Journal of Korean Medical Science
Vol. 2, No. 2, P 123–127. June 1987

Disseminated Neonatal Herpes Simplex Virus Infection with Necrotizing Encephalitis

— An Autopsy Case —

Yeon Lim Suh, M.D., Hyomin Kim, M.D., Je G. Chi, M.D.,
Hye Ran Byun, M.D.*, and Keun Lee, M.D.*

Department of Pathology, Seoul National University Children's Hospital and
*Department of Pediatrics, Ewha Womans University Hospital
Seoul, Korea*

An autopsy case of disseminated HSV type 2 infection occurring in a neonate at 32 weeks' gestation, delivered by cesarean section after premature rupture of membrane of 7 days duration, is presented. Herpes simplex virus type 2 was isolated from the vesicular skin lesion. The mother and patient had specific antibody to type 2 herpes simplex virus. Patient's parents had denied any herpetic orolabial or genital lesion during or before this pregnancy. Cultures from the cervical and vaginal swabs of the mother were negative for HSV. Postmortem examination showed hepatic necrosis, skin vesicle, devastating necrotizing inflammation of the brain, chorioretinitis and interstitial pneumonitis.

Key Words: *Herpes simplex, encephalitis, neonatal infection, virus infection*

INTRODUCTION

Herpes simplex virus (HSV) infection of neonate is a sporadic disease, usually produced by type II virus (HSV-2) acquired by passage through an infected birth canal (Torphy et al., 1970). The risk to the infant is said to be about 10% in cases of maternal genital herpes after 32 weeks' gestation rising to 40% at term (Nahmias et al., 1971). About 50% develop fatal disseminated disease (Wheeler et al., 1965; Chang et al., 1966; Von Herzen et el., 1977) or fatal brain disease (Golden et al., 1969). Of the remainder, about 30% will have devastating sequelae with brain damage and/or blindness (Young et al., 1965; Farris et al., 1973; Nahmias et al., 1976). Once infection becomes established in disseminated form, the liver and the adrenal are almost universally involved, as in the early description by Hass (1935). Herpes simplex virus infections of neonate often involve the CNS as the dominant clinical feature or as part of a multisystem disease (Rawls et al., 1966: Johnson et al., 1972; Finelli et al., 1975).

Recently we had a chance to examine an autopsy case of disseminated from of HSV-2 infection with CNS involvement in a 20 day old female baby.

Address for Correspondence: *Je G. Chi, M.D., Department of Pathology, Seoul National University Children's Hospital. 28 Yunkun-Dong, Chongno-Ku, Seoul 110, Korea, 02) 7601-3540, 3546*

CASE REPORT

The patient was the product of a 32 week gestation in a 27 year old primiparous woman who had had no orogenital lesion or other specific illness during this pregnancy. The father was 27 year old and healthy. He was free of herpetic orolabial or genital skin eruption. The pregnancy was complicated by spontaneous premature rupture of mem-

brane for 7 days and breech presentation. The baby was delivered by cesarean section and was meconium stained. The birth weight was 2.01 kg. Baby's activity and Moro reflex were fair. At birth large blisters of various size were noted on the left lower extremities, buttock and back. Among the laboratory findings on the admission, the hemoglobin was 17.0 gm/dl, hematocrit 51%, leukocyte count 23,000/mm^3 with a differential count of 21% polys, 69% lymphocytes, 10% eosinophils. The platelet count was 319,000/mm^3. Examination of CSF showed 150 red cells/mm^3, 60 white blood cells/mm^3 with 2% polys and 98% lymphocytes. Glucose was 15 mg/100 ml and protein was 9.0 mg/100 ml. The skin lesion became gradually vesiculated with yellowish fluid on erythematous base and spread to the right lower extremity and trunk 3 days later. At that time severe jitteriness was noted. Pathologic examination of skin biopsy and Tzanck smear from the vesicles showed intranuclear inclusions suggestive of herpes virus. The HSV-2 was also isolated from the vesicle by the tissue culture. But cultures and cytologic examination from the mother's vaginal and cervical swabs were negative for HSV. The serologic assay demonstrated high titer of IgM antibody to HSV in the patient and IgG antibody in her mother. The skin lesion was gradually regressed after administration of antiviral drug. On the 8th hospital day, vomiting and abnormal posture developed, and seizure activities were followed. The seizure was precipitated especially by tractile stimulation, being associated with apnea, cyanosis and bradycardia. The frequent attacks of seizure could not be controlled with anticonvulsive drugs. The skin lesion started to appear again. The attacks of seizure became more frequent and severe, and she expired at the 20th day of life.

