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# Herpes Simplex Encephalitis: CT Findings in the Neonate and Young Infant

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**The computed tomographic (CT) findings in six cases of neonatal herpes simplex encephalitis (HSE) are reviewed and compared with previous reports. The diagnoses were made on the basis of isolation of the virus from a brain biopsy specimen in one case, from cerebrospinal fluid in two cases, from tracheal aspirate in one case, and on clinical grounds in two cases. Five infants survived; all had significant neurologic deficits. CT showed bilateral cerebral involvement with relative sparing of the lower neuraxis in all cases. Bilateral patchy low-density zones involving the periventricular white matter more than the cortical gray matter were seen initially in four of the six infants. Hemorrhage and/or calcifications in the thalamus, insular cortex, periventricular white matter, and along the corticomedullary junction were present in five infants. Severe cerebral necrosis eventually resulted in all six infants. Unlike older patients, only one infant had predominantly temporal lobe involvement. These findings agree with the CT descriptions reported by others.**

Neonatal herpes simplex encephalitis (HSE) is a devastating disease that most often leads to death or severe neurologic sequelae such as seizures, microcephaly, micrencephaly, intracranial calcifications, microphthalmia, retinal dysplasia, ventriculomegaly, and multicystic encephalomalacia [1–5]. The risk of neonatal herpes infection is about one in 7500 deliveries [6]. The disease may be acquired by direct contact during or after birth or rarely by hematogenous transplacental infection in utero. Herpes simplex virus (HSV) type II occurs more often in the neonate [5], whereas HSV type I is more common in older patients. Only a limited number of cases illustrating the computed tomographic (CT) findings in neonates and very young infants afflicted with HSE have been reported [3, 7–11], despite numerous other reports without CT correlation [1, 2, 4, 12–18]. We describe the CT findings in varying stages of the disease in six neonates and young infants who were followed for up to 6 months.

## Materials and Methods

The clinical charts and CT scans of six neonates seen at LeBonheur Children's Medical Center and the Newborn Center of The Regional Medical Center of Memphis were reviewed (table 1). The diagnosis was based on isolation of the virus from a brain biopsy specimen in case 1, from cerebrospinal fluid (CSF) in cases 2 and 4, and from tracheal aspirate in case 3. The diagnosis was made on clinical grounds in cases 5 and 6. The diagnosis in case 5 was supported by a maternal painful genital rash, which healed without treatment, occurring 6–8 weeks before premature vaginal delivery. The infant had ventriculomegaly demonstrated by sonography 7 days before birth and neurologic signs at birth followed shortly by vesicular skin lesions on the right thumb. In case 6, the mother developed genital bullae and delivered vaginally in the fifth month of gestation. The infant had tonic-clonic seizures on the 14th day of life. Pleocytosis, elevated protein, and low glucose were found on examination of the CSF, consistent with herpetic meningoencephalitis.

The initial CT examinations were performed 3–19 days after the onset of neurologic signs.

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TABLE 1: **Summary of Clinical Information in Infants with Herpes Simplex Encephalitis**

| Case No.: Birth History | Age (in Days) of First Symptoms/Signs | Diagnosis | Interval between Neurologic Sign and CT (in days) |
|---|---|---|---|
| 1: Term; vaginal delivery | 16:Lethargy | +HSV isolation from brain biopsy | 3,32,49 |
| 2: Term; vaginal delivery | 21:Irritability, somnolence | +CSF culture for HSV at autopsy | 17,35 |
| 3: Term; breech presentation; cesarean delivery | 12:Lethargy, apnea<br>13:Cyanosis | +Viral culture tracheal aspirate | 5,58 |
| 4: Term; vaginal delivery | 1:Irritability, poor reflexes, seizure | +CSF culture for HSV | 18,50,195 |
| 5: Premature; vaginal delivery | −7:In utero ventriculomegaly on sonography<br>1:Hypotonic, poor reflexes<br>2:Eruption of vesicular lesions | Painful maternal genital rash 6–8 weeks before delivery; healed in 2–3 weeks without treatment | 19 |
| 6: Premature; vaginal delivery | 14:Seizure | Maternal history of vaginal bullae at 5 months; CSF consistent with viral encephalitis | 18,26 |

Note.—HSV = herpes simplex virus; CSF = Cerebrospinal fluid.

