Magnetic resonance imaging in neonatal hypoxic-ischaemic encephalopathy

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Introduction

- Neonatal HIE is a major cause of infant mortality and morbidity with long-term neurological squeals.
- It occurs in 1 to 2 per 1000 live births*, in 0.8% of term born and 1.4% of preterm born*.
- Ultrasonography is the first-line imaging technique for the evaluation of the newborn brain,
- These past few years have seen an increasing role of MRI in the investigation of HIE because of greater sensitivity and specificity.

Study purpose

- Illustrate the main MRI aspects of anoxic-ischemic encephalopathy seen in preterm and term periods.
- Demonstrate the role of advanced MRI techniques, such as DWI and MRS, and discuss the imaging findings.
MRI techniques
MRI techniques

- Tightly packing the baby
- Adequate sedation in young children++

High quality MR images
Parameters of the MR sequences have to be adapted to the brain composition of young infants.
Conventional sequences

- Longer repetition time (TR) and echo-time (TE) of T2-weighted images are necessary to adequately evaluate brain maturation compared to older children and adult.
Conventional sequences

Sequences parameters: 3 Tesla MRI (Siemens)
**Conventional sequences**

- **T1 WI, T2 WI++**
- **FLAIR:**
  - are not very useful to detect lesion in young infant less than 24 months due to brain maturation.
- **IR T1-weighted:**
  - Has been very helpful in the last two decades before generalization of high fields MRI as it gives excellent images of brain anatomy and maturation. It also shows accurately the differentiation between myelinated and unmyelinated WM.
Three-dimensional GE T1 weighted sequence (3DT1):
- allow 1 mm contiguous slices, which can be reconstructed in any anatomic plane.

T2*:
- to detect haemorrhagic lesions
It is now recommended that DWI should be performed between 2 days and 8 days of life.

Multiple studies have shown:

- DWI are more sensitive in the detection of HIE lesions than conventional MRI especially for early diagnosis.

MRI protocol

- Sagittal and axial T1 WI
- Axial and coronal T2 WI
- Axial T2*
- 3D T1
- FLAIR (older child)
- DWI
Lactate peak:
- due to anaerobic glycolysis
- found within 24 h of life

Subsequently, a reduction in N-acetyl aspartate (NAA) is evident due to neuronal loss

Term baby born by difficult vacuum extraction. MRI was performed on day 2 of life. (a) Axial T1 WI are normal. (b) T2 WI show diffuse increase in signal in the WM, and also loss of normal hypointense signal in the posterior limbs of the internal capsule. (c) DWI image at the same level shows restricted diffusion in the bilateral ventro-lateral thalami (arrows) and these lesions are better demonstrated than on T1 and T2 WI. (d) Single voxel proton MRS using echo time ¼ 144 ms of the basal ganglia shows an inverted lactate peak at 1.33 ppm (arrowhead)
**Advanced technique: Perfusion**

- **Arterial Spin-Labeled (ASL) Perfusion**
  - Recent advances in novel research imaging modality
  - Allows noninvasive evaluation of CBF (cerebral blood flow) using electromagnetically labeled arterial blood water as an endogenous contrast agent
  - Demonstrates low CBF in neonates who have suffered HIE and in infants and children after stroke

Donna et al. Noninvasive Cerebral Perfusion Imaging in High-Risk Neonates. Semin Perinatol2010;34:46-56
MRI of brain maturation
It is necessary to:

- know the normal cerebral appearance before interpret pathological aspect
- distinguish hypoxic-ischemic brain damage from normal myelination
Brain composition

Changes in brain composition:

- Changes in cellular density,
- Increase in complex lipids content due to the evolving process of myelination,
- Decrease in water content mostly in the WM

Shortening of T1
Shortening of T2
Preterm brain

- Preterm brain = fetal brain
- Gyration: begin at 8 weeks of gestational age
  - Before 5th month: lissencephaly
  - After: development of major groove

Brain morphology from 23 to 38 weeks in the sagittal plane. 23 weeks (A), 27 weeks (B), 31 weeks (C), 34 weeks (D)

Before 30 weeks: **multilayered pattern:**
From outside to inside:
- cortical ribbon (low signal intensity on T2WI),
- subcortical WM (bright signal on T2WI),
- layer of migrant cells (low signal intensity on T2WI),
- PVWM (bright signal on T2WI)

From 30 weeks, the majority of neuronal cells migrated and this aspect is not more visible.

