RadioGraphics

Neonatal Hypoxic-Ischemic Encephalopathy: Multimodality Imaging Findings[1]

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ONLINE-ONLY CME

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LEARNING OBJECTIVES

After reading this article and taking the test, the reader will be able to:

- Describe the clinical parameters that result in the patterns of brain injury.
- Identify the US, CT, and MR imaging characteristics of neonatal hypoxic-ischemic encephalopathy.
- Discuss the advantages and disadvantages of each imaging modality for evaluating the various patterns of hypoxic-ischemic brain injury.

TEACHING POINTS

See last page

Diffuse hypoxic-ischemic brain injury in the neonate results in neonatal hypoxic-ischemic encephalopathy (HIE). Because of differences in brain maturity at time of insult, severity of hypotension, and duration of insult, there are four distinct patterns of brain injury. Cranial ultrasonography and computed tomography reveal periventricular leukomalacia, germinal matrix hemorrhage, and hydrocephalus. Magnetic resonance imaging is the most sensitive modality for evaluating the patterns of brain injury. In preterm neonates, mild hypotension causes periventricular injury; severe hypotension results in infarction of the deep gray matter, brainstem, and cerebellum. In term neonates, mild hypotension causes parasagittal cortical and subcortical injury; severe hypotension causes characteristic injury of the lateral thalami, posterior putamina, hippocampi, corticospinal tracts, and sensorimotor cortex. Prompt recognition of these imaging findings can help exclude other causes of encephalopathy, affect prognosis, and facilitate earlier (although mostly supportive) treatment.

Abbreviations: EEG = electroencephalographic, HIE = hypoxic-ischemic encephalopathy, NAA = *N*-acetylaspartate, PVL = periventricular leukomalacia, RI = resistive index

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Introduction

Neonatal encephalopathy may result from a variety of conditions. When caused by diffuse hypoxic-ischemic brain injury, it has been called hypoxic-ischemic encephalopathy (HIE). HIE is one of the most common causes of cerebral palsy and other severe neurologic deficits in children, occurring in two to nine of every 1000 live births (1–3). Although the exact pathophysiology of HIE is not completely understood, the lack of sufficient blood flow in conjunction with decreased oxygen content in the blood leads to loss of normal cerebral autoregulation and diffuse brain injury. The exact nature of the injury depends on the severity of hypotension and the degree of brain maturation. There is no consensus regarding the gestational age demarcation at which an infant is considered preterm or term. However, most authors describe a pattern of injury in neonates who are less than 36 weeks gestation that is distinct from the pattern in neonates 36 weeks or older (4–6). Thus for the purposes of this discussion, it is reasonable to designate a preterm neonate as being one who is less than 36 weeks gestation. Accurate identification and characterization of the severity, extent, and location of brain injury rely on the selection of appropriate neuroimaging modalities, including ultrasonography (US), computed tomography (CT), and magnetic resonance (MR) imaging. Newer diagnostic techniques such as diffusion-weighted MR imaging and MR spectroscopy provide further insight into HIE and the potential for possible therapeutic intervention. The prognosis of neonatal HIE depends on the severity of the injury and the gestational age of the affected infant. Treatment has traditionally been primarily supportive, aimed at correction of the underlying cause of the hypoxia and ischemia. New emerging therapies, such as hypothermia and calcium channel blockers, are directed at the processes of ongoing injury.

In this article, we review the pathophysiology and clinical manifestations of HIE; discuss the strengths and weaknesses of US, CT, and MR imaging for evaluating the condition; describe the four patterns of brain injury observed; and briefly review prognosis and treatment.

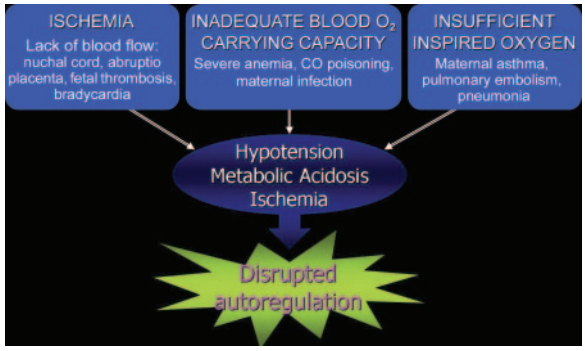


Figure 1. Diagram summarizes the causes of HIE.

Pathophysiology

Perinatal asphyxia is the most important cause of HIE, resulting in hypoxemia and hypercapnia. Hypotension and the resulting decreased cerebral blood flow lead to a cascade of deleterious events, including acidosis, release of inflammatory mediators and excitatory neurotransmitters, free radical formation, calcium accumulation, and lipid peroxidation. These biochemical substances result in loss of vascular autoregulation in the setting of cerebral hypoperfusion. These "events" result in biphasic energy failure, in which initial impairment of cell metabolism is followed by reperfusion prior to eventual neuronal cell death (7–11).

Impaired cerebral blood flow may result from fetal cardiac and vascular compromise, occurring either in utero or postnatally. Intrauterine asphyxia occurs when placental blood flow and gas exchange is interrupted. Such interruption may be caused by fetal factors (fetomaternal hemorrhage, fetal thrombosis, and fetal bradycardia), inadequate placental perfusion (maternal hypotension, preeclampsia, chronic vascular disease, abruptio placenta), impaired maternal oxygenation (asthma, pulmonary embolism, pneumonia, carbon monoxide poisoning, severe anemia), or disrupted umbilical circulation (tight nuchal cord, cord prolapse). Postnatal asphyxia results from underlying severe hyaline membrane disease, pneumonia, meconium aspiration, or congenital heart anomalies that cause neonatal pulmonary failure or hypotension (Fig 1) (9). Regardless of the cause of asphyxia, the ultimate fetal cardiac and vascular compromise leads to diminished cerebral blood flow, loss of cerebral autoregulation, and neuronal cell death.

Clinical Manifestations

The encephalopathic neonate may have low Apgar scores (slow heart rate, poor respiratory effort, abnormal color, decreased level of alertness, abnormal muscle tone, and a weak or absent cry) at delivery and metabolic acidosis documented in the cord blood. Within the first 24 hours of life, the infant may develop symptoms of apnea and seizures with abnormal electroencephalographic (EEG) results. Abnormal EEG results may be helpful in the prediction of clinical outcome, including the likelihood of death and significant long-term neurologic sequelae, such as spastic quadriplegia or diplegia (10).

Strengths and Weaknesses of Imaging Modalities in Evaluating HIE

Cranial US provides a convenient, noninvasive, relatively low-cost screening examination of the hemodynamically unstable neonate at the bedside. The examination also imparts no radiation exposure. Sonography is sensitive for the detection of hemorrhage, periventricular leukomalacia (PVL), and hydrocephalus. Doppler interrogation and the assessment of resistive index (RI) provide additional information on cerebral perfusion. Normally, the RI decreases with increasing gestational age, and thus correlation with gestational age is necessary for accurate interpretation of RI results (12). Decreased RI is noted to be an abnormal finding and is postulated to be caused by impairment in cerebral autoregulation and subsequent decreased cerebrovascular resistence and increase in end-diastolic flow. However, sustained asphyxia with subsequent development of intracranial hemorrhage or diffuse cerebral edema and loss of forward diastolic flow result in increased RI and is indicative of a poor outcome (13–15). Sonography is operator dependent, however, and less sensitive to structural abnormalities in the cerebral convexity and in the brainstem (16). Parenchymal abnormalities, such as PVL and cerebral edema, identified at US are also often nonspecific (17).

