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Profound Asphyxia in the Premature Infant: Imaging Findings

A. James Barkovich and Steven K. Sargent

PURPOSE: To investigate imaging findings in premature infants who had profound asphyxia.

METHODS: CT (three patients), MR (three patients), and ultrasonography (four patients) studies of five patients who had profound asphyxia before the postconceptional age of 32 weeks were retrospectively reviewed. The patients ranged from 1 day to 4 months old at the time of the imaging studies. An autopsy report was available in one patient. The results were compared with reports in the literature of patients with similar injuries at similar ages. **RESULTS:** Abnormalities of the thalami and basal ganglia were present in all infants examined with CT or MR. CT showed low attenuation in the basal ganglia and high attenuation (blood or calcium) in the thalami; thalamic cavitation and low attenuation of the upper brain stem were present in one infant. MR showed T1 and T2 shortening in the thalami in all patients. Variable MR changes were noted in the basal ganglia, ranging from diminished size with normal signal intensity to T1 and T2 shortening with normal size and complete cavitation. T1 and T2 shortening were seen in the dorsal brain stem in one patient. Sonography showed transient or persistent hyperechogenicity in the thalami in three patients and cavitation of the thalami in one patient. Damage to the perirolandic cortex was not present in any patient. **CONCLUSION:** Profound asphyxia before 32 weeks gestational age shows consistent injury to the thalami, basal ganglia, and brain stem that can be detected by all three imaging modalities. The pattern of injury seems to differ from that of partial asphyxia in premature infants and of profound asphyxia in term infants.

Index terms: Asphyxia; Brain, injuries; Infants, newborn

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Modern neuroimaging techniques (sonography, computed tomography [CT], and magnetic resonance [MR]) are useful tools in the analysis of brain damage in asphyxiated neonates. The typical imaging patterns of brain damage in term infants with partial and profound asphyxic injuries have been described (1–8), as have the imaging patterns of injury in premature infants with partial asphyxia (2, 9–13). In this communication, we report the neuroimaging findings of five infants who had profound asphyxic injuries in the first half of the third trimester. In addition,

we attempt to correlate these patterns with previously reported pathologic findings in this patient group and with pathophysiologic mechanisms.

Patients and Methods

The imaging studies of five infants who had profound asphyxia in the first half of the third trimester were retrospectively reviewed. Infants 1, 4, and 5 were the initial patients identified; we recognized similar mechanisms and patterns of injury in all three. A subsequent retrospective search through records of neuroimaging studies of premature neonates over the past 5 years revealed patients 2 and 3. The postconceptional age of the patients ranged from 27 weeks to 32 weeks at the time of the episode (Table). All patients had complete circulatory arrest except patient 4, who was the recipient of a twin-twin transfusion at the estimated age of 26 to 28 weeks. Patient 5 had a cardio-circulatory arrest in utero documented by absence of heartbeat detectable by cardiotocogram at the postconceptional age of 28 weeks. Heartbeat returned within 30 minutes, and the child was subsequently delivered by un-

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Five premature infants who had profound asphyxia

Patient	Postconceptional Age, Wk	Clinical History	Imaging/Age	Neuroimaging Findings	Outcome
1	32	Emergency cesarean section after motor vehicle accident. Maternal hemorrhage. Cardiotocogram shows heart rate of 40 beats per min. Marked respiratory difficulties after delivery. Bright red blood aspirated from nasogastric tube.	US/1 d /2 d /11 d MR/12 d	Normal Intraventricular hemorrhage Intraventricular hemorrhage T1 and T2 shortening lateral thalamus and globus pallidus and corticospinal tracts bilaterally; intraventricular hemorrhage	Abnormal neurologic exam at age 3 mo
2	28	Cardiocardiac arrest at birth for uncertain duration.	US/1 d /2 d /8 d CT/5 wk MR/4mo	Normal Periventricular/thalamic hyperechogenicity Normal Calcified thalami; hypodense basal ganglia; mild lateral ventricular irregularity T1, T2 shortening thalami; small basal ganglia; large lateral ventricles with irregular lateral margins	Abnormal neurologic exam at age 3 mo
3	27	Circulatory arrest at birth, duration uncertain.	US/3 d /5 d /1mo CT/9 wk	Normal Hyperechogenic thalami Hyperechogenic thalami Ventriculomegaly with irregularity lateral wall calcified; shrunken thalami; hypodense basal ganglia Ventriculomegaly; cystic basal ganglia; small, hyperechogenic thalami Large cerebrospinal fluid spaces; right subdural hematoma; cystic replacement of basal ganglia; small thalami with very short T1 and T2; very small brain stem and cerebellum; very short T1 and T2 of dorsal brain stem	Developmentally delayed and neurologically abnormal at age 9 mo
4	32	Recipient of twin-twin transfusion at postconceptional age 28 wk	US/3 d MR/4 d	Ventriculomegaly; cystic basal ganglia; small, hyperechogenic thalami Large cerebrospinal fluid spaces; right subdural hematoma; cystic replacement of basal ganglia; small thalami with very short T1 and T2; very small brain stem and cerebellum; very short T1 and T2 of dorsal brain stem	Died at age 5 d
5	32	In utero cardiac arrest (about 20–25 min) at postconceptional age 28 wk.	CT/2 d	Shrunken thalami with hyperdense periphery and central cavitation; hypodense basal ganglia; slightly prominent lateral ventricles; low attenuation in dorsal brain stem	Died at age 5 wk

