Magnetic resonance imaging spectrum of perinatal hypoxic-ischemic brain injury

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Abstract

Perinatal hypoxic–ischemic brain injury results in neonatal hypoxic–ischemic encephalopathy and serious long-term neurodevelopmental sequelae. Magnetic resonance imaging (MRI) of the brain is an ideal and safe imaging modality for suspected hypoxic–ischemic injury. The pattern of injury depends on brain maturity at the time of insult, severity of hypotension, and duration of insult. Time of imaging after the insult influences the imaging findings. Mild to moderate hypoperfusion results in germinal matrix hemorrhages and periventricular leukomalacia in preterm neonates and parasagittal watershed territory infarcts in full-term neonates. Severe insult preferentially damages the deep gray matter in both term and preterm infants. However, associated frequent perirolandic injury is seen in term neonates. MRI is useful in establishing the clinical diagnosis, assessing the severity of injury, and thereby prognosticating the outcome. Familiarity with imaging spectrum and insight into factors affecting the injury will enlighten the radiologist to provide an appropriate diagnosis.

Key words: Cortical highlighting; germinal matrix hemorrhage; hypoxic ischemic encephalopathy; hypoxic ischemic injury; periventricular leukomalacia

Introduction

Insufficient cerebral blood flow (ischemia) and decreased oxygenation in the blood (hypoxia) lead to loss of normal cerebral autoregulation. This results in diffuse brain injury and thereby causes hypoxic–ischemic encephalopathy (HIE). The incidence of HIE is 2.5 per 1000 nonanomalous term live births5 and approximately 7 per 1000 preterm births.[2] Despite improvements in perinatal care, hypoxic–ischemic injury (HII) results in 23% of world’s neonatal deaths[3] and causes permanent neurological deficits in 25% of the affected term neonates.[4]

The clinical diagnosis of HIE is based on evidence of fetal distress, low umbilical cord pH of <7.1 (acidosis), a poor Apgar score (0-3) at 5 min, necessity for resuscitation, abnormal neurology (seizure, coma, hypotonia), and multiorgan dysfunction. Even when all the criteria for HIE are fulfilled, it may be due to a pre-existing neurological condition predisposing to an abnormal delivery and HII. Hence, screening for infection, metabolic disorders, and congenital malformations are always warranted.

Although ultrasonography (USG), computed tomography (CT) and magnetic resonance imaging (MRI) comprise the imaging armamentarium, MRI is the most sensitive and specific modality. Because of the cost advantage, portability, and availability, USG remains the first investigation of choice. USG is sensitive for the
Findings in HII are highly variable and depend on brain maturity, severity, and duration of asphyxia, as well as timing of imaging studies. Pattern of injury in preterm neonates (<37 weeks gestational age) is distinct from that of the full-term neonates (≥37 weeks gestational age). Treatment is primarily supportive and aims at limiting the extent of brain injury. The role of MRI is in excluding structural anomalies and mainly in assessing the extent and nature of injury. Thereby, it helps in prognosticating the outcome and planning neurodevelopmental therapy.

In this pictorial essay, we intend to familiarize the readers with the different MRI patterns of HII and to provide a brief insight into the factors influencing the patterns of injury. An understanding on normal MRI appearances of neonatal brain is essential for appreciation of abnormal findings in perinatal HII.

**Magnetic Resonance Imaging Technique, Protocol and Basics of Interpretation**

A coil of an appropriate size, ideally a dedicated neonatal head coil, is used. As the diameter of the coil decreases, the signal-to-noise ratio (SNR) increases. The standard MR sequences used in an adult brain should be optimized for use in neonates. This is because of the higher water content and lower protein and lipid contents of neonatal brain. It is achieved by increasing the repetition time (TR) of both T1 and T2 weighted images (WI). Ideally for T1WI, the standard TR (400 ms) is increased to 800 ms, and for T2WI, the standard TR (4000 ms) is increased to 6500 ms. This optimizes the SNR and gray-white differentiation of the images.