CT is the least sensitive modality for evaluation of HIE because of the high water content in the neonatal brain and high protein content of the cerebrospinal fluid, which result in poor parenchymal contrast resolution. In addition, CT has the inherent disadvantage of radiation exposure. However, with present CT technology, it provides a rapid mode of cranial screening for hemorrhage in a sick neonate without the need for sedation (17).

Teaching Point

The most sensitive and specific imaging technique for examining infants with suspected hypoxic-ischemic brain injury is MR imaging (17). Although conventional MR imaging sequences are less sensitive than newer techniques in documentation of sequelae of an ischemic injury in neonates within the first few hours and days following the ischemic event, they can help exclude other causes of encephalopathy such as hemorrhage, cerebral infarction, neoplasms, or congenital malformations. Hypoxic-ischemic injury to gray matter (deep gray matter, cortex) demonstrates characteristic T1 hyperintensity and variable T2 intensity, depending on the time at imaging and the dominant underlying pathologic condition, such as hemorrhage or gliosis. Injury to white matter generally results in T1 hypointensity and T2 hyperintensity due to ischemia-induced edema (5,6). Diffusion-weighted MR imaging performed with apparent diffusion coefficient maps between 24 hours and 8 days of life is more sensitive for the detection of cytotoxic edema, as it reveals restricted diffusion earlier than the signal intensity abnormalities are evident on conventional T1- or T2-weighted images (18). However, the apparent diffusion coefficient value does not appear to correlate well with the extent of the ischemic injury and is not predictive of adverse outcome (10,11,19). MR spectroscopy provides gross biochemical analysis of the "compromised anaerobic" cerebral tissues, as it reveals changes in the concentrations of lactate, choline, creatine, *N*-acetylaspartate (NAA), and glutamine. Elevated lactate and diminished NAA concentrations are common findings in infants with late neurologic sequelae (20). Zarifi et al (11) showed that a lactate-choline ratio of 1 indicates a greater than 95% probability of adverse neurodevelopmental outcome, whereas the absence of lactate predicts a normal outcome. Barkovich et al (8) found that MR spectroscopy performed in the first 24 hours after birth is more sensitive to the severity of hypoxic-ischemic brain injury than diffusion-weighted MR imaging, which can demonstrate the injury but underestimates its extent.

Unfortunately, off-hours MR imaging is often not possible because of a combination of factors: the need for sedation in a sick neonate, lack of optimal safe transport, and limited access to the MR imaging unit at smaller facilities (17).

Patterns of Brain Injury

Although some overlapping features exist, four distinct patterns of brain injury are observed and result from various combinations of three primary factors: the level of brain maturation at the time of the insult and the severity and duration of the hypoperfusion event. The degree of brain maturation dictates the configuration of the vascular supply as well as the state of regional metabolism in the neonatal brain. In mild to moderate hypoperfusion, cerebral blood flow is redistributed to ensure perfusion to the hypermetabolically active gray matter structures including the basal ganglia, brainstem, and cerebellum; this redistribution results in injury predominantly to the intervascular zones of the cerebrum. In severe hypoperfusion, the vulnerable regions of the brain are the deep gray matter, myelinated fibers with higher concentrations of neurotransmitter receptors. The deep gray matter, especially the thalami, and the brainstem are most metabolically active in the immature brain (<36 weeks gestation), whereas injury involving the lateral thalami, globus pallidus, posterior putamina, hippocampi, brainstem, and sensorimotor cortex are seen in term infants (7,21). (Historically, the signal abnormalities have been described to be in the functionally defined "perirolandic cortex," which in recent years has been shown to correspond to the anatomic sensorimotor cortex in normal brains.)

The vascular supply to the brain changes with brain maturation. In the immature brain, ventriculopetal penetrating arteries extend inward from the surface of the brain to supply the periventricular regions; hence, PVL is the most common pathologic finding in hypoperfusion injury. With maturation of the brain (≥36 weeks gestation), vessels extend into the brain from the lateral ventricles, and the intervascular border zone moves peripherally to a parasagittal location (Fig 2). A hypoxic-anoxic event lasting for more than 10 minutes is required to induce parenchymal changes, and the extent of injury increases with prolonged duration of the insult (7).

The four distinct patterns of brain injury discussed herein are mild to moderate hypotension in preterm infants, severe hypotension in preterm infants, mild to moderate hypotension in term infants, and severe hypotension in term infants.

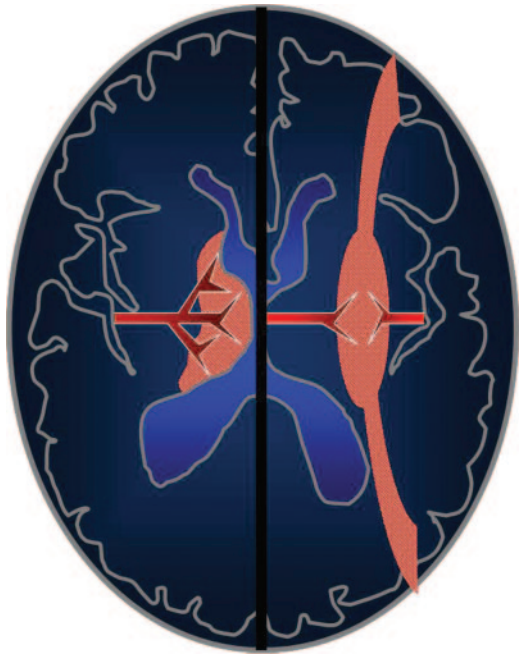


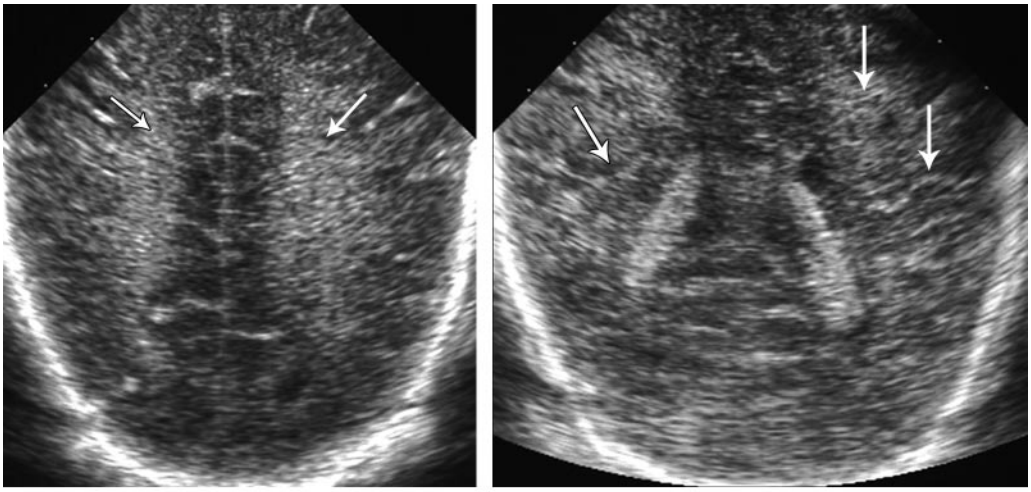
Figure 2. Patterns of brain injury in mild to moderate hypoperfusion. Schematic of the premature neonatal brain (left) and that of the term infant (right) illustrates how the vascular supply changes with maturation and affects the pattern of brain injury in HIE. The premature neonatal brain (left) has a ventriculopetal vascular pattern, and hypoperfusion results in a periventricular border zone (red shaded area) of white matter injury. In the term infant (right), a ventriculofugal vascular pattern develops as the brain matures, and the border zone during hypoperfusion is more peripheral (red shaded area) with subcortical white matter and parasagittal cortical injury.

