IMAGING OF HYPOXIC ISCHEMIC INJURY IN A NEONATE

FN3 STATE MEETING
NEMOURS CHILDREN'S HOSPITAL ORLANDO, FL
08/04/18

Dhanashree Rajderkar, MD
Assistant Professor
Department of Radiology
University of Florida in Gainesville, FL

Contact: rajdda@radiology.ufl.edu
OBJECTIVES:

- To discuss the role of Imaging in the neonates suspected to have Hypoxic Ischemic injury
- To assess imaging patterns in neonates with hypoxic-ischemic injury in term versus premature infants
- To discuss the technical aspects of obtaining the ideal imaging in the patients with suspected HIE
HEAD US: INDICATIONS-PREMATURE INFANTS

- To detect
  - Intracranial hemorrhage
  - Periventricular leukomalacia/ischemia
  - Hydrocephalus
  - Extra-axial fluid collections
HEAD US: INDICATIONS-PREMATURE INFANTS

- To follow
  - Intracranial hemorrhage, hydrocephalus, extra-axial fluid collections
  - Usually at day 7 ....
  - Day 1-PENUT, Seizures, decreased hematocrit, changes in neurologic status, bradycardia
  - < 32 weeks or < 1500 g
HEAD US: TECHNIQUE

- Transducers - 7-13 MHz for extraaxial fluid, dura, meninges, convexities
  - 3.5-6MHz for posterior fossa, entire brain

- Anterior fontanelle - large enough up to 6 months (closes 9-15 mths)

- Posterior fontanelle - posterior fossa

- Mastoid fontanelle - posterior lateral (open until 2 yrs)
PATIENT IMAGING-MRI

- Right preparation
- Imaging parameters
- Safety - Team, Suction pump, O2 supply, Laryngoscope, Monitoring devices
- Examination on the day of the study
- Swaddling - Feed and wrap technique
- Scan on side
- Adult knee coil

http://cfimedical.com/medvac/
MRI

- Neonates’ vital signs are prone to fluctuate, and several parameters must be closely monitored.
- STABLE- sugar, temperature, artificial breathing, blood pressure, and laboratory test results.
- High-quality coronal diffusion-weighted images also can be obtained. Neonates lack pneumatized paranasal sinuses.
### Protocol for MR Evaluation of Neonatal Encephalopathy

<table>
<thead>
<tr>
<th>Priority of Sequence</th>
<th>Type of Sequence</th>
<th>Acquisition Time</th>
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<tbody>
<tr>
<td>1</td>
<td>Diffusion-weighted imaging</td>
<td>45 sec</td>
</tr>
<tr>
<td>2</td>
<td>T1-weighted imaging</td>
<td>4 min 35 sec</td>
</tr>
<tr>
<td>3</td>
<td>T2-weighted imaging</td>
<td>3 min 17 sec</td>
</tr>
<tr>
<td>4</td>
<td>T2*-weighted imaging</td>
<td>3 min 47 sec</td>
</tr>
<tr>
<td>5</td>
<td>MR spectroscopy</td>
<td>5 min 38 sec</td>
</tr>
</tbody>
</table>
Indications
Periventricular leukomalacia (PVL)
Intraventricular hemorrhage (IVH)
Prematurity
Neonatal hypoxic ischemic encephalopathy (HEI)
# MR Brain Neonatal Screen without IV Contrast

<table>
<thead>
<tr>
<th>Acquisition</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6*</th>
<th>7*</th>
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<tr>
<td>Plane</td>
<td>Sagittal</td>
<td>Axial</td>
<td>Axial</td>
<td>Axial</td>
<td>Axial</td>
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<td>Axial</td>
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<tr>
<td>Sequence</td>
<td>T1</td>
<td>FLAIR FS</td>
<td>T1</td>
<td>T2</td>
<td>SWI/GRE</td>
<td>MDDW</td>
<td>3D MPRAGE</td>
<td>DWI</td>
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<tr>
<td>Contrast</td>
<td></td>
<td></td>
<td>4 / 1 mm</td>
<td>4 / 1 mm</td>
<td>4 / 1 mm</td>
<td>4 / 1 mm</td>
<td>2 mm</td>
<td>1.5 mm</td>
</tr>
<tr>
<td>SLT / SP</td>
<td>4 / 1 mm</td>
<td>4 / 1 mm</td>
<td>4 / 1 mm</td>
<td>4 / 1 mm</td>
<td>2 mm</td>
<td>1.5 mm</td>
<td>4 / 1 mm</td>
<td></td>
</tr>
<tr>
<td>FOV</td>
<td>16 cm</td>
<td>16 cm</td>
<td>16 cm</td>
<td>16 cm</td>
<td>16 cm</td>
<td>240 mm</td>
<td>256 mm</td>
<td>16 cm</td>
</tr>
</tbody>
</table>