Postmortem examination (CHA86-43) revealed a 1800 gm neonate with generalized skin lesions. Some of skin lesions were pigmented and encrusted, and the remainders vesiculated with tense and clear or yellow fluid. They were distributed in groups on the trunk, back and lower extremities and soles. Microscopic examination of the skin lesion showed intraepidermal vesicle produced by profound ballooning and reticular degeneration of epidermal cells (Fig. 1). In the vesicles a few balloon cells had a homogeneous eosinophilic cytoplasm. They had one nucleus or was multinucleated. There were a few eosinophilic inclusion bodies surrounded by halo in the nuclei of ballooned cells.

The heart, and abdominal organs remained intact except for several necrotic foci in the liver. The hepatic lesions measured 0.3 to 0.5cm. They were yellow tan, round to ovoid and flat, and were surrounded by a narrow red rim (Fig. 2). There were no collapse or wrinkling of the overlying capsule. Histologically, the hepatic lesion consisted of coagulative necrosis of parenchyma with calcification. Inflammatory cells were not encountered in the area of necrosis. The necrotic foci were separated from the viable adjacent tissue by the circumferential fibrosis, in which many plasma cells and lymphocytes are scattered (Fig. 3). A few intranuclear inclusions and multinucleated cells were seen in the hepatocytes at the necrotic foci. The surviving hepatocytes at the periphery contained large irregular staining nuclei, but not inclusion. Remaining viable hepatocytes had diffuse fatty vacuoles. Microscopic examination of the lung revealed diffuse in-

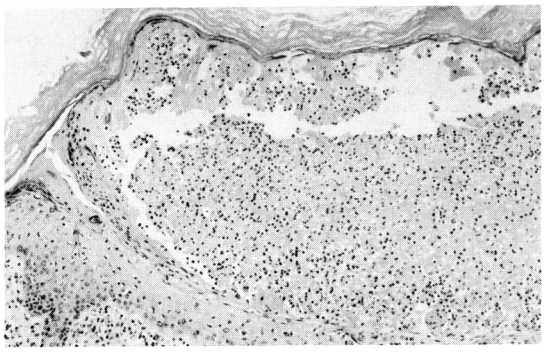

Fig. 1. Note an intraepidermal vesicle produced by profound ballooning and reticular degeneration of epidermal cells (H & E, X100).

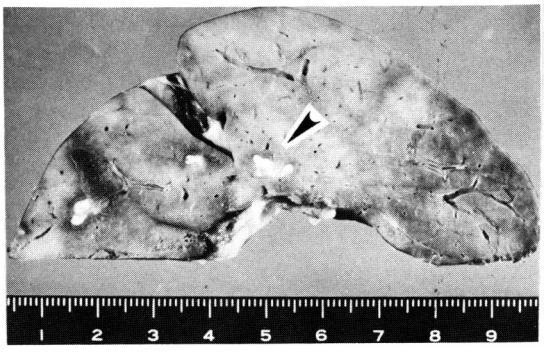

Fig. 2. Note the characteristic multiple discrete necrotic foci (arrowhead), 3 mm in diameter, scattered throughout the liver.

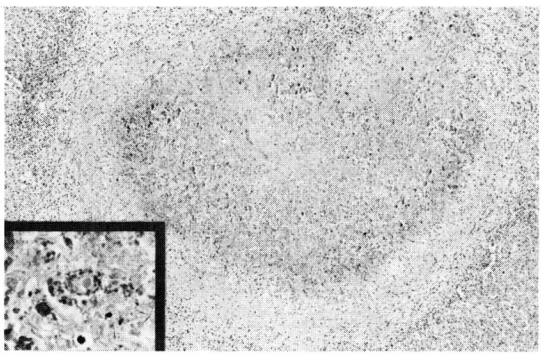

Fig. 3. Photomicrograph of hepatic lesion showing coagulation necrosis with calcification and little inflammation (H & E, X40). There is an intranulclear inlcusion in the hepatocyte at necrotic foci (inset; H & E, X400).