Hypoperfusion Injury in Preterm Infants

Mild to Moderate Hypotension.—The most common location for injury to the premature brain is the periventricular white matter, with ischemic parenchyma manifesting as PVL. The spectrum of imaging findings relates to the evolution of the ischemic parenchymal tissue. Initial sonograms show hyperechogenic globular change in the periventricular regions, and MR images depict areas of T1 hyperintensity within larger areas of T2 hyperintensity (Fig 3). Subsequent cavitation and periventricular cyst formation, features that are required for a definitive diagnosis of PVL, develop 2–6 weeks after injury and are easily seen on sonograms as localized anechoic or hypoechoic lesions (Fig 4). Progressive necrosis

Teaching Point

Figure 3. PVL in a preterm (30 weeks gestation) infant with a history of acute respiratory failure, mild to moderate hypotension, and necrotizing enterocolitis. **(a, b)** Initial coronal cranial US scans show symmetric, diffuse periventricular white matter echogenicity (arrows in **a**) and loss of regular parenchymal spacing. There are linear hyperechoic changes (arrows in **b**), findings suggestive of accompanying hemorrhage. **(c)** Follow-up axial T2-weighted MR image obtained at 36 weeks postconception shows hyperintense T2 signal in the periventricular white matter (*). Although this finding is often difficult to distinguish from inherent lack of myelination, when interpreted in conjunction with findings from the patient's other neuroimaging studies, it was believed to be real and consistent with leukomalacia. **(d, e)** Axial **(d)** and sagittal **(e)** T1-weighted MR images show curvilinear T1 hyperintense signal (arrows) in the periventricular white matter, a finding consistent with hemorrhage.



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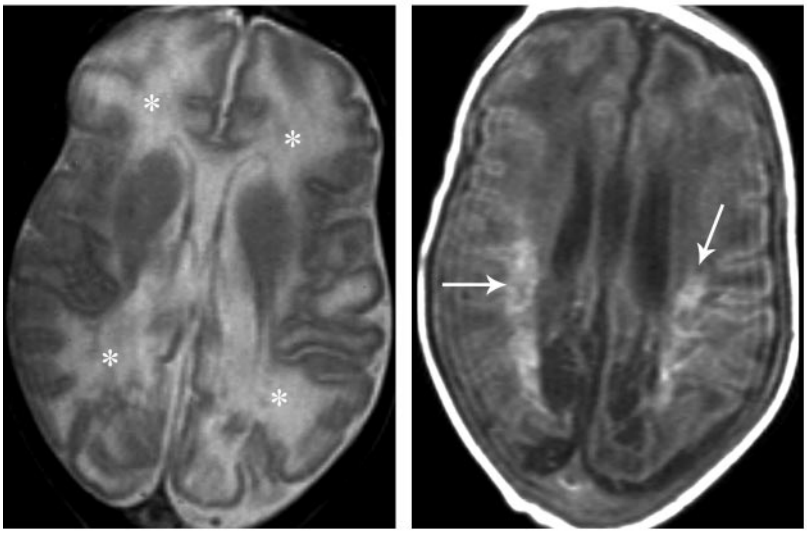

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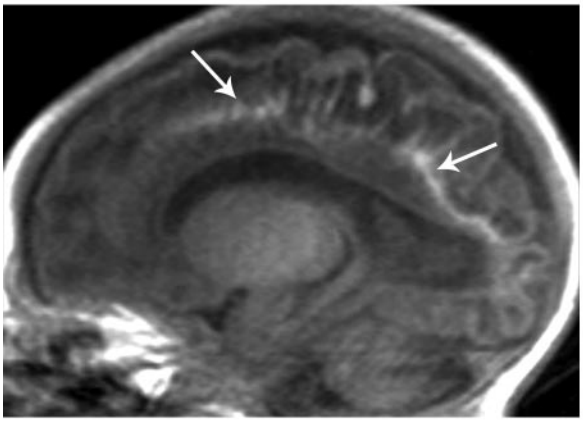

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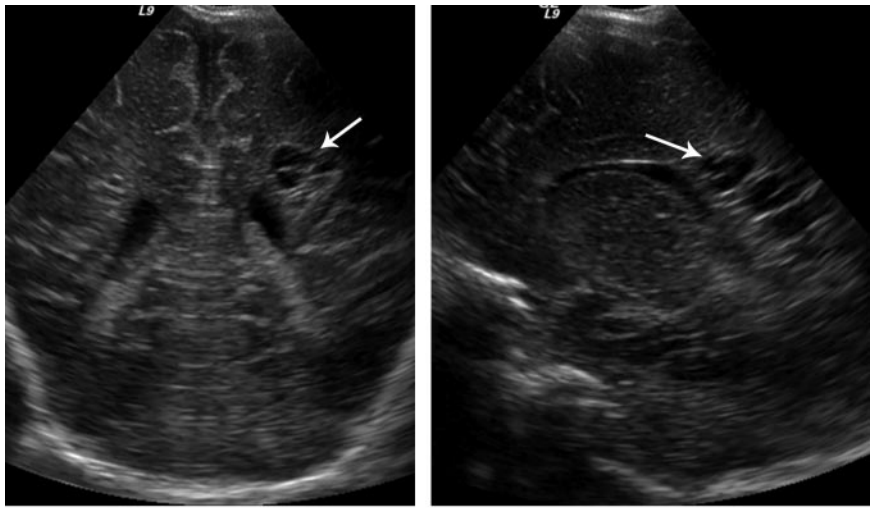
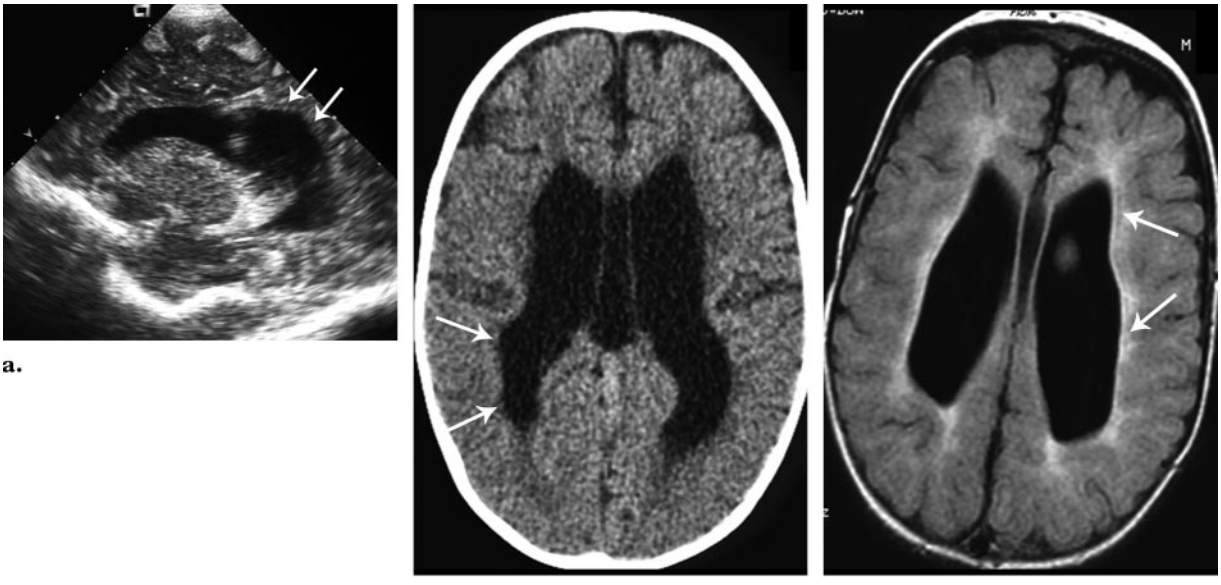