**SPECIAL INSTRUCTIONS:**

*Do Not Angle / whole head*
# MR Brain Neonatal HIE without IV Contrast

<table>
<thead>
<tr>
<th>Acquisition</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5*</th>
<th>6*</th>
<th>7**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plane</td>
<td>Axial</td>
<td>Axial</td>
<td>Axial</td>
<td>Axial</td>
<td>Axial</td>
<td>Axial</td>
<td>Loc</td>
</tr>
<tr>
<td>Sequence</td>
<td>T1</td>
<td>T2</td>
<td>SWI/GRE</td>
<td>DWI / ADC</td>
<td>3D MP RAGE</td>
<td>MDDW</td>
<td>mMRS</td>
</tr>
<tr>
<td>Contrast</td>
<td>SLT / SP</td>
<td>FOV</td>
<td>4 / 1 mm</td>
<td>4 / 1 mm</td>
<td>4 / 1 mm</td>
<td>1.5 mm</td>
<td>2 mm</td>
</tr>
<tr>
<td></td>
<td>16 cm</td>
<td>16 cm</td>
<td>16 cm</td>
<td>16 cm</td>
<td>256 mm</td>
<td>24 cm</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**SPECIAL INSTRUCTIONS:**
For neonatal brains, post warming protocol
* *Do NOT angle volume slab.*
** Place slab for multi-voxel MRS in right or left basal ganglia region. Voxel volume has to be > 2.5 cc.

### Indications
Suspected neonatal HIE
Neuro protective cooling

- FLAIR-Poor due to high water content
- Imaging best -1-2 week
- Diffusion-False negative < 24 hrs
- Pseudonormalize- 6 day
SPECIAL INSTRUCTIONS:
For neonatal brains, post warming protocol
* Do NOT angle volume slab.
** Place slab for multi-voxel MRS in right or left basal ganglia region. Voxel volume has to be > 2.5 cc.
NORMAL MRS IN A TERM INFANT

NORMAL MRS IN AN ADULT

Premie MRSpectroscopy

Varies
Preterm may contain lactate
PROGRESSION OF MYELINATION

Rostral to caudal; Posterior to anterior; Central to peripheral
Myelination

- 20 weeks: Pons, Post medulla
- 29 weeks: Sup and Inf cerebellar peduncles
- 32 weeks: Midbrain
- 33 weeks: Inferior colliculi, lateral putamen, ventrolateral thalami
- 35 weeks: Post limb of Internal capsule
- 35 weeks: 2 mths: Optic tracts, medial temporal lobes, perirolandic fissures, calcarine, central white matter, rest of the basal ganglia
Cortical folding

25 week

30 week

33 week

Term equivalent (37 weeks)

Adult

Term control

Courtesy: Dr. Robert McKinstry
Sulcation

- 16 weeks - Interhemispheric and sylvian
- 22 weeks - Parietooccipital, Hippocampal, Callosal
- 23-24 weeks - Calcarine
- 24 weeks - Cingulate
- 26 weeks - Central
- 27 - Precentral, Superior temporal, marginal
- 28 weeks - Post central
- 29 weeks - Superior frontal, Inferior frontal
- 33 weeks - Inferior temporal
33 WEEKS
PRE-TERM (26 WKS)
PRE-TERM (30-WEEK)
34-WEEK PRETERM INFANT
Fig 2. Representative MRI of the three grades of abnormality in gray matter gyral maturation in the premature infants on MRI at term: A, grade 1 with normal gyral maturation at term; B, grade 2 demonstrating a reduction in complex gyral folding but secondary gyri in the transverse sulci and gyri consistent with 36 to 37 weeks' gestational age; and C, grade 3 demonstrating severe impairment in gyral development in all regions consistent with 34 weeks' gestational age.
26 WK

MRI of the Neonatal Brain - Mary A Rutherford
32 WK
Sulcation

- 16 weeks-Interhemispheric and sylvian
- 22 weeks-Parietooccipital, Hippocampal, Callosal
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- 26 weeks- Central
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- 28 weeks- Post central
- 29 weeks- Superior frontal, Inferior frontal
- 33 weeks- Inferior temporal
Medial Sulci