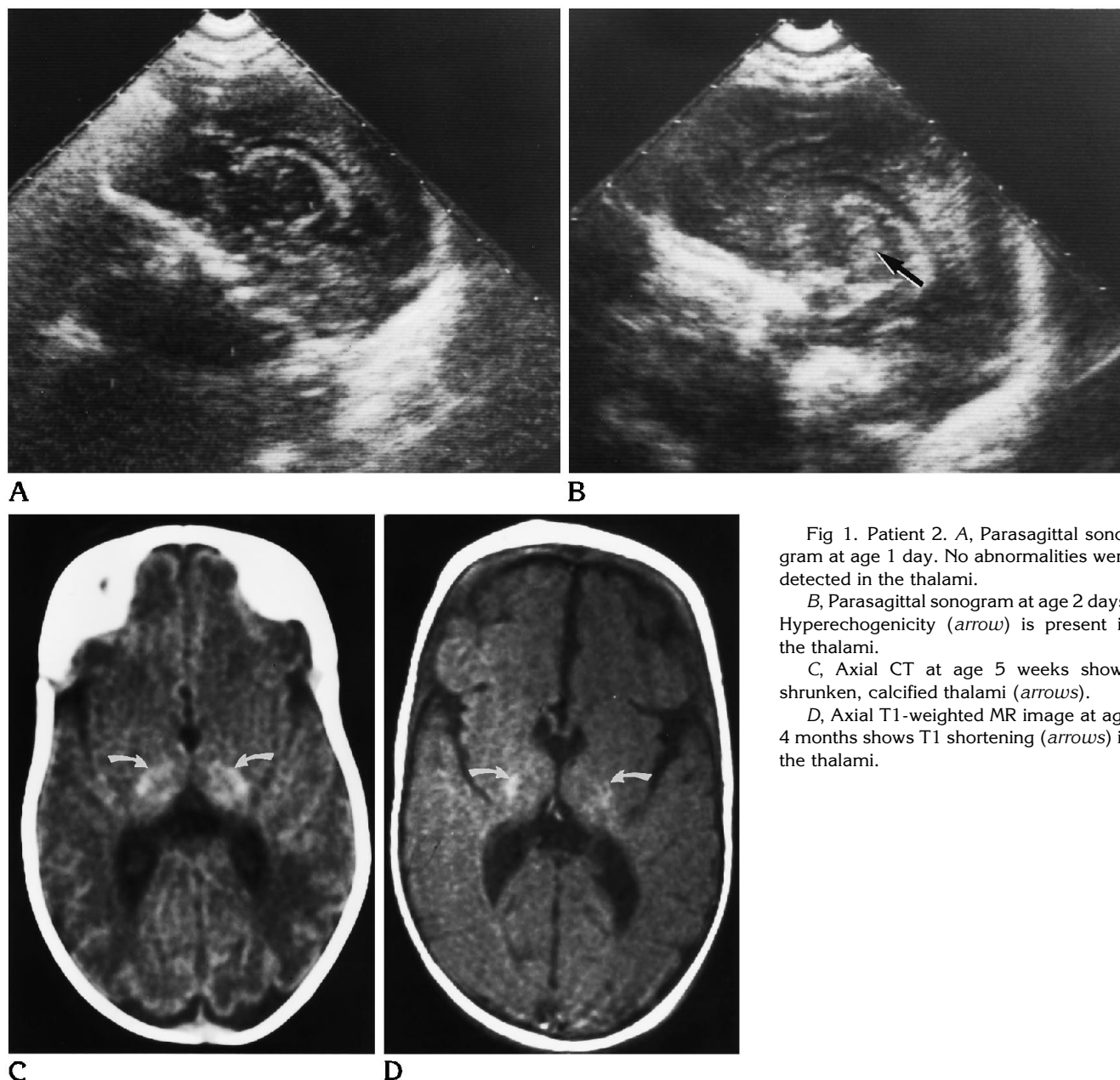


Fig 1. Patient 2. A, Parasagittal sonogram at age 1 day. No abnormalities were detected in the thalami.