Figure 4. Cystic PVL in a preterm (28 weeks gestation) infant with a history of central apnea and moderate hypotension. Coronal **(a)** and sagittal **(b)** cranial US scans show multiple anechoic cysts in the periventricular region (arrow).

Figure 5. End-stage or chronic PVL in a preterm (28 weeks gestation) twin delivered prematurely because of maternal preeclampsia. **(a)** Sagittal cranial US scan of the 7-month-old infant shows enlarged lateral ventricles with irregular margins (arrows). **(b)** Follow-up axial CT scan obtained at 1 year of age shows the same findings (arrows), which are consistent with decreased myelination in the periventricular location and ex vacuo ventricular dilatation. **(c)** Axial fluid-attenuated inversion-recovery MR image obtained at 1 year of age shows a thin band of T2 hyperintensity along the ventricular surface (arrows), representing gliosis. Note that the deep, prominent sulci nearly abut the ventricular surface due to loss of white matter volume.



of the periventricular tissue with resulting enlargement of the ventricles is called end-stage PVL. CT and MR imaging findings of end-stage PVL include ventriculomegaly with irregular margins of the bodies and trigones of the lateral ventricles, loss of periventricular white matter with increased T2 signal (Fig 5), and thinning of the corpus callosum (Fig 6) (7,17,21,22).

Subsequent reperfusion to the ischemic tissues in the setting of weakened capillaries and increased venous pressure result in germinal matrix hemorrhage, ranging in severity from subependymal hemorrhage (grade 1) to intraventricular hemorrhage without (grade 2) and with (grade 3) ventricular dilatation (Fig 7), to parenchymal extension and coexisting periventricular venous infarction (grade 4).

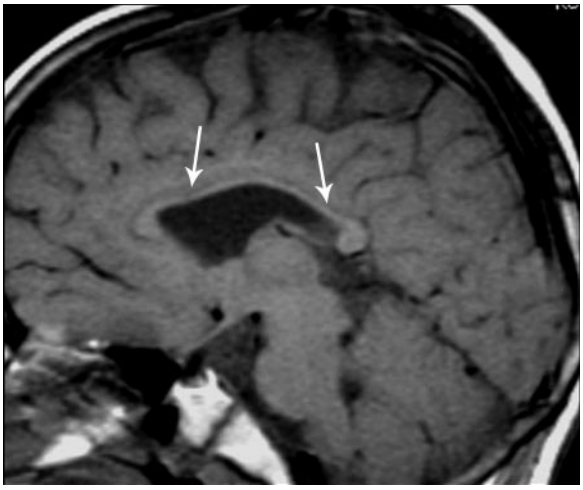


Figure 6. End-stage or chronic PVL in a 9-year-old boy, who was born prematurely and had a perinatal history of moderate hypotension. Midsagittal T1-weighted MR image shows thinning of the body of the corpus callosum (arrows), a finding indicative of chronic leukomalacia.