- Uncus
- Midbrain
- Parahippocampal gyrus
- Collateral sulcus
- Hippocampal sulcus
- Temporal lobe
- Collateral sulcus
- Corpus callosum
- Cingulate sulcus
- Commissural sulcus
32 WK
Germinal matrix

- 5-14 wk - Ventricular zone - Ependymal
- 15-36 wk
  - Subependymal, deep WM, Ganglionic eminences - 20% cortical, BG, amygdala, hippocampus
  - Lateral sparse/dense cellular-glial cells

Cerebral Cortical Development

1. VZ/SVZ, germinal matrix
2. Periventricular fiber rich zone/SVZ (axons CC)
3. Intermediate zone/SVZ
   - Neuronal migration
   - Astrocyte proliferation
   - Oligodendrocytes
4. Subplate zone
   - Neuron rich large extracellular matrix
   - Synapses between subcortical fibers (thalamus, brainstem, basal forebrain) not yet final destination in the cortical plates
5. Cortical plate
Normal preterm MRI

- Germinal matrix-Low on T2, high on T1
- WM-Low T1, high T2
- 20-30 Weeks-Band of low T2 and high T1-Migrating cells
- Crossroads by frontal horns-36 weeks
GMH/IVH

- < 3 days Hypo T1, Marked hypo T2
- 3-7 days - Hyper T1, Hypo T2
- 7 days - months - Hypo to CSF T1, hyper to CSF on T2

**Table 1** Evolution of signal intensity in parenchymal haemorrhage

<table>
<thead>
<tr>
<th>Age of haemorrhage</th>
<th>T1 weighted imaging</th>
<th>T2 weighted imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 days</td>
<td>Not seen/high signal intensity rim</td>
<td>Low signal intensity</td>
</tr>
<tr>
<td>3–10 days</td>
<td>Not seen/high signal intensity</td>
<td>Low signal intensity (with high signal intensity periphery)</td>
</tr>
<tr>
<td>10–21 days</td>
<td>High signal intensity</td>
<td>High signal intensity</td>
</tr>
<tr>
<td>3–6 weeks</td>
<td>High signal intensity</td>
<td>High signal intensity (with low signal intensity periphery)</td>
</tr>
<tr>
<td>6 weeks – 10 months</td>
<td>Not seen/minimal high signal intensity</td>
<td>Not seen/low signal intensity</td>
</tr>
<tr>
<td>10–22 months</td>
<td>Not seen</td>
<td>Minimal low signal intensity/not seen</td>
</tr>
</tbody>
</table>
### TABLE 2: Scoring systems

<table>
<thead>
<tr>
<th>Score</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Basal ganglia (BG)</strong></td>
</tr>
<tr>
<td></td>
<td>0 = Normal or isolated focal cortical infarct</td>
</tr>
<tr>
<td></td>
<td>1 = Abnormal signal in thalamus</td>
</tr>
<tr>
<td></td>
<td>2 = Abnormal signal in thalamus and lentiform nucleus</td>
</tr>
<tr>
<td></td>
<td>3 = Abnormal signal in thalamus, lentiform nucleus, and perirolandic cortex</td>
</tr>
<tr>
<td></td>
<td>4 = More extensive involvement</td>
</tr>
<tr>
<td></td>
<td><strong>Watershed (W)</strong></td>
</tr>
<tr>
<td></td>
<td>0 = Normal</td>
</tr>
<tr>
<td></td>
<td>1 = Single focal infarction</td>
</tr>
<tr>
<td></td>
<td>2 = Abnormal signal in anterior or posterior watershed white matter</td>
</tr>
<tr>
<td></td>
<td>3 = Abnormal signal in anterior or posterior watershed cortex and white matter</td>
</tr>
<tr>
<td></td>
<td>4 = Abnormal signal in both anterior and posterior watershed zones</td>
</tr>
<tr>
<td></td>
<td>5 = More extensive cortical involvement</td>
</tr>
<tr>
<td></td>
<td><strong>Basal ganglia/watershed (BG/W)</strong></td>
</tr>
<tr>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>Abnormal signal in basal ganglia or thalamus</td>
</tr>
<tr>
<td>2</td>
<td>Abnormal signal in cortex</td>
</tr>
<tr>
<td>3</td>
<td>Abnormal signal in cortex and basal nuclei (basal ganglia or thalamus)</td>
</tr>
<tr>
<td>4</td>
<td>Abnormal signal in entire cortex and basal nuclei</td>
</tr>
<tr>
<td></td>
<td><strong>Summation (S)</strong></td>
</tr>
<tr>
<td></td>
<td>Arithmetic sum of BG and W</td>
</tr>
<tr>
<td></td>
<td><strong>Enhancement (E)</strong></td>
</tr>
<tr>
<td>0</td>
<td>No enhancement</td>
</tr>
<tr>
<td>1</td>
<td>Enhancement in white matter only</td>
</tr>
<tr>
<td>2</td>
<td>Enhancement in deep gray matter nuclei</td>
</tr>
<tr>
<td>3</td>
<td>Enhancement in cerebral cortex</td>
</tr>
<tr>
<td>4</td>
<td>Enhancement in cortex and deep gray matter or white matter</td>
</tr>
</tbody>
</table>

