden death in a neonate.

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Address requests for reprints or additional information to
Edward S. Traisman, M.D.
1325 Howard St.
Evanston, IL 60202