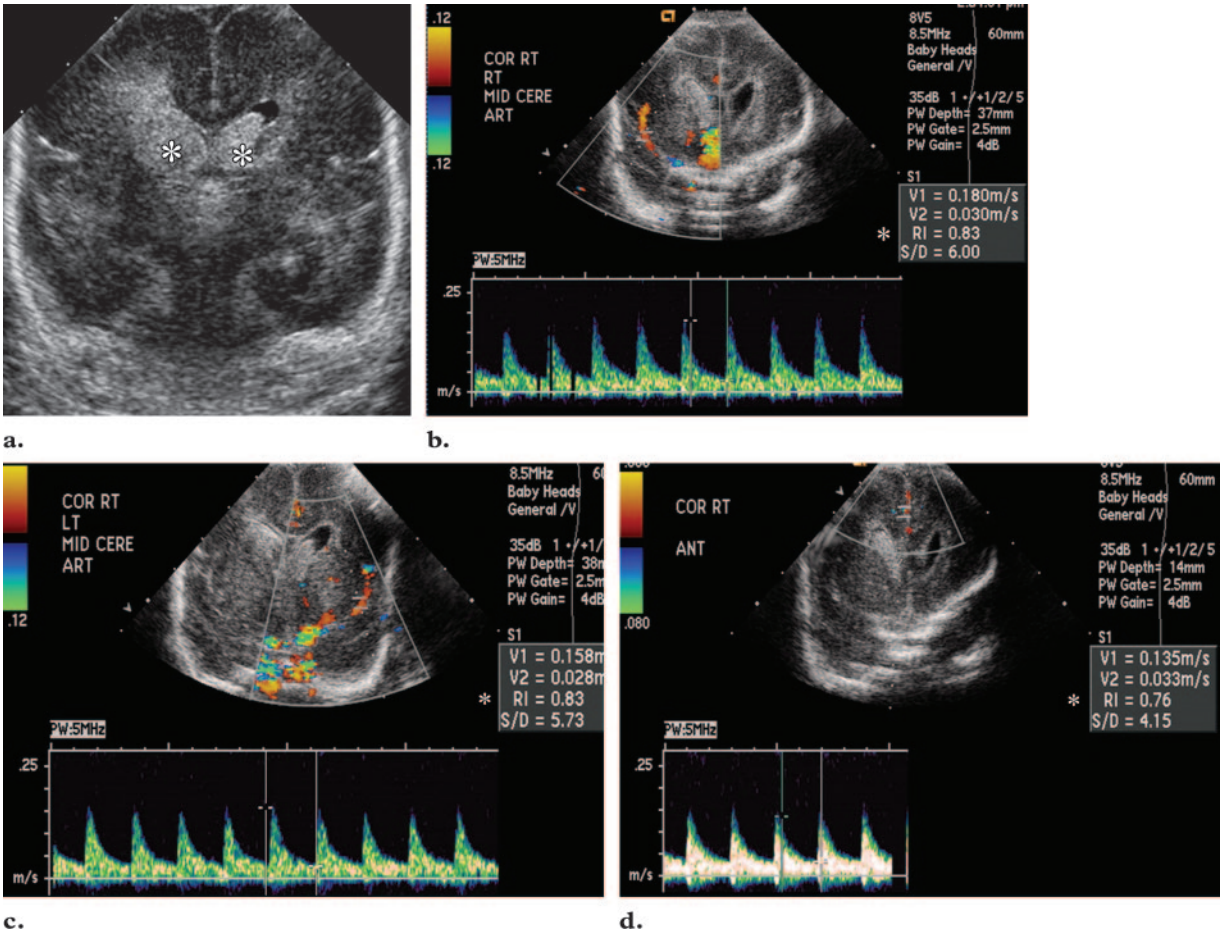


Figure 7. Germinal matrix hemorrhage in a preterm (28 weeks gestation) infant with Apgar scores of 4 at 1 and 5 minutes, delivered to a mother with test results positive for the human immunodeficiency virus, hepatitis B virus, and syphilis. **(a)** Coronal US scan obtained on day 11 of life shows bilateral grade 3 germinal matrix hemorrhage (*). **(b–d)** Duplex Doppler images show that the RIs (*) of the right **(b)** and left **(c)** middle cerebral arteries and of the anterior cerebral artery **(d)** are moderately decreased for an infant of this age (expected RI for age = 0.90).

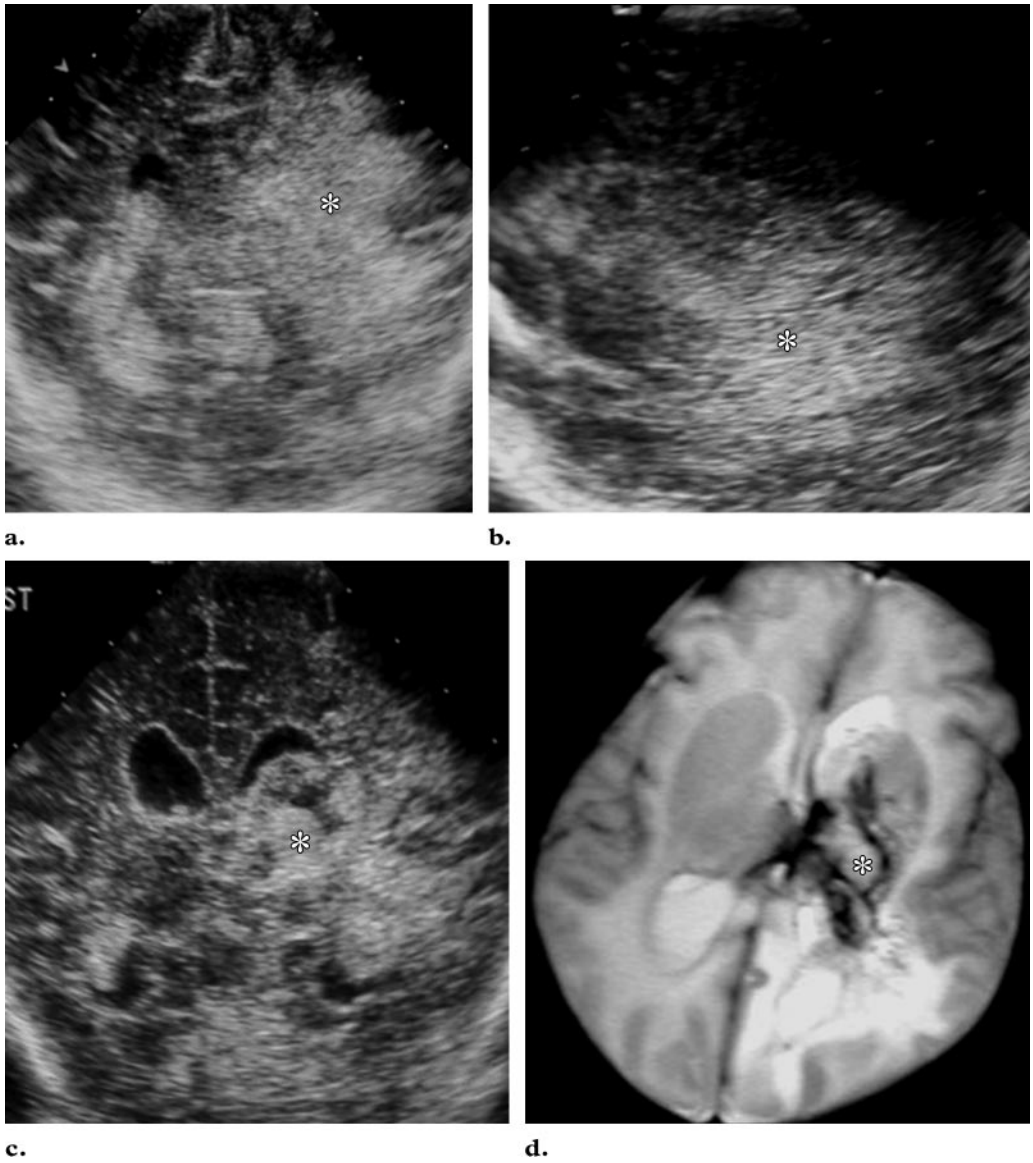


Figure 8. Deep gray matter injury in a preterm (34 weeks gestation) infant who was delivered emergently because of fetal bradycardia and who developed severe hypotension. **(a, b)** Initial coronal **(a)** and sagittal **(b)** cranial US scans show diffuse hyperechogenicity, loss of deep gray matter definition (*), and left ventricular effacement. **(c, d)** Follow-up coronal cranial US scan **(c)** shows residual increased echogenicity (*) in the deep gray matter, with corresponding T2 hyperintensity (*) on the axial T2-weighted MR image **(d)**, findings consistent with parenchymal hemorrhage.

Teaching Point

Severe Hypotension.—Because the thalami, brainstem, and cerebellum in the immature brain have high metabolic activity, they are more susceptible to injury in severe hypotension, and the insult manifests as hyperechogenicity of the injured brain at US, hypoattenuation at CT, and restricted diffusion and variable T2 signal at MR imaging. Coexisting periventricular white matter injury and germinal matrix hemorrhage may be present (Fig 8) (4).