Report gestational age
Age at time of scan

Scoring System from A. James Barkovich, MD
HIE IN PRETERM

• 50% of cases of cerebral palsy – Premature infants
• Up to 19% of infants born before 28 weeks of gestation develop cerebral palsy
• Hypoperfusion – Watershed Ischemia – Premyelinating neurons
• Lack of autoregulation
PREMATURE INFANTS

- White Matter Injury (WMI) of Prematurity
  - Focal (cystic/noncystic)
  - Diffuse
- Encephalopathy of prematurity
- Cerebellar Injury
- Hemorrhagic HIE of premature-WM Injury
- Chronic WM injury-mixed pattern
- Chronic WM injury
FOCAL NON CYSTIC EX 30 WEEK EGA

MRI at term

Follow up MRI
WHITE MATTER INJURY (WMI) OF PREMATURITY
• FOCAL, NONCYSTIC

Common- 20-50%
• Difficult to detect with US
• Microscopic focal necroses-glial scar
• Foci of increased T1, decreased T2
• Foci disappear on follow-up MR scans
• Decreased ADC in acute stages
* Need to look at ADC map as trace DWI images can look “normal”
2 PATIENTS WITH CYSTIC TYPE INJURY
WHITE MATTER INJURY (WMI) OF PREMATURITY
FOCAL, CYSTIC

Declining incidence, <5% of WMI in VLBW

• Large cysts can be detected with US or MRI
• Cysts shrink - volume loss seen at follow-up MRI
• Risk Factor: NEC

Periventricular leukomalacia is most commonly seen adjacent to the trigones of the lateral ventricles and to the Monro foramen, areas that correspond to the watershed zones in periventricular white matter in the premature brain

Kidokoro et al Peds 2014
WHITE MATTER INJURY (WMI) OF PREMATURITY FOCAL, CYSTIC

• The condition probably represents toxic injury -cerebral ischemia, reperfusion, or both

• End-stage periventricular leukomalacia manifests as a reduction in volume of the periventricular white matter and the centrum semiovale, with passive dilatation and irregularity of the ventricular wall
CEREBELLAR GM HEMORRHAGE
HEMORRHAGIC HIE OF PREMATURE-CEREBELLAR INJURY

• Increasingly recognized form of preterm injury (10-40%)
• Common, esp in VLBW (<1500g)
• Germinal matrix hemorrhages in external granule cell layer- cerebellar germinal zone 28-40wks
• Large hemorrhages can be seen with US, MRI
• Small hemorrhages best seen with MRI
• Best seen on T2, SWI
• Increase detection with 3T
• Can lead to cerebellar hypoplasia
HEMORRHAGIC HIE OF PREMATURE-WM INJURY
MORE EXAMPLES
CHRONIC WM INJURY-MIXED PATTERN
Thinning of the corpus callosum, particularly in the posterior body and splenium, is a characteristic late feature of periventricular leukomalacia.
PREMATURE- SEVERE INJURY

- Severe-deep gray nuclei/brainstem
- Thalami
- Dorsal brainstem
- Anterior vermis
- Lentiform nuclei
- Perirolandic gyri
- Cerebral cortex spared
- WM/GMH
31 WEEK EGA ABRUPTION
Diffusion in the cortex is more restricted because of the higher ratio of cells to extracellular space.