MRI images accompanying the essay was done in a 1.5-T scanner (Magnetom Vision, Siemens Medical Solutions, Erlangen and GE Signa HDxt, GE healthcare, United States). T1 and T2 WI in axial plane, T2WI in coronal and sagittal planes, Diffusion WI (DWI) in axial plane with apparent diffusion coefficient (ADC) map generation, gradient-echo T2* WI, and fluid-attenuated inversion recovery (FLAIR) in axial plane are the key protocol employed.

Axial T1WI is ideal for detecting myelination, ischemia, and subacute hemorrhage. Axial T2WI provides good contrast between gray and white matter and is useful in delineating white matter signal abnormalities. Gradient-echo T2* or susceptibility WI (SWI) is ideal for demonstrating hemorrhage and distinguishing it from ischemic gray matter lesions and astrogliosis.

HII to gray matter (deep gray matter and cortex) results in characteristic T1 hyperintensity and variable T2 signal intensity. White matter injury results in abnormal T1 hyperintensity without marked T2 hypointensity, denoting astrogliosis, and low T1 signal intensity, denoting cavitation or edema. In general, DWI is most useful in the first week of life and conventional T1 and T2WI are most diagnostically useful from the second week onwards. The recommended
timing for MRI is between 5 and 14 days from birth. Early neonatal imaging (before 5 days) may underestimate the injury, however, it is useful in taking decision on ventilated patients.\(^7\)

**Normal Magnetic Resonance Imaging Appearances of Neonatal Brain**

Adult brain differs from neonatal brain in degrees of myelination. MR signal intensities of myelinated and unmyelinated white matter differ. Myelination appears as increased signal intensity on T1WI and reduced signal intensity on T2WI relative to the gray matter. Myelination starts in the second trimester and the child brain appears almost like an adult brain by 18 months of age.

Our interest is specifically confined to the posterior limb of internal capsule and to a lesser degree to the ventrolateral nucleus of the thalamus. Increased T1 signal intensity of myelination is seen in the posterior half of the posterior limb of the internal capsule in normal neonates after 37 weeks of gestational age. This should be seen at least for one-third of the length of the posterior limb of the internal capsule [Figure 1A-D]. This and the corresponding T2 hypointensity can be seen usually during the first 24 hours of life.

In normal neonates, the thalamus may occasionally show subtly increased signal intensity confined to the posterolateral quadrant [Figure 1C and D]. This corresponds to myelination of the ventrolateral nucleus of the thalamus\(^{10}\) (just medial to the terminal portion of the posterior limb of the internal capsule).

**Patterns of Distribution of Brain Injury in Hypoxia–Ischemia**

A hypoxic–ischemic event lasting for more than 10–15 min is required to induce brain damage in the perinatal period. Basal ganglia and thalami, internal capsule, cortex, subcortical and periventricular white matter, and medial...
temporal lobe are the usual sites of brain injury in HII. Although some overlapping features exist, four major patterns of brain injury are observed. These patterns are influenced by the combinations of the level of brain maturity at the time of the insult and the severity and duration of the hypoperfusion event.

**Mild-to-moderate asphyxia pattern of brain injury (less severe)**

During mild-to-moderate hypoperfusion, autoregulation causes redistribution of blood flow to the hypermetabolically active deep gray matter structures. This results in injury predominantly to the watershed zones of the cerebrum. The vascular supply of the brain changes with brain maturation. In the preterm brain, ventriculopetal penetrating arteries supply the periventricular regions by extending inward from the surface of the brain. Thus, hypoperfusion results in a periventricular border zone of white matter injury [Figure 2]. In the full-term, ventriculofugal vessels also extend into the brain from the lateral ventricles and the intervascular border zone moves peripherally to a parasagittal location [Figure 2]. This results in subcortical white matter and parasagittal cortical injury during hypotension.