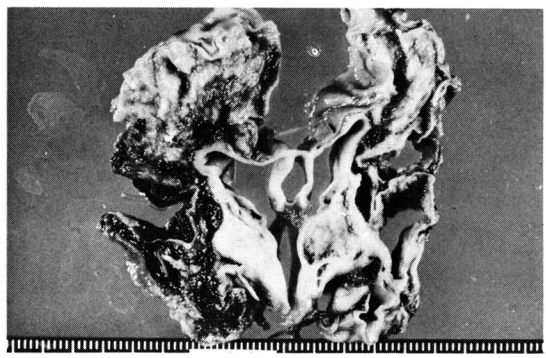

Fig. 4. Coronal section view of cerebrum showing extensive hemorrhagic necrosis together with multicystic or reticular changes of various size.

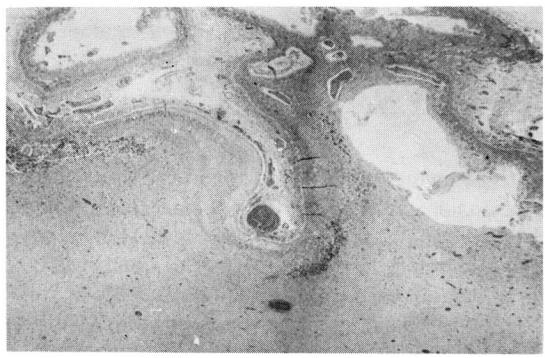

Fig. 5. Low power photomicrograph to show extensive parenchymal necrosis and micro-and macrocystic breakdown of cerebral parenchyma (H & E, X10).

terstitial thickening produced by edema and mononuclear cell infiltration. Eyeballs were normal in size and shape, but microscopic examination showed focal retinal detachment and necrosis with calcification. A few mononuclear cells infiltrated the ciliary body, iris, choroid and retina. The brain was small and soft. It weighed 93 gm. The leptomeninges were diffusely dusky and xanthochromic, which was particularly evident on the both temporal lobes. There were two foci of subarachnoid hemorrhage, 4 x 2 cm over both parietal lobes. The cerebral hemispheres showed no significant gyral abnormalities. But the brain was generally collapsed with wrinkling due to underlying parenchymal cystic degeneration and extensive necrosis. Coronal sections of the cerebrum revealed extensive necrosis together with multicystic or reticular change of various size, raning from microscopic size to 4cm in diameter (Fig. 4). These changes were widespread and involved the gray and white matter of the frontal, parietal and temporal lobes, and small part of the occipital lobe. The necrosis was partly associated with hemorrhage and there was an intracerebral hematoma, 5 x 2 cm, which occupied the left parietal and temporal lobes and ruptured into the subarachnoid space. The cerebral parenchyma was relatively preserved in the small portion of the thalamus, hypothalamus and a part of the right occipital lobe. In this area parenchyma was also soft and dusky yellow in color. The ventricular system was generally dilated and showed whitish smooth ependymal surface with rather thickened ventricular wall. The cystic necrosis was seen in the ventral area of the pons and medulla. The cerebellum showed focal necrosis of folia. Microscopically, there was leptomeningitis which was diffuse and of mononuclear, with lymphocytes and macrophages predominating. Sections of cerebrum showed widespread and extensive neuronal necrosis, and micro-and macrocystic breakdown of parenchyma, in which foamy macrophages around blood vessels were collected (Fig. 5). Adjacent areas to the necrosis and cystic degeneration showed marked proliferation of capillaries and hypertrophic astrocytes, collections of macrophages and calcification (Fig. 6). Grossly normal looking cerebrum also showed marked proliferation of hypertrophic astrocytes and microglial cells, and perivascular infiltration of mononuclear cells. The cerebellum showed focal necrosis and gliosis in the areas of folia close to the leptomeninges. There were several fibrin thrombi in

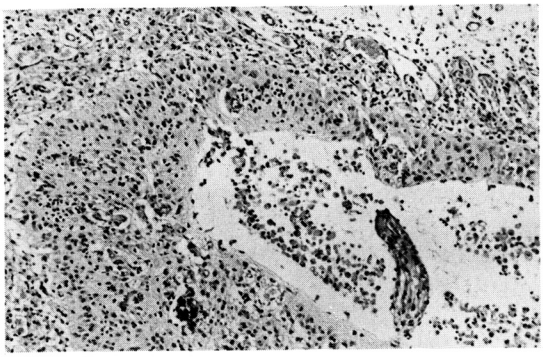

Fig. 6. Photomicrograph showing devastating necrotizing inflammation with gliosis and calcification in the brain (H & E, X100).

the blood vessels of the cerebellar white matter. No inclusion bodies were seen in the brain.