TABLE 2: **CT Findings in Neonates and Young Infants with Herpes Simplex Encephalitis**

| CT Findings | No. of Patients | |
|---|---|---|
| | Initial Study ($n = 6$) | Follow-up ($n = 5$) |
| Normal | 1* | 0 |
| Bilateral cerebral involvement with relative sparing lower neuraxis: | | |
| Patchy low attenuation without parenchymal loss | 4 | 0 |
| Diffuse and/or cystic encephalomalacia | 1† | 4 |
| Temporal encephalomalacia | 0 | 1 |
| Total no. of patients affected | 5 | 5 |
| Increased attenuation consistent with hemorrhage and/or calcification: | | |
| Thalamus | 1 | 3 |
| Basal ganglia | 0 | 1 |
| Periventricular | 1 | 4 |
| Insula | 0 | 3 |
| Centrum semiovale corticomedullary junction | 0 | 3 |
| Total no. of patients affected | 2 | 5 |
| Ventriculomegaly | 2 | 5 |

* Case 6: Initial CT examination was "normal," but study was performed with older scanner.

† Case 5: In utero–acquired herpes simplex encephalitis. Patient was lost to follow-up. No further scanning was performed.

Follow-up CT examinations were performed 26–195 days after the onset of neurologic signs. Four patients had at least one contrast-enhanced CT study (3 ml/kg, 282 mg I/ml) in addition to routine unenhanced scans. Evaluation of CT numbers of abnormal areas was not possible for three reasons: (1) margins of abnormal regions were often poorly defined, (2) scan data was not always available, and (3) several different CT scanners were used (GE 8800, Seimens DR3, and Ohio Nuclear Delta 50). Five patients were treated with Ara-A and one with Acyclovir. Five survived; all had significant neurologic deficits.

## Results

The CT findings in our patients are summarized in table 2. All six patients eventually had predominant bilateral supratentorial involvement. Findings were characterized by periventricular and cortical foci of low attenuation occurring in a patchy fashion (fig. 1A). The periventricular white matter was more involved than the cortical gray matter in all of these patients. With progression of the disease, loss of brain tissue increased with fusing of the patchy areas of low attenuation into confluent zones of low density separated from one another by thin strands of residual brain tissue (figs. 1B and 2). Often, the attenuation of these regions approached that of CSF. The CT findings in case 2 (fig. 2) correlated with multicystic cerebral degeneration (encephalomalacia) at postmortem examination. Even with advanced disease there was relative sparing of the basal ganglia, brainstem, and cerebellum (figs. 1B and 1C). Only case 3 had primary involvement of both temporal lobes (fig. 3).

Areas of increased attenuation were present within the thalami in three cases (figs. 2A and 4A). In one patient, increased attenuation was present in the basal ganglia as well. Histologic examination in case 2 revealed both hemorrhagic necrosis and foci of dystrophic calcification to account for the increased parenchymal attenuation. Punctate 2–3 mm areas of high density developed in the insular cortex, periventricular region, and to a lesser degree the cortical gray-white junction of the centrum semiovale. These densities were assumed to be small areas of calcification (fig. 4B).

Ventriculomegaly was seen initially or developed over the course of the disease in all six patients. Most often the lateral and third ventricles were dilated, with associated evidence of brain atrophy (figs. 1 and 2). Massive dilatation of the lateral ventricles with sheetlike periventricular calcifications, marked thinning of the cerebral hemispheres, and calicification of the ocular globes were evident in case 5 on a CT scan at 19 days of age (fig. 5). This infant was believed to have acquired HSE in utero because a prenatal sonographic examination had