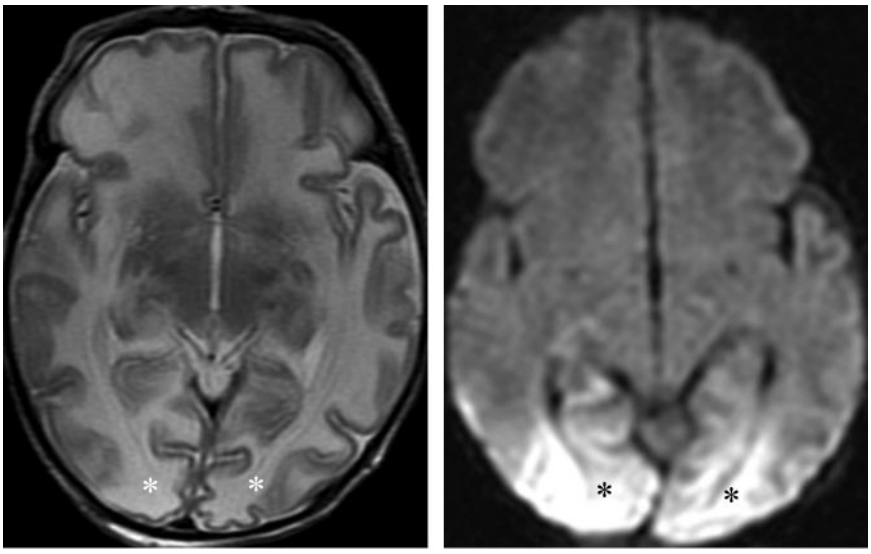


Figure 10. Parasagittal cortex and subcortical white matter brain injury in a term (38 weeks gestation) infant with a history of birth asphyxia, low Apgar scores, and moderate hypotension. Axial T2-weighted image **(a)** and diffusion-weighted MR image **(b)** obtained on day 10 of life show mild hyperintense T2 signal and restricted diffusion (*) in the parasagittal cortex and subcortical white matter in both occipital lobes.

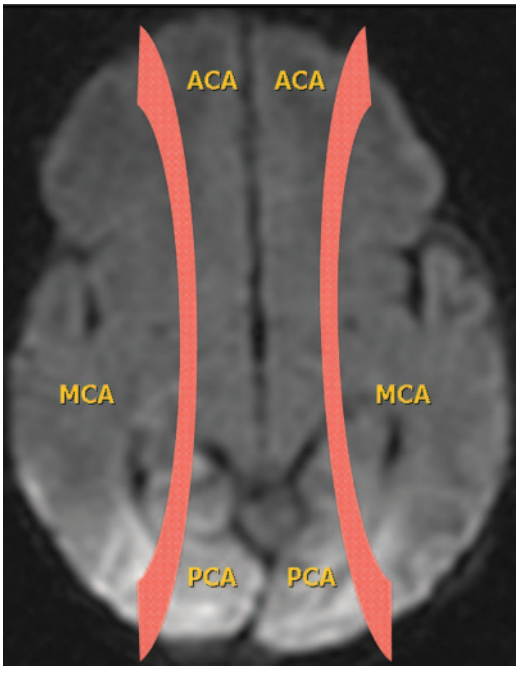


Figure 9. Definition of parasagittal distribution. Cerebral parenchyma between major vascular territories (ie, between the anterior cerebral arteries *[ACA]* and middle cerebral arteries *[MCA]* and between the middle and posterior cerebral arteries *[PCA]*) is called the watershed zone. In combination with the previously defined border zone (refer to Fig 2), the parasagittal parenchyma (areas shaded red on axial MR image) is at risk for ischemic injury from hypoperfusion.

Hypoperfusion Injury in Term Infants

Mild to Moderate Hypotension.—The primary locations of ischemic injury in the term neonatal brain are the intervascular watershed zones between the anterior and middle cerebral arteries and between the middle and posterior cerebral arteries and the border zone (Fig 9). Both the cortex and the underlying subcortical white matter in the parasagittal locations demonstrate restricted diffusion. The accompanying hyperintense T2 signal and hypointense T1 signal change are difficult to evaluate with US and CT owing to the close proximity to the calvaria (Fig 10). MR spectroscopy reveals increased lactate concentration in the intervascular zone compared with in the deep gray matter (Fig 11) (21).

Teaching Point

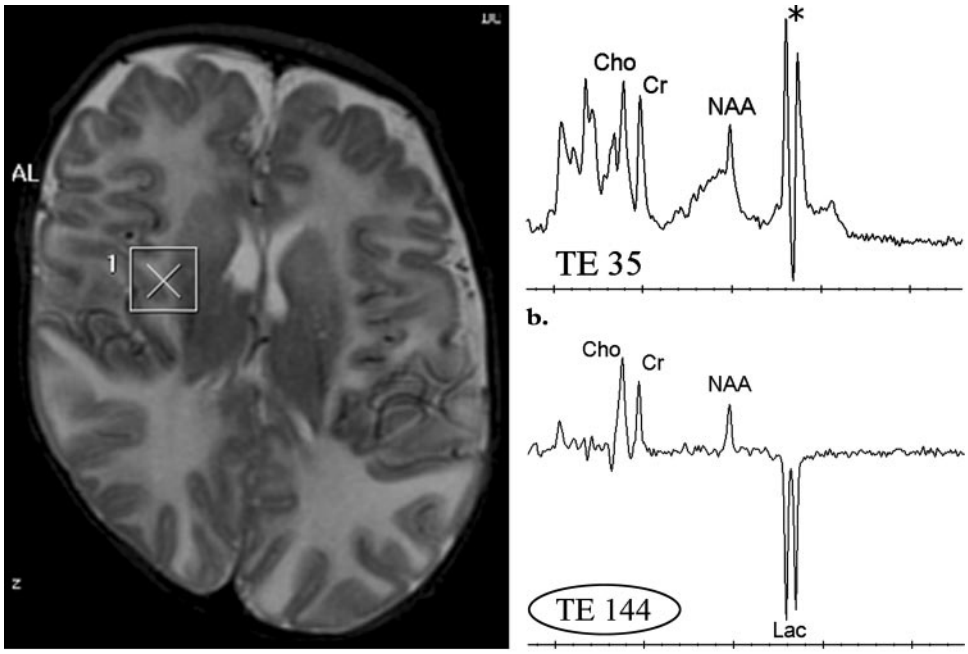
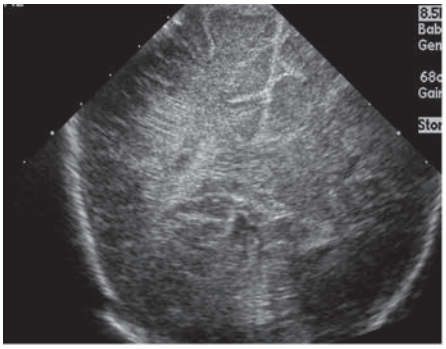


Figure 11. Changes in cellular metabolism at MR spectroscopy in a term neonate with a significant perinatal history of prolapsed cord, low Apgar scores, and moderate hypotension. **(a)** MR spectroscopy of a single voxel in the interarterial boundary zone was performed at echo times of 35 msec and 144 msec. **(b)** At an echo time of 35 msec, the spectrum demonstrates nonspecific accumulation of metabolite at 1.2–1.3 ppm (*), with a characteristic "doublet" configuration. *Cho* = choline, *Cr* = creatine, *NAA* = *N*-acetylaspartate. **(c)** Spectrum obtained at an echo time of 144 msec shows inversion of the same metabolite, which is characteristic for lactate.