Multilayered pattern of the cerebral hemisphere at 24 weeks.

Premature newborn at 28 weeks’ PMA, 34 weeks of corrected age.

- **Unmyelinated WM** displays a bright signal on T2 and a low signal on T1.
- The cortex displays a low signal on T2 and a bright signal on T1.
- the basal ganglion display a bright signal on T1

**Myelination process:**

- **begins:** 26 weeks
- **it progresses in a specific direction:**
  - Central to peripheral
  - Caudal to rostral
  - Dorsal to ventral
Myelination is characterized in mature brain by bright signal on T1 WI and low signal on T2 WI.

In neonates brain contrast is reverse compared to the mature brain.

5 days

5 years

Myelination is characterized in mature brain by bright signal on T1 WI and low signal on T2 WI.
The gyration is finished.

Myelination continues well after birth (at least into the 2 years)

**Term neonate:** brainstem (posterior), cerebellum, posterior limb of the internal capsule, the calcarine area and central area

Subcortical hyperintensity was also evident in the frontopolar regions.

Subcortical T2 hyperintensity is recognizable in both temporopolar (A) and temporolateral (B) areas.

peritrigonal linear areas
Diffusion (A) and ADC (B)

- Myelination process in WM tracts is detected before conventional T1 and T2 sequences
- **ADC is lower** (arrows):
  - Myelinated WM
  - Posterior fossa,
  - Unmyelinated WM shows low signal on DWI and high signal on ADC.

The diagnosis of HIE requires the presence of all three of the following criteria:

- Clinically recognized encephalopathy within 72 h of birth
- No other cause which could explain the encephalopathy
- Multiorgan system dysfunction
Clinical criteria for diagnosis

Diagnostic checklist for perinatal HIE related to intrapartum events

1. The presence of a clinically recognized encephalopathy within 72 h of birth (encephalopathy is defined as the presence of at least three of the following findings):
   - Abnormal level of consciousness: hyper-alertness, lethargy, stupor or coma
   - Abnormal muscle tone: hypertonia, hypotonia or flaccidity
   - Abnormal deep tendon reflexes: increased, depressed or absent
   - Seizures: subtle, multifocal or focal clonic
   - Abnormal Moro reflex: exaggerated, incomplete or absent
   - Abnormal suck: weak or absent
   - Abnormal respiratory pattern: periodic, ataxic or apnoeic
   - Oculomotor or pupillary abnormalities: skew deviation, absent or reduced, doll’s eyes or fixed unreactive pupils

2. Three or more supporting findings from the following list:
   - Arterial cord blood pH < 7.00
   - Apgar score at 5 min of 5 or less
   - Evidence of multiorgan system dysfunction involving one or more of the following systems within 72 h of birth:
     - Renal: oliguria or acute renal failure
     - Gastrointestinal: necrotizing enterocolitis, hepatic dysfunction
     - Haematological: thrombocytopenia, disseminated intravascular coagulopathy
     - Endocrine: hypoglycaemia, hyperglycaemia, hypocalcaemia, syndrome of inappropriate ADH secretion (SIADH)
     - Pulmonary: persistent pulmonary hypertension
     - Cardiac: myocardial dysfunction, tricuspid insufficiency
     - Evidence of foetal distress on e.g. persistent late decelerations, reversals of end-diastolic flow on Doppler flow studies of the umbilical artery or a biophysical profile of 2 or less
     - Evidence on CT, MRI, Technetium or ultrasound brain scan (preferably performed within 7 days of birth) of diffuse or multifocal ischaemia or of cerebral oedema
     - Abnormal EEG: low amplitude and frequency, periodic, paroxysmal or isoelectric

3. The absence of an infectious cause, a congenital malformation of the brain or an inborn error of metabolism which could explain the encephalopathy

The imaging patterns of HIE can be classified into 3 types:

- lesions predominantly located in the PVWM,
- lesions predominantly located in the basal ganglia or thalamus,
- multicystic encephalomalacia
The pattern of injury is postulated to depend on:

- the type of hypoxia–ischaemia (acute and profound or prolonged and partial)
- the gestational age (term or pre-term)
HIE in preterm infant
Risk factors

- **Pregnancy:**
  - Gestational age/weight, previous preterm birth, spontaneous preterm labor

- **Intrapartum:**
  - Abruption, pre-eclampsia, premature rupture of membranes, chorioamnionitis, group B Strep

- **Peri & postnatal factors:**
  - Respiratory distress, sepsis, anemia, apnea, bradycardia, cardiac arrest
General feature

- ++ PVL

+/− associated to:

- Germinal matrix and IVH
- PV hemorrhagic infarction
- Cerebellar infarction
Definition:
- PVL is the HIE driven periventricular white matter (PVWM) necrosis seen in very low birth weight premies (<1500g).