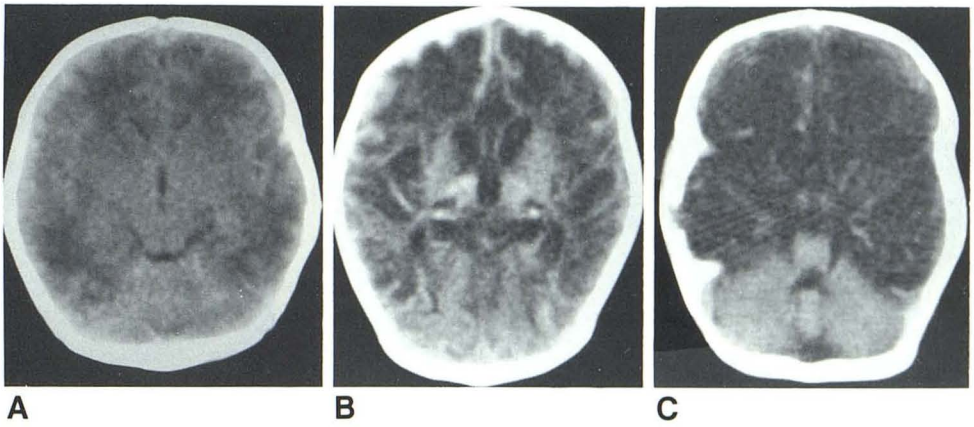


Fig. 1.—Case 1. Progression of CT findings in neonatal HSE, typical of our cases. **A**, Initial unenhanced scan. Term neonate at about 2½ weeks of age. Multifocal areas of decreased attenuation in frontoparietal regions. **B**, Unenhanced scan 17 days after initial examination. Fusing of zones of decreased attenuation with parenchymal thinning; ventriculomegaly. Less involvement of basal ganglia and increased attenuation in thalami, which could be from hemorrhage and/or calcification. **C**, Unenhanced scan 24 days after initial examination. Further parenchymal loss of supratentorial brain with diffuse low attenuation (approximating that of CSF), but relative sparing of posterior fossa structures.

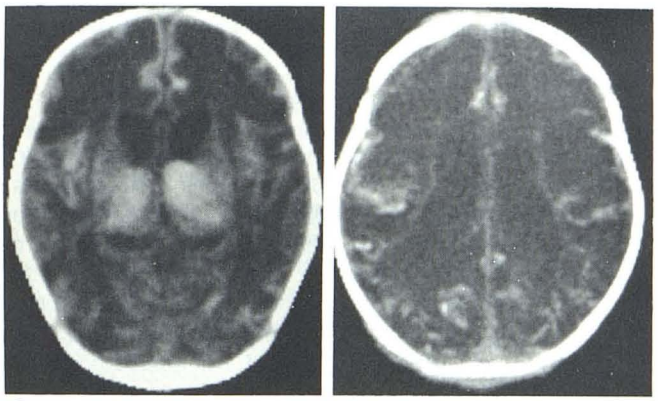


Fig. 2.—Case 2. End-stage CT findings of neonatal HSE. At autopsy thin remnants of brain parenchyma separated multiple proteinaceous fluid-filled spaces indicative of cystic encephalomalacia. Hemorrhagic necrosis with focal dystrophic calcification was present in thalami and some of parenchymal remnants. (Cf. figs. 1B and 1C).

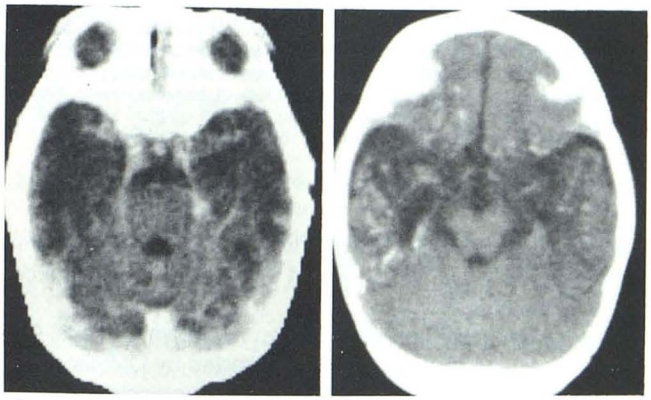


Fig. 3.—Case 3. Predominant bilateral temporal lobe involvement in neonatal HSE, an atypical finding occurring in only one infant in our series. **A**, Initial, enhanced scan. Confluent zones of decreased attenuation in temporal lobes. **B**, Unenhanced scan 46 days later. Focal encephalomalacia on right more than left with punctate areas of increased attenuation, presumably calcifications, in temporal and frontal lobes. (CF. fig. 4B.)

demonstrated dilatation of the lateral ventricles.