Teaching Point

Severe Hypotension.—The metabolically active tissues in the brain of the term neonate are most susceptible to injury in profound hypotension and include the lateral thalami, posterior putamina, hippocampi, brainstem, corticospinal tracts, and the sensorimotor cortex. US findings may include hyperechogenicity of involved structures and/or abnormal RI on duplex Doppler images (Fig 12). Changes on CT scans may be subtle, with mild hypoattenuation of the thalami and basal ganglia, which appear isoattenuated compared with the surrounding white matter. On MR images, abnormal T1 hyperintensity and variable T2 hyper- or hypointensity are also subtle; diffusion-weighted imaging is more sensitive and shows restricted diffusion in the affected areas (Fig 13). MR spectroscopy reveals an elevation of lactate concentration in the basal ganglia and thalami (20).

Figure 12. Central gray matter pattern of injury in a term (36 weeks gestation) infant with a history of low Apgar scores, abnormal cord pH of 6.8, and severe hypotension. **(a, b)** Coronal **(a)** and sagittal **(b)** cranial US scans obtained on day 1 of life show increased echogenicity of the brain parenchyma and small ventricles, findings consistent with cerebral edema. **(c)** Duplex Doppler US scan shows an RI that is abnormally low (expected RI for age = 0.83). **(d, e)** Axial T1-weighted **(d)** and T2-weighted **(e)** MR images obtained on day 10 of life show bilateral T1 hyperintensity and subtle T2 hypointensity of the posterior putamina and lateral thalami (*). **(f, g)** These same areas also demonstrate restricted diffusion, which appears bright on the diffusion-weighted MR image **(f)** and dark on the apparent diffusion coefficient map image **(g)**.



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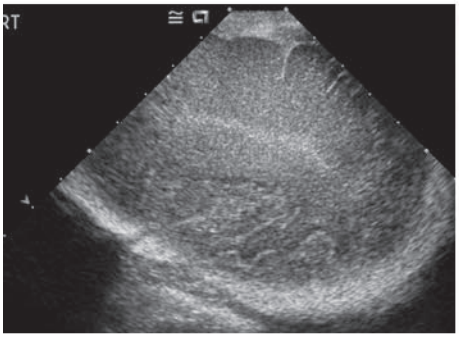

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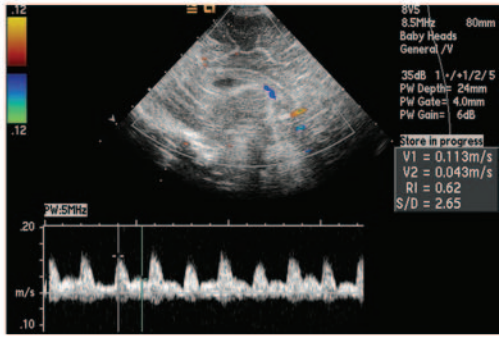
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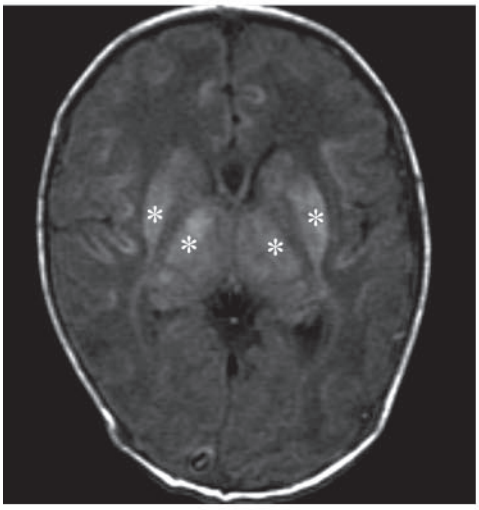

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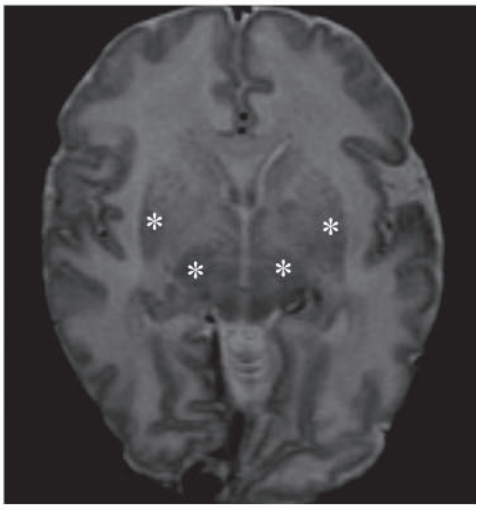

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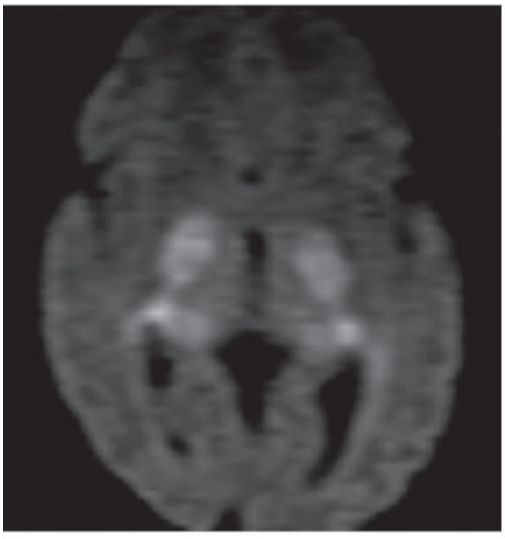