**Profound asphyxia pattern of brain injury (severe)**

In severe hypoperfusion, there is loss of autoregulation. The vulnerable regions are the deep gray matter and the early or actively myelinating fibers with higher concentrations of neurotransmitter receptors. In preterm neonates, severe asphyxia preferentially injures the thalami, dorsal brainstem, and anterior vermis with relative sparing of the basal ganglia and cortex. Severe asphyxia in term neonates causes injury to the posterior putamina, ventrolateral thalami, hippocampi and dorsal brainstem, and occasionally the sensorimotor cortex.

**Hypoxic–Ischemic Injury in Preterm Neonates**

HII is more common in preterm neonates than in term neonates. Clinical diagnosis of early HII is difficult in very low birth weight preterm neonates. The prevalence of injury shows an inverse relationship to gestational age at birth.

**Mild-to-moderate hypoxic-ischemic injury in preterm neonates**

The spectrum of brain injury in this group is broad and include white matter injury of prematurity (WMIP),

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**Figure 3 (A-C):** A 31-day-old infant born preterm (31 weeks) shows mild-to-moderate hypoxic ischemic injury. The infant also had refractory hypoglycemia. (A) Axial T1WI at the level of lateral ventricles shows frontal and posterior periventricular white matter cysts. (B) Axial fluid-attenuated inversion recovery (FLAIR) and T2WI at the level of lateral ventricles show frontal and posterior periventricular white matter cysts (C) with gliosis (arrows)

**Figure 4 (A and B):** A 76-day-old infant born preterm (30 weeks + 4 days) with maternal h/o pre-eclampsia and born by lower segment Cesarian section (LSCS) shows mild-to-moderate hypoxic ischemic injury to the brain. (A) Axial T2WI at the level of lateral ventricles shows germinal matrix hemorrhage at right caudothalamic groove (black arrow). (B) Axial FLAIR image at the level of lateral ventricles shows left periventricular white matter cyst (white arrow)

**Figure 5 (A and B):** A 3½-year-old child with cerebral palsy, born preterm with low birth weight, shows features of periventricular leukomalacia as sequelae to hypoxic ischemic brain injury. (A, B) Axial T2WI at the level of lateral ventricles shows significant reduction in volume and gliosis of the periventricular white matter. Also note mild dilatation and wavy margins of the lateral ventricles (black arrows)

**Figure 6 (A-C):** An 18-month-old child born preterm at 32 weeks of gestation with prolonged mild-to-moderate hypoxic ischemic injury. (A) Mid-sagittal plane T2WI shows thinning of corpus callosum (black arrows). Coronal T2WI (B) and axial T2WI (C) show thinning of corpus callosum (black arrows), lateral ventriculomegaly, and volume loss with hyperintensity (gliosis) of the periventricular white matter (white arrow)
germinal matrix–intraventricular hemorrhage, or a combination of both.

**White matter injury of prematurity or periventricular leukomalacia**

The most recent concept is that PVL is caused by the selective vulnerability of cells of oligodendrocyte precursors to changes of HII and damage to subplate neurons.\[11\]

Histological evolution of PVL follows a characteristic pattern—initially necrosis, often progressing to cavitation; then cysts collapse and result in gliosis and marked loss of the periventricular white matter.

DWI usually show early restriction of diffusion (after 24 hours of birth) and pseudonormalize within 5–7 days. Usually by 3–4 days, early white matter injury causes reactive astrogliosis and manifests as periventricular foci of T1 hyperintensity (without corresponding T2 hypointensity). Subsequently, by 6–7 days, these foci show mild reduction in T2 signal intensity. In contrast, hemorrhage manifests as T2 hypointensity initially itself
and show blooming artifact on T2* or SWI. By 2–6 weeks of age, some cases show periventricular cysts (cystic variant) [Figures 3 and 4] and end-stage PVL occurs by 6 months of life.