B, Parasagittal sonogram at age 2 days. Hyperechogenicity (arrow) is present in the thalami.

C, Axial CT at age 5 weeks shows shrunken, calcified thalami (arrows).

D, Axial T1-weighted MR image at age 4 months shows T1 shortening (arrows) in the thalami.

eventful cesarean section at postconceptional age of 32 weeks.

Sonograms were obtained between the ages of 1 and 8 days in all five patients. CT was obtained in three patients between the ages of 2 days and 9 weeks; MR was obtained in three patients between the ages of 4 days and 4 months (Table). Sonograms were obtained by sequential imaging in the parasagittal and coronal planes through the anterior fontanelles using a 7.5-MHz transducer. CT was done in the axial plane with contiguous 5- or 10-mm-thick images; intravenous contrast was not administered. MR was done with standard 4-mm sagittal spin-echo T1-weighted images (500–600/11–15/2 [repetition time/echo time/excitations]) in the sagittal and axial planes, supplemented

with standard 4-mm axial spin-echo T2-weighted (3000/60,120/1) images.

An autopsy report was available for one patient.

Results

The imaging studies showed various patterns of damage in the thalami and basal ganglia bilaterally in all patients. The thalamic abnormality was detected as hyperechogenicity on sonography in four patients (Fig 1), although the thalami appeared normal, even in retrospect, on early scans in two of the four (Fig 1).

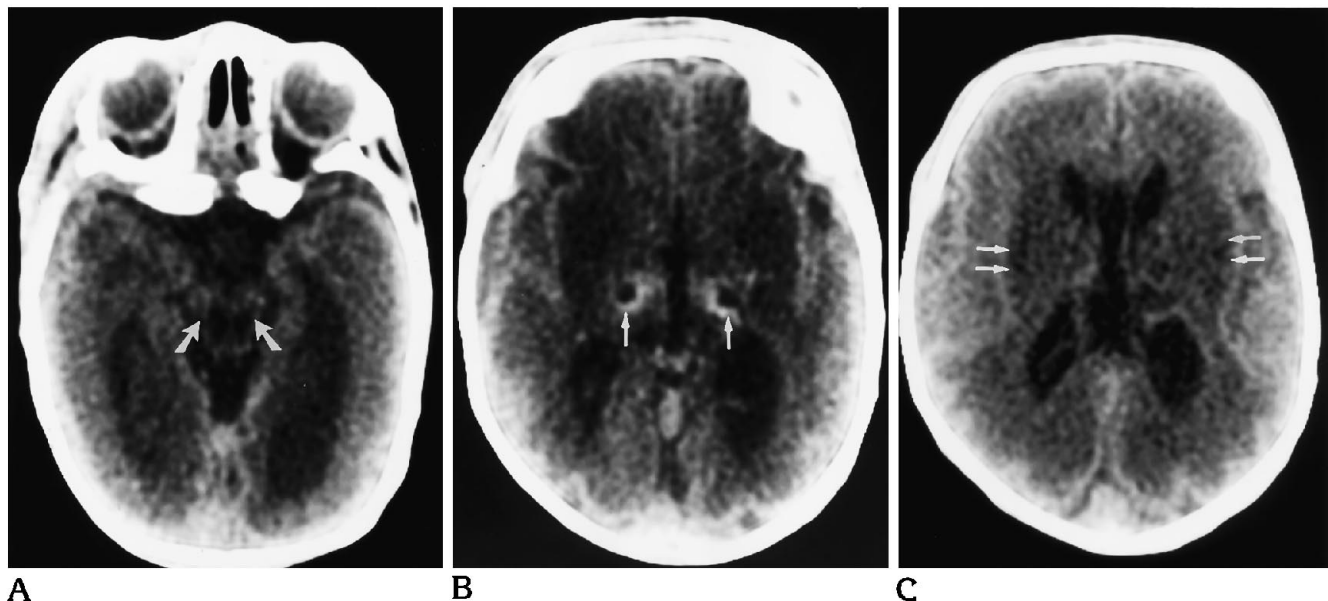


Fig 2. Patient 5, injured at postconceptional age of 28 weeks and born at postconceptional age of 32 weeks. CT performed 2 days after birth.