Epidemiology
- Birth weight < 1500 g → 45% incidence of PVL (higher if associated with IVH)
- Gestational age < 33 weeks → 38% incidence of PVL
- > 50% of patients with PVL or grade III IVH develop cerebral palsy
Perfusion of PVWM (site of immature oligodendroglia)

Oligodendrocyte vulnerable:
PV vascular anatomical (arterial end zones)
• Cerebral ischemia-impaired cerebrovascular autoregulation-pressure passive cerebral circulation
• Intrinsic vulnerability of cerebral white matter of the preterm newborn (free radicals, glutamate, cytokines)

Reperfusion of ischemic tissue

PVL

hemorrhagic necrosis
Location

- **PVL**:  
  - symmetrically distributed WM necrosis dorsal and lateral to the external angles of the lateral ventricles  
  - focal (adjacent to frontal horns and trigones)  
  - or diffuse

- **Without any cortical abnormalities**

- **Preterm HIE profound**:  
  - extension of gliosis to: Brainstem, thalamus, striatum, amygdala
# MRI findings

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<th>Early</th>
<th>Late</th>
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<td><strong>T1WI</strong></td>
<td>▪ Passive ventricular enlargement (Ventriculomegaly,)</td>
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<td>↑T1 signal in PVWM (hemorrhagic necrosis),</td>
<td>▪ PV WM volume loss,</td>
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<td>+/- ↑T1 signal in dorsal pons, thalami or</td>
<td>▪ +/- PV cavitation,</td>
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<tr>
<td>basal ganglia</td>
<td>▪ thin callosum</td>
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| **T2WI**                                   | ▪ gliosis,                                                          |
| ↑T2 signal in PVWM (edema, ischemia, or   | ▪ thalamic scarring,                                                |
| infarction), focal T2 signal (hemorrhagic  | ▪ PV cyst ≤ 2-3 mm                                                  |
| necrosis)                                   | ▪ larger cysts carry poorer prognosis                              |
|                                            | ▪ Demyelination                                                    |

| **FLAIR**                                  | PV signal (gliosis) if >24-26 week gestation, +/- PV cysts, WM      |
|                                            | volume loss                                                        |

| **T2***                                    | Signal at sites of hemorrhagic necrosis                            |
|                                            | Signal at sites of hemorrhagic necrosis                            |

| **DWI**                                    | ADC values "normalize" within 10-12 days                          |
| ▪ Normal before 24 h of life.              |                                                                      |
| ▪ Restricted diffusion between days 1–3   |                                                                      |
|    of life                                |                                                                      |
Shrinkage and T2WI hyperintensity of the deep WM

- **DWI:**
  - Normal before 24 h of life.
  - Restricted diffusion between days 1–3 of life

- +/- T2* hypointensity at sites of hemorrhagic necrosis
Bilateral lesions of cystic PVL in the posterior areas. Ventricular dilatation.
Fig. PVL. Lesions on bright signal on T2, FLAIR of PVWM. Increased ADC in the same areas.
Fig. Cystic PVL sequel.
Thin callosum
Evolution:

- Passive ventricular enlargement (Ventriculomegaly)
- PV WM volume loss,
- +/- PV cavitation (PV cyst ≤ 2-3 mm, larger cysts carry poorer prognosis)
- thin callosum
6 days

Fig. PV WM volume loss and passive ventricular enlargement. Cerebellar atrophy
5 years, seizure

Fig. Bilateral lesions of cystic PV leukomalacia. No hemorrhage, no ventricular dilatation. Cystic PV leukomalacia.
3 years,

Fig. Dilatated and irregular aspect of the lateral ventricles. Cystic PVL sequel. Thin corpus callosum.
Imaging Recommendations

- Cranial sonography (US):
  - First, between 7 and 14 days,
  - Repeat before discharge from the hospital

- MRI, DWI, MRS
  - When US is abnormal: MRI precise lesion extension and aide in prognosticating,
  - Defining injury in VLBW neonates with "normal" US
Prognosis