End-stage PVL shows a characteristic appearance due to gliosis and loss of volume of the periventricular white matter and centrum semiovale [Figures 5 and 6]. This results in ventriculomegaly with dilatation of the trigones and occipital horns, as well as wavy ventricular contour. Thinning of the corpus callosum is a characteristic late feature and is particularly noted posteriorly [Figure 6] (involving the posterior body and splenium). PVL is most commonly seen as white matter hyperintensity adjacent to lateral ventricle at peririgonal and foramen of Monro region [Figure 6]. PVL may also present as scattered punctate white matter abnormalities. Approximately two-third of PVL cases are associated with hemorrhage. If PVL is seen as isolated white matter hyperintensity at peritrigonal region [Figure 7], then it should be differentiated from the terminal zones of myelination (TZM). TZM show a thin band of low signal between the ependymal margin of ventricle and high intensity zone in coronal T2 weighted and FLAIR images [Figure 8]. However, in PVL, the high intensity zone generally extends to the ventricular ependyma [Figures 6 and 7]. TZM also show a triangular shape with superior orientation of apex in coronal images.[13]

Germinal matrix–intraventricular hemorrhage
Germinal matrix–intraventricular hemorrhage (GM-IVH) is unique to the immature brain and is never seen beyond the neonatal period. GM-IVH occurs approximately in one-fourth of the low birth weight preterm neonates. It is found in late antenatal or immediate postnatal period in one-third of the cases.[13] The spectrum of GM-IVH [Figures 4, 9, and 10] is classically described in the literature as follows.

Grade I: Subependymal germinal matrix hemorrhage (GMH) ± minimal ventricular extension [Figure 4]
Grade II: GMH extending into the ventricle, intraventricular hemorrhage (IVH)
Grade III: IVH with hydrocephalus [Figures 9 and 10]
Grade IV: Periventricular parenchymal hemorrhagic infarction (PVHI).

GM is a highly cellular and vascularized zone of fetal brain. It is most active between 8 and 28 weeks of gestation and gives rise to both neurons and glia. GM lines the walls of the lateral ventricles. It is also seen at the external granular cell layer of the cerebellum and subependymally at the roof of the fourth ventricle. It regresses gradually in the first half of third trimester, and the last area to involute is at the posterior aspect of caudothalamic groove. Hence, GM hemorrhages mostly originate from here.

Hypoxic ischemia causes damage to the capillaries of the GM and subsequent reperfusion results in GMH. Cerebellar GMH is usually crescentic in shape and located peripherally at the dorsal aspects of the hemispheres. Cranial ultrasound is generally adequate in this group, and MRI is used to detect concomitant deep grey matter injury and PVL.

PVHI is not a true GMH but a complication of it. Usually, it manifests as unilateral (83%) triangular hemorrhagic lesion, however, bilateral lesions (17%) can also occur.[14] PVHI results from thrombosis of the periventricular medullary veins. It may be localized to the frontoparietal (26%), parietooccipital (46%), or may involve the entire periventricular region (28%). Sequelae of GM-IVH include GM destruction and encephalomalacia. A combination of GM-IVH and PVL is also seen in prolonged mild-to-moderate asphyxia [Figures 4 and 10].
Profound Hypoxic–Ischemic Injury in Preterm Neonates

Severe hypotension most frequently injures the early myelinating and metabolically active thalami, dorsal brainstem, and anterior vermis. Relatively low involvement of the basal ganglia, hippocampus, perirolandic cortex, and corticospinal tract are also observed. This regional preference of injury is explained by the early myelination of thalamus and globus pallidus by 24–25 weeks of gestation and late myelination of corpus striatum (caudate nucleus and putamen) and perirolandic cortex beyond 35–36 weeks of gestation. There may be associated GMH or PVL.

The earliest MRI finding is diffusion abnormality in thalami, which is usually evident within the first 24 hours. Increased T2 signal intensity is seen by the 3rd day of injury and increased T1 signal intensity by the 4th day. The increased T1 signal intensity persists into the chronic stage, and the decreased T2 signal intensity replaces the T2 hyperintensity by approximately 7 days. When involved, the basal ganglia shows cavitation and volume loss without gliosis.

Magnetic Resonance Imaging Spectrum of Hypoxic–Ischemic Injury in Term Neonates

The pattern of injury in full-term neonates is broadly divided into two groups depending on the involvement of the deep gray matter structures. The mild-to-moderate group have watershed predominant pattern of injury and the profound type has basal ganglia and thalamus injury. Injury to corpus callosum and internal capsule is also seen.