A, Axial CT image shows hypodensity (arrows) in the dorsal mesencephalon.

B, Axial CT image shows high attenuation (arrows) surrounding cavitation in the lateral thalami.

C, Axial CT image 5 mm superior to B shows enlarged ventricular trigones and low attenuation of the basal ganglia (arrows), which are isodense to white matter.

The thalami appeared shrunken and hyperdense, either calcified or hemorrhagic, on CT (Figs 1, 2); central cavitation was present in one patient (Fig 2). MR showed the thalami to have T1 and T2 shortening in all three cases (1, 3, 4); the thalami were shrunken in the two cases imaged in the chronic phase after the injury (Figs 1, 4).

The basal ganglia abnormalities were more variable than those of the thalami. Ultrasound showed basal ganglia abnormality only in patient 4 (Fig 3), revealing cystic degeneration with hypoechogenicity and increased through transmission. CT showed hypodense basal ganglia (Fig 2) in all three patients imaged. MR showed T1 and T2 shortening in the globus pallidus in patient 1 (Fig 3), imaged at 12 days; cystic replacement of the basal ganglia in patient 4 (Fig 4), imaged at age 4 days (but presumably several weeks after injury); and small basal ganglia without signal abnormality in patient 2, imaged at age 4 months.

Damage to the periventricular white matter was indicated by T1 and T2 shortening in the periventricular region in patients 1 and 4 (Fig 3) and ventriculomegaly with focal bulging of the ventricular bodies in patients 2, 3, and 5. Patient 4 had, in addition, severe diminution of the ce-

rebral hemispheric white matter; milder white matter diminution was present in patients 2 and 3.

The brain stem and cerebellum appeared small in patients 2 through 5. Patient 4 had abnormal T1 and T2 shortening (Fig 4) in the dorsal brain stem; patient 5 had abnormally low attenuation in the dorsal pons and mesencephalon (Fig 2). The temporal horns were enlarged, and the hippocampi appeared somewhat small in all patients in the study; however, coronal images clearly documenting the hippocampal atrophy (Fig 4) were obtained only in patient 4.

Autopsy of patient 4 revealed extensive white matter infarction of the cerebral hemispheres, with and without cystic changes. Marked gliotic thickening was reported in the paraventricular region, and the ependymal surface was noted to be disrupted with foci of ependymal cells within the paraventricular gliotic scar. These findings are compatible with periventricular leukomalacia. Extensive cystic changes were noted in the basal ganglia. Large ventricles suggested hydrocephalus ex vacuo. The thalami showed severe cystic changes with frequent lipid-laden macrophages and neuronal ferrugination. The cerebellum was noted to show normal architec-