- Poor outcome if:
  - IVH plus PVL,
  - PVL with volume loss, widespread infarction, or seizures
  - PVL with enlarged cysts
Differential diagnosis: PVL mimics

- **Normal periventricular halo**
  - Normal hyperechoic "blush" posterosuperior to the ventricular trigones,

Axial T2 and FLAIR show peritrigonal linear areas of hyperintensity that can be referred to perivascular spaces.
Pelizaeus-Merzbacher disease (PMD)
- Sudanophilic leukodystrophy, classically X-linked recessive, may mimic cerebral palsy
- MR shows striking lack of myelination

Congenital CMV infection
- Microcephaly, periventricular calcifications, variable PV demyelination and gliosis, +/- polymicrogyria

Oculocerebrorenal syndrome (Lowe syndrome)
- Congenital ocular abnormalities, mental retardation, renal tubular dysfunction, and metabolic bone disease
- MR shows PV cysts, demyelination, and gliosis
HIE in term infant
2 types of mechanism

Prolonged partial (PP) injury:
As nuchal cord..

Chronic repetitive stress

CFB redistribution
preserve deep structures

to basal ganglia/brainstem/cerebellum

Profound acute (PA) injury:
uterine rupture, uterine abruption or cord prolapse

Acute stress

No CBF redistribution
Deep structures damaged

Other risk factors:
Infection/inflammation, hypoglycemia, and hemodynamic instability
2 main patterns are clearly distinguished:

- **basal-ganglia-thalamus pattern:**
  - affecting bilaterally the central gray nuclei and perirolandic cortex.
  - +/- Associated involvement of the hippocampus and brain stem

- **WM pattern:**
  - overlying cortex in the vascular watershed zones
  - uni-or bilateral and predominantly posterior and/or anterior.
Subcortical WM/cortex damaged, (Parasagittal "border zone" injury)
- deep gray nuclei/basal ganglia spared

Basal ganglia damaged,
- Posterior mesencephalon,
- hippocampi
- peri-Rolandic cortex injury
- WM/cortex spared
Clinical presentation

Sarnat stages of HIE:

- Sarnat I (mild): Hyperalert/irritable, mydriasis, EEG normal
- Sarnat II (moderate): Lethargy, hypotonia, seizure
- Sarnat III (severe): Stupor, flaccid, reflexes absent, seizure
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<td><strong>Acute:</strong></td>
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|  • hyper T1 signal: "Bright" cortex at bottom of sulci (laminar necrosis)  
  • T2, FLAIR: Blurring of gray-white junction  
  • Restricted diffusion |  • Hypo T1 signal of normally myelinated posterior limb internal capsule |
| **Chronic:** | **Chronic:** |
|  • Border zone damage gliosis  
  • +/- cystic encephalomalacia |  • Atrophy/hyper signal posterior putamina/lateral thalami and Rolandic cortex |
16 months,

Fig. Lesions on bright signal on T2 (b) and FLAIR (d) and low signal on T1 (a) on the putamen (arrows) and PVWM (c, d). Increased signal in the ADC map in the same areas (f, g).
3 ans, seizure

Fig. Atrophy of the parietal cortical ribbon with bright signal on T2 (b, d) and FLAIR (a, b) in border zones corresponding to gliosis.
8 years, mental retardation

Fig. 1. Widespread abnormal signal intensity of the cortical ribbon extending to WM on the bilateral parietal, occipital areas and left frontal area. Passive enlargement of left lateral ventricle.
Fig. Lesions on bright signal on T2 on the left basal ganglion with atrophy and passive enlargement of lateral ventricle. Bright signal on T2 and FLAIR of PVWM and nucleus of Luys.
11 months, neonatal encephalopathy

Fig. PVWM loss and atrophy. Passive enlargement of lateral ventricle. Bright signal on T2 on FLAIR of PVWM.
6 months, neurologic neonatal distress.

Fig. Lesions on bright signal on T2 (a) and low signal on FLAIR (b) on the basal ganglion (thalami and lentiform nuclei)
1 year, hypotonia

Fig. Lesions on bright signal on T2 (a) and low signal on T1 (b) on the basal ganglion (thalami and lentiform nuclei) and on bilateral parietal areas.
Fig. Foci of hemorrhage of both cerebellar hemispheres on bright signal on T1 and low signal on T2. The subarachnoid spaces are enlarged, small ventricular dilatation.

Fig. IVH on bright signal on T1 and low signal on T2 with ventricular dilatation and parenchymal hemorrhage of the left PVWM.