Profound hypoxic–ischemic injury in full-term neonates (acute severe asphyxia, basal ganglia-thalamus pattern, selective neuronal necrosis)

This pattern of injury is usually seen following an acute sentinel event such as ruptured uterus, placental abruption, or cord prolapse. Hence, this is also referred as a pattern following “acute near severe asphyxia.” Because the injury primarily involves the bilateral ventrolateral thalami and posterior putamina, it is also known as basal ganglia–thalamus pattern (BGT) [Figure 11].

The injury primarily affects the deep gray matter–posterior putamina, ventrolateral thalami, hippocampi,
and dorsal brainstem, and occasionally involves the perirolandic cortex. Usually minor cortical injuries may be seen, and more prolonged insults result in diffuse cortical involvement [Figure 12]. As described, DWI is the first sensitive modality beginning from the first day of life [Figure 13E and F]. The involved regions show T1 hyperintensity beginning from the 2nd day of life and persist for several months [Figure 11A and B, 12A and B, 13A and B]. These regions may show mildly increased T2 signal intensity (denoting edema), beginning from the 3rd day of life [Figure 13C and D]. By 7–10 days, basal ganglia and thalami...
Varghese, et al.: MRI of perinatal Hypoxic ischemic brain injury

Normal signal of PLIC and focal nature of the basal ganglia lesion are typical of mild variety. Moderate form is characterized by abnormal signal from the PLIC and focal lesions, involving the posterolateral lentiform nucleus and lateral thalamus. A severe form is marked by abnormal PLIC and widespread changes in the basal ganglia and thalamus, often extending to mesencephalon. Involvement of the cerebral cortex and white matter is also frequently observed in the severe form if the insult is prolonged [Figure 12].

The abnormal mild T1 hyperintensity noted in the basal ganglia and thalami is nonspecific in the first week of life because of some overlap between the MRI findings of normal and severe hypoxic neonates [Figure 1C and D]. Hence, these findings should not be interpreted in isolation.

Mild-to-moderate hypoxic–ischemic injury in full-term neonates (prolonged partial asphyxia, watershed pattern)

Prolonged partial asphyxia results in injury to the watershed zones of cerebrum, i.e., parasagittal white matter, and whenever severe, extending to the overlying cortex [Figures 14-17]. This is due to the relative hypoperfusion of these areas as the result of autoregulation. The major etiologies for this type of injury are prolonged difficult delivery and long standing antenatal risk factors. Again, DWI is the earliest to change and show cortical and subcortical white matter restriction [Figure 14A]. By the 2nd day, T2WI may often show cortical swelling, loss of gray-white differentiation, and hyperintensity in the cortex and subcortical white matter. T1WI show abnormal cortical high signal intensity beginning from the 3rd day of life, reaches the maximum during the 2nd week, and lasts for several weeks. This is referred to as cortical highlighting [Figure 14C and 15C and D]. On T2WI, the abnormal cortex may show subtle low signal intensity [Figure 14E].

Ulegyria (shrunken cortex with flattened mushroom shaped gyri) and diminished white matter volume, predominantly in the parietooccipital region, is seen in the chronic stage [Figure 17C].

Neonatal Encephalopathy—Few other Causes Concerning Radiologist

If MRI reveals a different pattern or evolution of brain injury, other causes of neonatal encephalopathy such as perinatal stroke, metabolic causes, infections, or birth trauma need consideration. However, in reality, a neonatologist excludes common metabolic causes and infection before ordering MRI. Neurosonogram in neonatal intensive care unit also aids in forming a working diagnosis. In our practice, neonates after stabilization undergo MRI for confirmation of the diagnosis and prognostication of outcome.