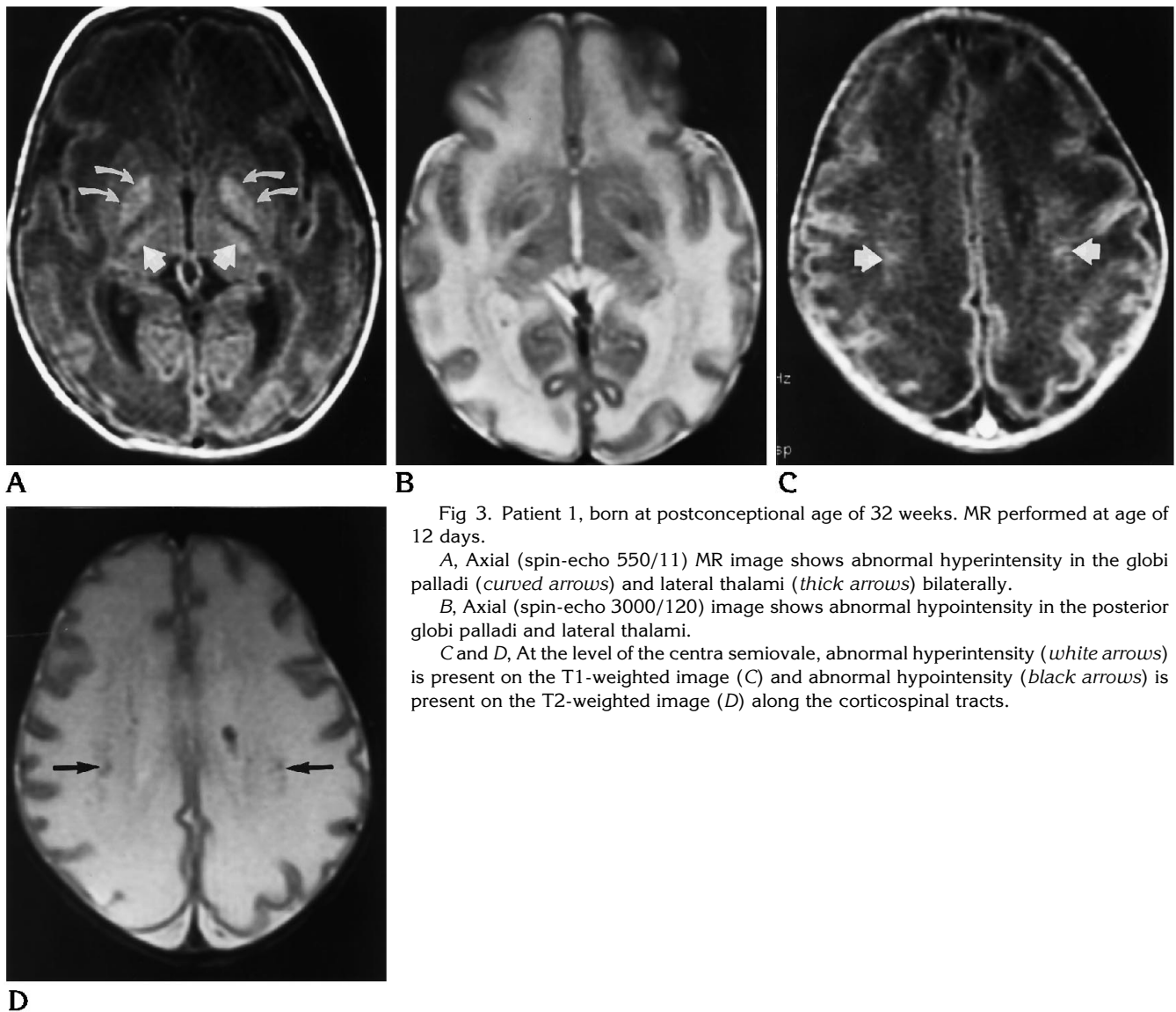


Fig 3. Patient 1, born at postconceptional age of 32 weeks. MR performed at age of 12 days.

A, Axial (spin-echo 550/11) MR image shows abnormal hyperintensity in the globi palladi (*curved arrows*) and lateral thalami (*thick arrows*) bilaterally.

B, Axial (spin-echo 3000/120) image shows abnormal hypointensity in the posterior globi palladi and lateral thalami.

C and D, At the level of the centra semiovale, abnormal hyperintensity (*white arrows*) is present on the T1-weighted image (C) and abnormal hypointensity (*black arrows*) is present on the T2-weighted image (D) along the corticospinal tracts.

ture with extensive neuronal loss and calcification of the remaining neurons. Sections from the midbrain showed severe neuronal damage, neuronal ferrugination, lipid-laden macrophages, and focal white matter infarction.

The limited follow-up data available for these patients is presented in the Table. Two patients died within the first 5 weeks after birth, and the other three were neurologically impaired.

Discussion

The patients reported in this paper all show similar imaging abnormalities, indicating that profound asphyxia in the premature infant gives a characteristic pattern of damage on neuroim-

aging. Patients showed diminution of cerebral hemispheric white matter and shrunken basal ganglia, thalami, brain stem structures, and cerebelli. The damaged thalami appeared hyperdense on CT (Figs 1, 2) and were hyperechoic on sonography (Fig 1), whereas the basal ganglia and cerebella showed signal abnormality on CT and MR without obvious calcification. This pattern of injury differs considerably from that in premature infants with less severe hypotension (partial asphyxia, secondary to such disorders as hyaline membrane disease or patent ductus arteriosus); partial asphyxia generally results in damage to the periventricular white matter with relative sparing of gray matter structures (2, 14–16).