DISCUSSION

Herpes simplex virus is recongnized as a cause of neonatal infection, congenital malformation and abortion (South et al., 1969). Most newborns become infected from the mother's genital tract, either by an ascending route, particularly if the membranes have ruptured, or during the second stage of labor. It seems likely that our patient's infection was acquired by the ascending route from the birth canal before birth for the following reasons (1) the presence of premature rupture of membrane for 7 days and (2) onset of skin lesion at birth. Since it is estimated that the incubation period of HSV infection may vary from 2 to 12 days with average of 6 days, the amniotic fluid was contaminated with virus after rupture of membrane. Therefore cesarean section was too late in this instance. The majority of neonatal infections is due to HSV-2, but about 20% are due to HSV-1 (Nahmias et al., 1967a) Nahmias and his associates reported that over 90% of isolates recovered from infected newborns were type 2 (Nahmias et al., 1967B). The true incidence of HSV infection is known to be difficult to ascertain because of the wide spectrum of manifestations, ranging from none to devastating disseminated disease. In Korea the precise figure on the incidence is not available. There are two publications available in Korean literature. One is an autopsy case of neonatal infection occurring in monozygotic twin Kim et al., 1986) and the other is a case of acute fulminant hepatitis induced by herpes virus hominis (Chung et al., 1982). In the united states, it has been estimated that symptomatic herpetic infection in the newborn occurs in approximately 1 per 7500 birth (Florman et al., 1952). Approximately 40% of infected infants are premature and are the first born infants of young mothers (Hanshaw, 1973). Premature infants appear to be even more prone to develop lethal forms of the disease. It has been suggested that the premature infants are more vulnerable because they lack the full complement of maternal IgG antibody or impairement of immunological function (Singer, 1981).

Since hepato-adrenal necrosis was reported by Hass, description of HSV lesion have been noted in practically every tissue in the body. A few organs are consistently affected. These are the liver, adrenal, skin, eye, esophagus and brain. The liver may be considered the prototypical organ infected by HSV. The skin is moderately vulnerable to HSV. The sites involved in the neonate are always those with the longest and most direct contact with mother's infected birth canal, i.e., the scalp in cephalic presentation and the buttocks in frank breech presentation. Central nervous system involvement was discernible clinically during life or on postmortem examination in about half of the patients with disseminated HSV infection. Two types of herpes simplex virus, the oral strain (type 1) and the genital strain (type 2) may produce encephalitis in man. Type 2 is the more common cause of HSV encephalitis in the neonate, whereas type 1 is the more common cause in the elder infant, child and adult (Stalder et al., 1973). In newborn with disseminatd disease, five different patterns of infection in the CNS have been described; 1) Virus is not recoverable from the brain and no histopathologic findings are detected. 2) Virus is recoverable from the brain, but minimal histopathologic findings or none are observed. 3) Virus is isolatable from the brain, which usually shows multiple foci of involvement.4) Virus is not recoverable from the brain, but histopathologic findings associated with acute infection or with sequelae such as ventricular dilatation, porencephaly or intracranial calcification are noted. In present case the CNS lesion was compatible with those of the 5th pattern.

Reported sequelae of HSV encephalitis in the neonate include mental and developmental retardation, microcephaly, porencephaly, multicystic encephalomalacia, seizure, chorioretinitis and motor deficits. These lesions have also been included among the congenital anomalies, in the rare

case of transplacental infection. In most reported cases the nature of cerebral lesion has been demonstrated by the clinical, radiological and EEG findings. The histologic features of CNS described in the literature are devastating encephalitis, vasculitis and meningitis. The necrosis and inflammation center around small vessels. Brain lesion of this case is of interest in both gross and microscopic findings that are supposed to be similar with those of cases reported by Von Herzen (1976) and Smith (1977). The histopathologic findings of CNS in our patient is interpreted as evidence for devastating encephalitis, most likely secondary to the encephaloclastic effects of the virus on the brain. Another possible cause for brain necrosis may be ischemia produced by vascular occlusion that are evident by the presence of several fibrin thrombi in the cerebellar vessels.