In two patients, the initial CT examination was originally interpreted as normal (cases 4 and 6). On review, small foci of decreased attenuation were indeed present in the cerebral hemispheres in case 4. The initial CT study in case 6 was performed with an older unit, and small areas of decreased attenuation could not have been resolved easily.

Four infants (cases 2, 3, 4, and 6) received intravenous contrast material as part of their CT examinations, and in no instance was enhancement abnormal. In three infants the initial contrast-enhanced CT examinations were performed 17–18 days after the onset of symptoms, which was probably after the acute inflammatory process had subsided. The examination in case 3 was performed 5 days after the onset of symptoms, which should have been during the acute inflammatory phase; however, no abnormal contrast enhancement occurred. Those patients in whom more than one contrast-enhanced CT examination was performed continued to show normal enhancement of residual brain parenchyma with progressive cerebral degeneration.

## Discussion

Meningoencephalitis in neonates and infants is usually diffuse and overwhelming, resulting in nonfocal neurologic signs and widespread brain destruction [19]. The premature infant is particularly susceptible to HSV infection, although overall survival is about the same in the premature and full-term infant [6]. Several factors predispose to more severe and generalized infection in neonates: (1) a deficiency of maternal IgG, (2) immature cellular-mediated immunity, (3) impaired vascular autoregulation, and (4) in utero or neonatal timing of the insult [3].

Dublin and Merten [8] reported the CT findings in one case of in utero–contracted HSE as showing massive hydrocephalus and heavy periventricular calcifications. This description resembles our case 5, also with a clinical diagnosis of in utero HSE. Other findings in the congenital form of HSE include microcephaly, microphthalmia, and intracranial calcifications conforming to atrophic cerebral hemispheres. Of the cases reviewed in the literature and in our series, ventriculomegaly

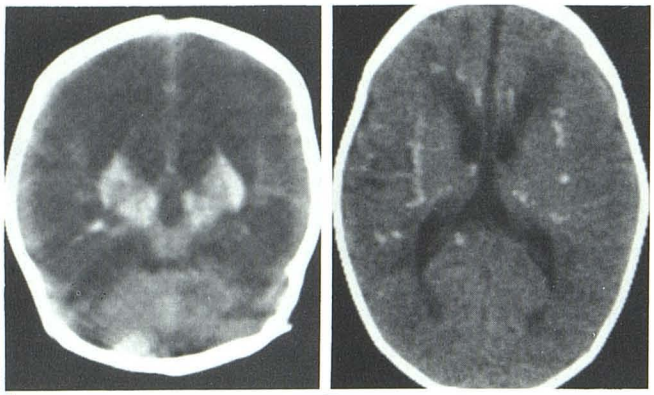


Fig. 4.—Unenhanced CT scans in two infants late in course of neonatal HSE showing different patterns of increased attenuation. **A**, Case 4. Increased attenuation in thalamus and lateral basal ganglia with widespread parenchymal destruction. Combination of hemorrhage and calcification with multicystic encephalomalacia probably accounts for findings, judging from similarity to case 2 (fig. 2). **B**, Case 3. Multifocal areas of increased attenuation, presumably calcifications because of punctate nature and lack of adjacent edema. Similar densities in temporal and frontal lobes (cf. fig. 3B) and centrum semiovale on scans at different levels. Also mild dilatation of lateral and third ventricles.

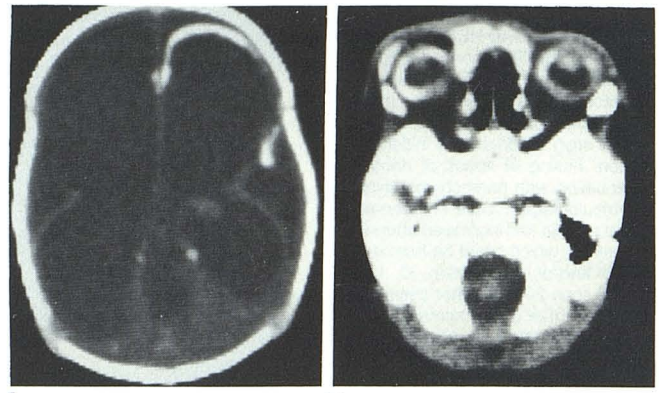


Fig. 5.—Case 5. In utero–acquired HSE. Unehanced scans at 19 days of age. **A**, Massive dilatation of lateral ventricles with thin remnant of brain parenchyma and periventricular calcification. Nodular calcifications along inferior aspect of temporal horns seen on lower scans. **B**, Focal calcification of ocular globes.

was generally most pronounced with in utero HSE as compared with those patients in whom the disease was acquired at or shortly after birth.