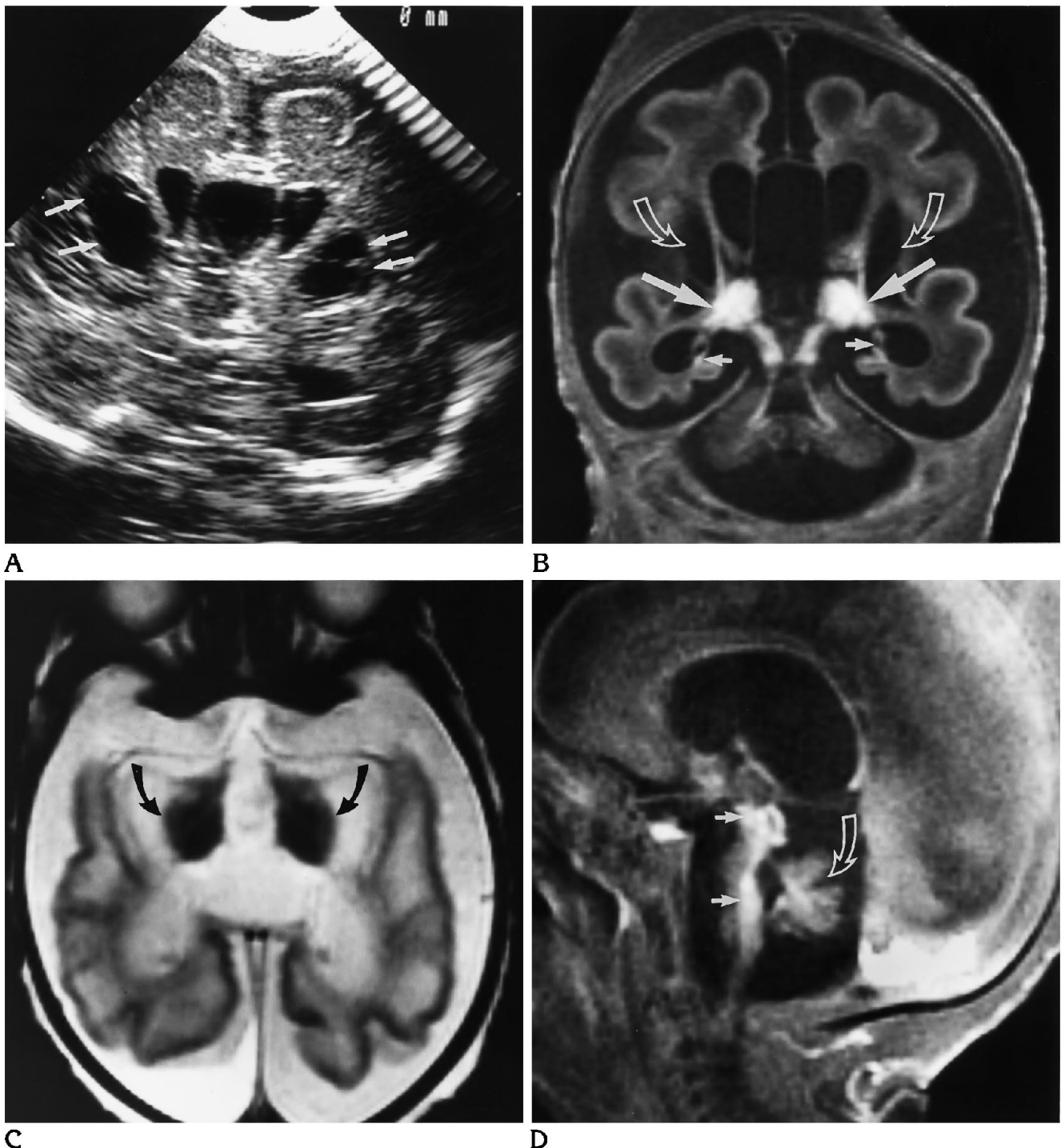


Fig 4. Patient 4, recipient of twin-twin transfusion at postconceptional age of 26 to 28 weeks, born at postconceptional age of 32 weeks.

A, Coronal sonogram on postnatal day 3 shows cystic degeneration (*arrows*) in the region normally occupied by the lentiform nuclei.

B, Coronal (spin-echo 600/13) MR image on postnatal day 4 shows water intensity (*open curved arrows*) in the region normally occupied by the lentiform nuclei. The thalami (*large solid arrows*) are small and markedly hyperintense. The hippocampi (*small arrows*) are very small, resulting in enlargement of the temporal horns of the lateral ventricles.

C, Axial (spin-echo 3000/120) MR image shows the thalami (*arrows*) to be markedly hypointense.

D, Sagittal (spin-echo 500/13) MR image shows a small brain stem with marked heterogeneous hyperintensity dorsally (*solid arrows*). The cerebellum (*open curved arrow*) appears small but has normal signal intensity.