REFERENCES

Chang TW, Solomon P, Weinstein L: *Generalized fatal herpes simplex infection in a newborn infant. J Pediat 68: 473-475, 1966.*

Chung HJ, Chung KS, Yun DJ, Kim JS: *A case of acute fulminant hepatitis induced by herpesvirus hominis. J Kor Pediatr Assoc 25: 616-621, 1982.*

Florman AL, Mindlin RL: *Generalized herpes simplex in an eleven-day-old premature infant. Am J Dis Child 83: 481-486, 1952.*

Farris WA, Blaw ME: *Multicystic encephalomalacia in a infant due to Herpesvirus hominis type II, abstracted. Neurology 23: 415, 1973.*

Finelli PF: *Herpes simplex virus and the human nervous system: current concepts and review. Milit Med 140: 765-771, 1975.*

Golden B, Bell WE, McKee AP: *Disseminated herpes simplex with encephalitis in a neonate. JAMA 209: 1219-1221, 1969.*

Hass GM: *Hepato-adrenal necrosis with intranuclear inclusion bodies: Report of a case. Am J Pathol 11: 127-142, 1935.*

Hanshaw JB: *Herpes hominis infection in the fetus and the newborn. Am J Dis Child 126: 546-555, 1973.*

Johnson KP, Resenthal MS, Lerner PI: *Herpes simplex encephalitis: The course in five virologically proven cases. Arch Neurol 27: 103-108, 1972.*

Kim KH, Seo JW, Kim KH, Lee K: *2 cases of herpes simplex virus infection in the neonate. J Kor Pediatr Assoc 29: 101-107, 1986.*

Nahmias AJ, Josey WE, Naib ZM: *Neonatal herpes simplex infection. JAMA 199: 132-136, 1967a.*

Nahmias AJ, Naib ZM, Josey WE, Clepper AC: *Genital herpes simplex infection: Virologic and cytologic studies. Obstet Gynecol 29: 395-400, 1967b.*

Nahmias AJ, Alford CA, Korones FB: *Infection of the newborn with herpesvirus hominis. Adv Pediatr 17: 185-226, 1970.*

Nahmias AJ. Josey WE, Naib ZM, Freeman M, Fernandez R, Wheeler J: *Perinatal risk associated with maternal genital herpes simplex virus infection. Am J Obstet Gynecol 110: 825-837, 1971.*

Nahmias AJ, Visintine AM: *Herpessimplex. In Remington JS and Klein J O (eds) Infectious disease of the fetus and newborn. WB Saunders Company, Philadelphia, pp 156-190, 1976.*

Rawls WE, Dyck PJ, Kiass DW, Greer HD, Herrmann: *Encephalitis associated with herpes simplex virus. Ann Intern Med 64: 104-115, 1966.*

Singer DB: *Pathology of neonatal herpes simplex virus infection. Perspect Pediatr Pathol 6: 243-278, 1981.*

Smith JB, Groover RV, Klass DW, Houser W: *Multicystic cerebral degeneration in neonatal herpes simplex virus encephalitis. Am J Dis Child 131: 568-572, 1977.*

South MA, Tompkins WAF, Morris CR, Rawls WE: *Congenital malformation of the central nervous system associated with genital type (type 2) herpesvirus. J Pediatr 75: 13-18, 1969.*

Stalder H, Oxman MN, Dawson DM, Levin MJ: *Herpes simplex meningitis: Isolation of herpes simplex virus type 2 from cerebrospinal fluid. New Engl J Med 289: 1296-1298, 1973.*

Torphy DE, Ray CG, McAlister R, Du JNH: *Herpes simplex virus infection in infants: A spectrum of disease. J Pediatr 76: 405-408, 1970.*

Von Herzen JL, Benirschke K: *Unexpected disseminated herpes simplex infection in a newborn. Obstet Gynecol 50: 728-730, 1977.*

Wheeler CE Jr, Huffines WD: *Primary disseminated herpes simplex of the newborn. JAMA 191: 455-460, 1965.*

Young GF, Knox DL, Dodge PR: *Necrotizing encephalitis and chorioretinitis in a young infant: Report of a case with rising herpes simplex antibody titers. Arch Neurol 13: 15-24, 1965.*