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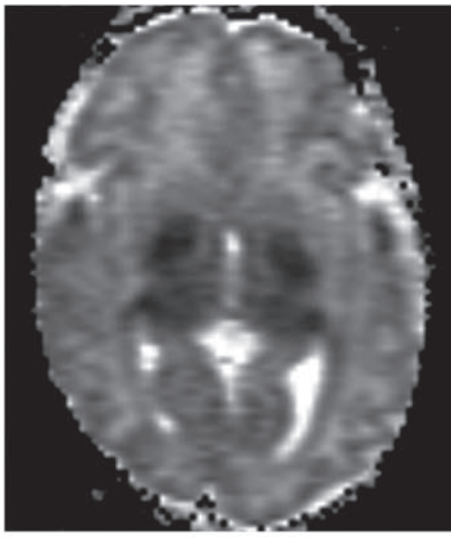
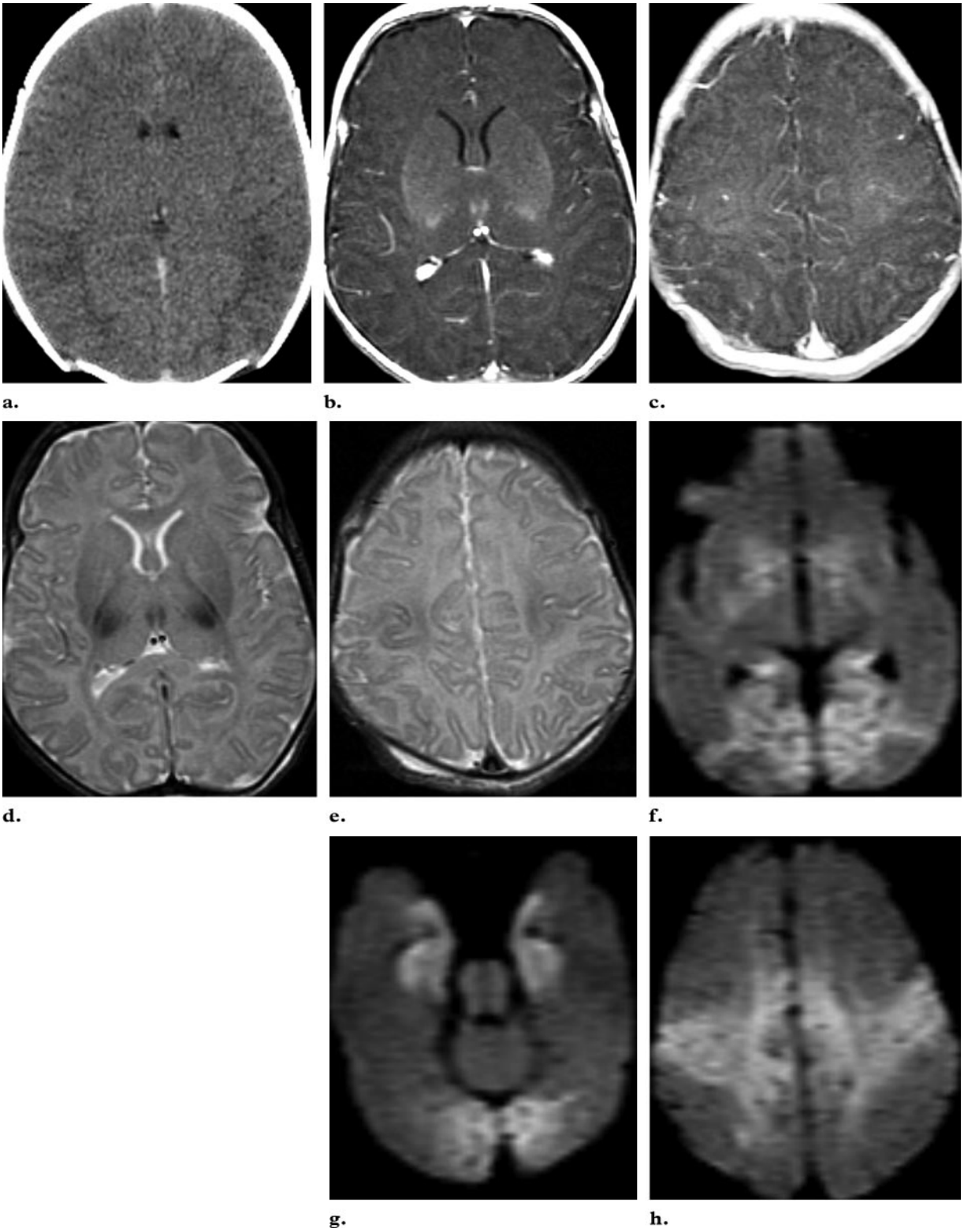


g.

Figure 13. Mixed pattern of injury in a term (42 weeks gestation) infant delivered by emergency cesarean section due to late deceleration on fetal monitoring and who developed severe hypotension. **(a)** Axial CT scan obtained on day 1 of life shows subtle bilateral hypoattenuation of the basal ganglia and thalami, which are isoattenuated compared with surrounding white matter. **(b–e)** Axial T1-weighted MR images **(b, c)** obtained on day 5 of life show T1 hyperintensity and axial T2-weighted MR images **(d, e)** depict corresponding T2 hypointensity in the posterior putamina, lateral thalami, and the sensorimotor cortices bilaterally. **(f–h)** Diffusion-weighted MR images reveal hyperintensity in the basal ganglia **(f)**, hippocampi and occipital lobes **(g)**, and the sensorimotor cortices **(h)**, findings consistent with restricted diffusion and acute ischemic injury. These changes are not apparent on the conventional MR images.



Prognosis and Treatment

The degree of neonatal encephalopathy, specific neuroimaging appearances, and EEG results help to prognosticate patient outcome. Increased severity of encephalopathy; the presence of cortical and basal ganglia abnormalities on conventional MR images, on diffusion-weighted MR images, and at MR spectroscopy; and severe EEG abnormalities portend a poor outcome (9,11,23). Although term infants with mild encephalopathy generally make a full recovery, 20% of affected infants die in the neonatal period and another 25% develop significant neurologic sequelae (9). For preterm infants, compared with term infants, the overall prognosis is worse (24).

Studies estimate a short therapeutic window of 2–6 hours during which interventions may be efficacious in reducing the severity of ultimate brain injury; thus, early identification of a neonate who has sustained a hypoxic-ischemic insult is a paramount objective for optimal management and treatment (10). Supportive care includes maintenance of adequate ventilation; avoidance of hypotension; maintenance of normal metabolic status including blood glucose, fluid, and nutritional status; control of seizures; and control of brain edema. Recent trials have shown beneficial use of therapeutic hypothermia in the form of selective brain cooling to improve outcomes among HIE infants with moderate EEG abnormalities. Research on the potential benefits of calcium channel blockers, magnesium, nitric oxide inhibitors, and other neuroprotective agents is ongoing (9,10).

Conclusions

HIE is an important cause of morbidity and mortality in the neonatal period and of cerebral palsy as a late neurologic sequela in the postnatal period. Although intervention is limited and mostly supportive at this time, it is still important to promptly and accurately identify neonates who have sustained a hypoxic-ischemic brain injury to facilitate optimal management. Cranial US, CT, and MR imaging, each with its own advantages and disadvantages, show characteristic patterns of brain injury that correlate well with the degree of hypotension and the level of brain maturity at the time of the insult, thus excluding other causes of encephalopathy and limiting the diagnosis to HIE.

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Neonatal Hypoxic-Ischemic Encephalopathy: Multimodality Imaging Findings

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Page S161
The most sensitive and specific imaging technique for examining infants with suspected hypoxic-ischemic brain injury is MR imaging (17).

Page S162
The most common location for injury to the premature brain is the periventricular white matter, with ischemic parenchyma manifesting as PVL.

Page S166
Because the thalami, brainstem, and cerebellum in the immature brain have high metabolic activity, they are more susceptible to injury in severe hypotension, and the insult manifests as hyperechogenicity of the injured brain at US, hypoattenuation at CT, and restricted diffusion and variable T2 signal at MR imaging.

Page S167
The primary locations of ischemic injury in the term neonatal brain are the intervascular watershed zones between the anterior and middle cerebral arteries and between the middle and posterior cerebral arteries and the border zone (Fig 9). Both the cortex and the underlying subcortical white matter in the parasagittal locations demonstrate restricted diffusion.

Pages S168
The metabolically active tissues in the brain of the term neonate are most susceptible to injury in profound hypotension and include the lateral thalami, posterior putamina, hippocampi, brainstem, corticospinal tracts, and the sensorimotor cortex.