Pattern of Injury

The pattern of injury observed in the premature infants in the present study is similar to that described in term infants who have profound asphyxia; MR imaging shows injury to the thalami, basal ganglia, hippocampi, and corticospinal tracts in profoundly asphyxiated term infants (3, 17–19). However, some differences from the pattern in term infants are apparent. One difference seems to involve the perirhinal cerebral cortex, which often is involved in profound asphyxia in the term infant (3) but was spared in our preterm neonates. Another difference seems to be that the basal ganglia are less affected and, when affected, tend to cavitate and shrink without associated scarring in the preterm infant, whereas the basal ganglia of term infants show considerable scarring, particularly in the posterior putamina (3, 20).

The finding of differential involvement of the thalami and basal ganglia in premature infants having profound asphyxia, as compared with term infants with similar injuries, seems to be borne out in pathologic studies of presumed profound asphyxic injuries to infants before 33 weeks of postconceptional age. In their pathologic analysis of a twin injured during the second trimester, Jolly and Norman noted significant thalamic scarring but atrophy with relatively little scarring in the basal ganglia (21). Parisi et al reported a case of a neonate, who died 32 days after birth at approximately 36 weeks' gestation, who manifested patchy areas of severe neuron loss, intense fibrillary astrogliosis, and many mineralized neurons in the thalami. Injury was estimated to have occurred in utero, because the infant showed persistent hypertonic posturing and flexion contractures were present at birth at the ankles, knees, and elbows. There was a history of premature labor at 32 weeks, arrested by medical therapy; thus, the fetus was presumed to have been injured at 32 weeks. A marginal reduction of Purkinje cells in the cerebellar vermis and "questionable gliosis" in the brain stem tegmentum were reported as well. The cerebral cortex, basal ganglia, and hippocampi were reported as unremarkable (22). Hallervorden described cavitation of the globi palladi, atrophy of the striatum, and nearly complete loss of nerve cells in the lateral thalamic nuclei in a fetus after maternal carbon monoxide poisoning at the 24th gestational week (23); cortical polymicro-

gyria was noted as well. Cohen and Roessmann report the autopsy findings of a child born at 33 weeks after maternal respiratory arrest at 28 gestational weeks (the child died at age 7 months as a result of multiple respiratory infections [24]). They report neuronal loss, scarring, and calcification in the lateral thalamic nuclei and dorsal brain stem, with loss of cerebellar Purkinje cells but little basal ganglia damage. Wilson et al reported a case of a 32-week neonate with presumed prenatal injury who was "moribund" at birth and died at age 3 hours. Autopsy showed damage to the periventricular white matter and clusters of neuronal ferrugination, neuronal loss, and astrogliosis symmetrically distributed in the thalami and hypothalamus; somewhat random individual neuronal changes (not specified) were detected in the basal ganglia (25). Thus, pathology studies seem to support the hypothesis that profound injury before approximately 32 weeks of postconceptional age results in thalamic scarring, and sometimes calcification, with less severe scarring and less severe damage to the basal ganglia. In contrast, significant basal ganglia scarring and damage are detected on pathologic examination of term infants who have had profound asphyxia (7, 17, 26).

The reason for the decrease in damage to and decreased scarring within the basal ganglia before 33 weeks is unknown, but it is interesting to note that the thalami myelinate at 23 to 25 weeks' gestational age, before the basal ganglia, which myelinate at 33 to 35 weeks' gestational age (27). The onset of myelination in specific white matter tracts is generally accepted to be related to the onset of essential functions, and, thus, increased neuronal activities within those tracts (28–30). Indeed, the locations of highest glucose uptake within the brain of the neonate (31) correlate almost exactly with the locations of most advanced myelination (27). Because they have higher metabolic activity, it is expected that the tracts that are myelinated would have higher energy requirements and be more susceptible to damage secondary to loss of substrates (such as oxygen and glucose). In addition, because oligodendrocytes, which make myelin, develop from astrocytic precursors, it is interesting to speculate that the astrocytes develop earlier in regions that myelinate earlier. If so, astrocytic response to injury may develop at an earlier time in the thalami than in the basal ganglia. Before the

development of an astrocytic response to injury, the brain reacts to injury by resorption of the damaged tissue without significant astrocytosis (gliosis) (32–34). Thus, with a mild or moderate degree of neuronal injury, one might expect a structure to shrink (secondary to neuronal loss) without significant scarring, as observed in patient 2, whereas a severe injury would be expected to result in cavitation, similar to that noted in the basal ganglia in patient 4.