Degenerative changes were shown to evolve on serial CT studies in a case of neonatal HSE reported by Dubois et al. [7], as well as in five of our six cases. Progression of low-density lesions in the periventricular white matter and corticomedullary junction may lead to cystic encephalomalacia, focal hemorrhagic necrosis, and parenchymal calcifications, as found at autopsy in our case 2. If the patient survives HSE, the most common outcome seems to be multicystic cerebral degeneration in the neonate [3, 9] and young infant [10], but this outcome is much less common in the older patient [19].

Relative sparing of the basal ganglia, thalami, brainstem, and cerebellum has been seen with CT in infants with HSE [7, 9] and was found in our patients as well. Wolf and Cowen [20], in a clinical and pathologic review of the cerebral atrophies and encephalomalacias of infancy and childhood, noted: "In the face of severe lesions found in the white matter and cortex of the hemisphere, the lower portions of the neuraxis [i.e., basal ganglion, thalamus, brainstem, and cerebellum] suffer remarkably little damage."

CT findings of infarction, hemorrhage, and multicystic encephalomalacia with sparing of the lower neuraxis can be seen in neonates who have suffered a sudden fall in perfusion pressure and cerebral blood flow secondary to asphyxia [3] and twin-to-twin transfusion [21]. A variety of other viral and bacterial infections have also been implicated as causes of meningoencephalitis-induced multicystic encephalomalacia in neonates [10].

The determination of abnormal attenuation in the neonatal brain is complicated by the normal maturation of white matter. Neonatal white matter has increased water content and decreased lipid and protein content as compared with that in the 9- to 12-month-old child. On CT scans these features result in low attenuation of white matter, which tends to be symmetric and most pronounced in the frontal lobes in term neonates, but more generalized in premature infants [22, 23]. Disease processes producing low attenuation often occur in a patchy or asymmetric distribution and may involve gray matter. Symmetric abnormal zones of low attenuation may be difficult to detect on the initial examination, but serial studies may show persistence of low density or evolution of encephalomalacia, which should lead to recognition. Multiple processes including infection, hypoxia, and metabolic abnormalities may produce abnormal areas of low attenuation.

HSE usually has nonspecific clinical features, and the diagnosis is often difficult to confirm in the laboratory [19]. Within our series, both cases 5 and 6 had a presumptive clinical diagnosis of HSE without specific laboratory or biopsy proof. Only occasionally can one isolate HSV in the CSF of the neonate with HSE [6]. Likewise, it is difficult to obtain the diagnosis by biopsy in the younger patient [24]. Often only a presumptive clinical diagnosis is used before administration of Ara-A [19].

The CT findings of herpes encephalitis in older children and adults have been well described. Most typical is a unilateral temporal lobe area of low density associated with a mass effect and streaky enhancement within the lesion. One should not expect these findings in the neonate or young infant with HSV encephalitis.

In summary, the earliest CT manifestations of neonatal HSE may be subtle, with patchy areas of low attenuation occurring in both cerebral hemispheres but with relative sparing of the basal ganglia, thalami, and posterior fossa structures. Hemorrhage and/or calcifications in the thalami, insular cortex, periventricular white matter, and along the corticomedullary junction may develop during the course of the disease. If the infant survives, the end result is often gross brain destruction with multicystic encephalomalacia. The initial

CT findings in an infant with HSE depend on the stage of the encephalitic process and therefore may vary considerably. Recognition of patchy areas of low attenuation in both cerebral hemispheres of a neonate should prompt consideration of HSE so that the earliest diagnosis possible can be made in these seriously ill infants.

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