Anthonioz C et al. Aspects IRM de l’encéphalopathie anoxo-ischémique du nouveau-né à terme et du prémature J Radiol 2006;87:1651-70
Axonal pathway changes/HIE:

- Restricted diffusion within the splenium of the corpus callosum of term infants with HIE:
  - associated with extensive brain injury,
  - an early neuroradiologic marker of poor outcomes.

- In our study, there is no change in corpus callosum.
Fig. MRI of a patient with extensive supratentorial restricted diffusion. Axial diffusion weighted imaging (A) demonstrated restricted diffusion in the splenium of the corpus callosum (black arrows) and corresponding changes on the apparent diffusion coefficient (white arrows) (B). Axial DWI (C) and the corresponding ADC (D) at the cerebellar level indicated extensive restricted diffusion in the cerebral hemispheres (White arrowheads). This patient died.
Ulegyria

- Typically affects full-term infants
- Usually associated with drug-refractory epilepsy
- The damage involves the deeper sulcal portion of the convolutions and spares the crowns ("mushroom gyri");
- MRI: the subcortical white matter undergoes atrophic changes and gliosis.

19 years, seizure

Fig. Right parietal ulegyria. Hypersignal T2 and FLAIR of PVWM.
Multicystic encephalomalacia

The terms "multicystic encephalomalacia" is used to describe the presence of areas of necrosis that develop into cystic lesions inside the brain.
17 days, **neurologic neonatal distress**

Cystic lesions on low signal on T1WI and bright signal on T2WI of the cerebral hemispheres. No lesion on the brainstem and the cerebellum. **Multicystic encephalomalacia.**
The diagnosis of diffuse injury remains difficult and should take into account the age and brain maturation.

The calculation of ADC may be helpful in detecting diffuse injury.

In few study, we found:

- increased ADC values in injured WM areas
- decreased in gray matter involvement.
- maximally decreased between days 1–3 of life

DWI may be negative or may underestimate the lesion size when performed:

- early (before 24 h of life)
- Late (after 8-10 days)
Imaging recommendations

- **Standard MR imaging limited by:**
  - hypomyelination
  - water content of neonatal brain

- **DWI crucial**
  - Extremely sensitive for early, acute ischemia
  - "positive" after 48 hours
  - But may "pseudonormalize" in 1 week

- **MRS:**
  - crucial in first 24 hours
  - Lactate may be first or only abnormal finding
Differential diagnosis

- **Kernicterus**
  - Mimics profound injury on acute T1WI;
  - It has confirmed:
    - hyperbilirubinemia
    - Location: globus pallidus, (not putamen or thalamus)
    - Abnormal on follow-up

- **Metabolic disorder**
  - Mitochondrial encephalopathy, methylmalonic acidemia
Prognosis/Evolution

- It varies from normal outcome (Sarnat I) to spastic quadriparesis, developmental delay, microcephaly, and seizure (Sarnat III)

- Severe HIE:
  - 50% mortality,
  - significant morbidity in 80% of survivors

- Choreoathetosis after 1 year common in PA survivors
There are very few studies reporting neurodevelopmental outcomes in children with HIE:

Van Kooij et al (2005):
- Children with normal or solitary WM lesions on their neonatal scans were still at increased risk of motor and cognitive impairment at 9-10 years compared with controls.
- Signal intensity in the posterior limb of the internal capsule is one of the best imaging predictors of motor outcome and ability to walk at 2 years.

Martinez et al (2012): Infants with HIE and selective WM/cortical injury have a low prevalence of cerebral palsy.
**Perinatal asphyxia** is the most important cause of acute neurological injury in the newborn.

**MRI** is increasingly being used to provide early diagnosis of perinatal hypoxic-ischemic insults and to predict outcomes after HIE.
Preterm infant
- PVWM necrosis
- Deep gray nuclei/basal ganglia spared

Term infant
- Subcortical WM/cortex damaged
- "Border zone" injury
- Basal ganglia damaged
Conclusion

Severe diffuse brain injury, lesions in the thalamus and basal ganglia, higher lactate and choline ratios, poor neurological outcome
Abbreviation

- MRI: magnetic resonance imaging
- MRS: magnetic resonance spectroscopy
- DWI: diffusion-weighted imaging
- ADC: apparent diffusion coefficient
- GE: Gradient echo
- WI: weighted image
- WM: white matter
- PV: periventricular
- HIE: hypoxic ischaemic encephalopathy