Perinatal stroke

Perinatal stroke comprises perinatal arterial ischemic stroke (PAIS), perinatal hemorrhagic stroke (PHS), and sinovenous thrombosis. PAIS is defined as cerebrovascular accident occurring between 28 weeks of gestational age and...
28 days after delivery, with radiological or pathological evidence of focal arterial infarction.\(^\text{[17]}\) The incidence of perinatal arterial ischemic stroke recognized during neonatal period was 1 in 2300 in term infants.\(^\text{[18]}\) The most common type of PAIS is ischemic lesions involving the middle cerebral artery (Figure 18). DWI has the highest sensitivity at acute phase and also detects prewallerian degeneration of the corticospinal tract (Figure 18E and F).

PHS was coined by Armstrong-Wells et al.\(^\text{[19]}\) and included intracerebral hemorrhage or subarachnoid hemorrhage, excluding pure GM-IVH. They found a population prevalence of 6.2 in 100,000 live births for PHS. However, some overlap exists between these conditions due to hemorrhagic transformation of PAIS and venous infarcts (Figure 19).

Cerebral sinovenous thrombosis (CSVT) should be suspected in neonates presenting with seizures and/or lethargy and without a history of perinatal asphyxia. It showed an incidence of 1.4 to 12 per 100,000 term live births.\(^\text{[20]}\) Presence of an IVH with a unilateral thalamic hemorrhage should arouse suspicion for CSVT.\(^\text{[21]}\) MRI combined with MR venography is the preferred diagnostic modality.

**Hypoglycemic brain injury**

Neonatal hypoglycaemia (<46 mg/dL) can occur in 5 to 15% of normal term neonates. The injury patterns described are white matter abnormalities (most common), cortical abnormalities, white matter hemorrhage, basal ganglia–thalamic lesions, and PLIC abnormalities. A predominant parietooccipital distribution of abnormalities is seen in approximately 30% of the patients [Figure 20].\(^\text{[22]}\) Neonates with hypoxic ischemic encephalopathy (HIE) are at increased risk developing concurrent hypoglycemia [Figure 3]. These neonates show predominant pattern of HII as well as specific imaging features of hypoglycemia [Figure 21]. It is impossible to differentiate hypoglycemic brain injury.
Clinical features and outcome in relation to regions of injury

Pattern of brain injury can dictate neurodevelopmental outcome. The clinical features and the history (ante and perinatal events) also points toward the pattern of injury.

Neonates with the BGT pattern had the most intensive need for resuscitation at birth, severe encephalopathy, and clinical seizures. BGT pattern is associated with cerebral palsy and cognitive deficits. Abnormal PLIC, a structure involved in the BGT pattern is associated with abnormal motor outcome (ability to walk at 2 years of age). \[^{23}\] Cognitive deficits are better explained by the frequent occurrence of watershed injury in the BGT group. Watershed pattern is associated with predominant cognitive, visual, language, behavioral, and seizure problems at a median age of 2 years. \[^{24,25}\]

The most common long-term neurologic outcome of PVL is motor and visual impairment. Majority of children with minimal changes of PVL progresses with normal psychomotor development and rest shows high frequency of neuromotor delay. Most of the children with severe changes of PVL show severe neurodevelopmental problems (cerebral palsy, different cognitive deficits, vision impairment, and epilepsy). \[^{26}\]

Thus, a radiologist can likely predict the neurodevelopmental outcome of the infant, depending on the pattern of injury. However, the amazing plasticity of the infantile brain should not be forgotten, and at least in few cases, the appropriate neurodevelopmental therapy may surprise, both the radiologists and clinicians.

Conclusion

There are three main patterns of HII depending on the severity of the insult and maturity of the neonatal brain.

1. Watershed pattern (WS): Seen in term neonates affected by mild-to-moderate asphyxia and injury involves the parasagittal cortex and subcortical white matter.
2. PVL or GM-IVH: Associated with mild-to-moderate asphyxia in preterm neonates.
3. Deep gray matter or basal ganglia thalamic pattern: Associated with profound hypoxia, irrespective of maturity.

Preterm neonates show less severe involvement of basal ganglia. Term neonates show frequent involvement of periorolanic cortex. There are varying degrees of cortical or white matter injury, depending on the nature of insult.

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Conflicts of interest

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References