It also is of interest to note that the autopsy studies referred to in prior paragraphs almost all describe damage to the dorsal brain stem. The relative absence of signal abnormalities in the brain stem on imaging studies of patients with profound asphyxia has been mentioned in previous studies on imaging of patients after perinatal hypoxic-ischemic injury (2, 3, 35). One of those authors (3) has commented that one could not determine whether the lack of imaging abnormality resulted from the lack of injury in a subgroup of patients who were less severely injured or from a lack of sensitivity to brain stem injury by imaging modalities. Patients 4 and 5 in this study had significant signal abnormality in the dorsal brain stem (Figs 2, 4), low attenuation on CT in patient 5, and T1 and T2 shortening on MR in patient 4. The MR signal changes in patient 4 probably represent the neuronal injury, ferrugination, and lipid-laden macrophages that were reported in the brain stem at autopsy. These observations would support the concept that neuroimaging can detect brain stem injury, but the children who suffer injury severe enough to cause brain stem injury may not live long enough to undergo imaging. Indeed, patients 4 and 5 both died before the end of the first week of life.

It appears, however, that MR imaging may not be very sensitive to injury of the cerebellar cortex. It is well known from autopsy and experimental studies that the Purkinje cells of the cerebellar cortex are very vulnerable to injury from hypoxic-ischemic insults (17–19, 26). However, cerebellar injury has not been reported as a finding in neuroimaging studies of asphyxiated neonates. In the patients studied for this paper, the cerebellar vermis and hemispheres appeared to have normal shape and normal signal characteristics with all three imaging modalities. Other than in patient 4, the size of the cerebellum was judged to be normal, as well. However, the autopsy of patient 4 showed extensive neuronal loss and no recog-

nizable external granular layer, Purkinje cell layer, or internal granular layer of the cerebellar cortex. No obvious explanation for the lack of sensitivity to the cerebellar cortical injury is apparent.

Cause of the Signal Changes

A number of earlier manuscripts on MR of hypoxic-ischemic injury in the neonate have commented upon regions of T1 and T2 shortening in the basal ganglia (3, 5–7, 12). Some have attributed this signal abnormality to hemorrhage (5, 6). Others, noting that the T1 shortening develops several days before the T2 shortening (the opposite from what is expected in hemorrhage) have speculated that calcium or myelin breakdown products are a more likely cause of the signal abnormality (12). The autopsy of patient 4 showed lipid-laden macrophages and neuronal ferrugination, but no evidence of calcification or hemorrhage, in the thalami and brain stem. Thus, it is likely that the lipid breakdown products of myelin, phagocytized by macrophages, are responsible for the T1 shortening. This explains why the T1 shortening in asphyxiated neonates is seen predominantly in regions that are already myelinated at birth. The T2 shortening, which usually appears 6 or 7 days after the injury, may be the result of chemical modifications of the lipids within the lysosomes of the macrophages, the ferrugination of the neurons, calcification, or a combination of these factors.

Injury to Twins

An interesting aspect to this collection of cases is the injury to patient 4, who was the recipient of a twin-twin transfusion at approximately 28 postconceptional weeks. Ischemic brain injury in twin gestation is an interesting subject and deserving of some discussion. The incidence of prenatal mortality is high in twins; as many as 80% of twin pregnancies diagnosed with routine sonography in the first trimester are singletons by the time of birth (36, 37). The incidence of brain injury in twin pregnancies also is relatively high, estimated at 30% in monochorionic twins. (By contrast, the incidence in dichorionic twins is about 3% [19, 38–41].) The ischemic brain injury is primarily the result of the presence of placental vascular anastomoses (artery to vein or vein to vein),

which are nearly always present in monochorionic placentas (42); the process has been termed *twin-twin transfusion*. The type of ischemic brain injury is dependent on the age of the fetuses at the time of the transfusion. Injuries reported from events during the second half of pregnancy include localized cerebral infarctions (single or multiple), porencephaly, hydranencephaly, multicystic encephalomalacia, and periventricular leukomalacia (19, 38–41). Mechanisms of injury that have been elucidated include: (a) disseminated intravascular coagulation caused by transfer of thromboplastin material from the dead twin; (b) embolism from the dead fetus or placenta; (c) severe hypotension and cerebral ischemia resulting from transfusion of blood from the surviving fetus to the dead fetus; and (d) placental circulatory stasis resulting in impaired umbilical cord blood flow or embolism (38, 39, 41). Mechanism d is currently believed to be the most common (42) and is the likely mechanism of injury in patient 4 because of the presence of ischemic damage and the lack of embolic foci or their residua in the brain or any other organs.

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