Figure 6. (a) ADC map obtained in a neonate at 26 weeks of gestation shows moderately decreased cortical water diffusion and increased white matter water diffusion. (b) ADC map obtained in a neonate at 38 weeks of gestation shows more limited water diffusion than in (a), with resultant lower signal intensity in white matter. Note the region of slight signal hypointensity in the lateral aspect of the thalamus (arrow), a finding that represents myelination.
NEURODEVELOPMENTAL DEFICITS IN WM DISEASE OF THE PREMATURE

• Outcomes:
  • Cognitive and motor delay-Spastic diplegia/quadriplegia
  • Neurosensory Impairment –Visual

• Predictors/Term equivalent
  • Moderate to severe WM abnormalities
  • Grey matter less strongly associated
  • US-III/IV;Cystic PVL
  • Postnatal steroids
DIFFUSE EXCESSIVE HIGH SIGNAL INTENSITY IN WM (DEHSI)

- Controversial
  - WM
  - Increase diffusion
  - Poor neurologic outcome
- Transient normal process
- No difference; No difference ADC values with controls
ENCEPHALOPATHY OF PREMATURITY

- Selective vulnerability of pre-oligodendrocytes and immature oligodendrocytes AND subplate neurons to H-I and inflammation
- Impaired pre oligodendrocyte maturation-decreased myelin
- Subplate neurons-role in thalamocortical and associative/commissural cortico-cortico connections
- Likely combination of 1° destructive process and 2° maturation/trophic disturbance
FULL TERM INFANTS

• Severe, basal ganglia pattern
• Severe, total hypoxia
• Mixed pattern
2 day old 36 week EGA boy

Hypointense T1 signal in post. Limb of internal capsule. This is normal for age in 36 wk EGA

Range of variation in signal intensity that can be seen in normal brain—basal ganglia show moderately hyperintense signal, although less than that typically seen in hypoxia.
Injury to the basal ganglia and thalamus

Basal Ganglia Pattern

High T1 signal in basal ganglia and thalamus from intracellular calcium shift and necrosis
MRI FINDINGS IN THE NEONATE WITH SEVERE, TOTAL HYPOXIA
Abnormal high signal throughout the WM on T2-weighted images.

Blurring of GW differentiation more evident on B=0 than conventional T2-weighted images.
Reduction in glutamate release

Decrease in intracellular acidosis and lactic acid accumulation

Prevention of blood-brain barrier disruption and brain edema

Preservation of endogenous antioxidants

Reduction of leukotriene production

Inhibition of apoptosis

Reduction in cerebral metabolism
38 WEEK EGA GIRL INFANT BORN AFTER INDUCTION FOR MATERNAL PRE-ECLAMPSIA

Hypoxic ischemic injury s/p cooling. Infant is now 5 days old and is being re-warmed.
Inc T1 signal in corticospinal tracts, lentiform nuclei and thalami (subtle), and decreased T1 signal in posterior limbs of internal capsule.
Subtle decreased signal on ADC map in corticospinal tracts, lentiform nuclei and posterior limbs of internal capsules. No DWI changes because they've already normalized.
KEY POINTS

- HIE usually manifests within the first few hours after birth
- A few days after birth - without an obvious reason, metabolic and infectious causes must be considered
- Normal Neonate MR Findings->37 weeks EGA
  - ↑ T1 & ↓T2 signal in posterior half of posterior limb of internal capsule
  - At a minimum, 1/3 of the length should be T1 hyperintense
  - Usually seen during first 24 hours of life
- If <36 weeks EGA: no ↑ T1 in this region = normal finding
Severe hypoxic-ischemic insults to the premature brain typically affects:

- Thalamus
- Anterior part of the vermis
- Dorsal brainstem
- Injury to the basal ganglia is usually less severe and common

Severe hypoxic-ischemic injury in term baby involves:

- Ventral and lateral aspects of the thalamus
- Posterior aspect of the putamen
- Perirolandic regions
- Corticospinal tracts
Mild to moderate hypoxic-ischemic injury may result in a germinal matrix hemorrhage, periventricular leukomalacia, or both.

Hypoperfusion causes periventricular border zone of white matter injury.

Mild to moderate hypoxic-ischemic injury in term baby causes lesions in:
- Watershed areas
- Parasagittal cortex
- Subcortical white matter
- Spares the brainstem, cerebellum, and deep gray matter structures
METABOLIC DISORDERS PRESENTING WITH ENCEPHALOPATHY IN NEONATAL PERIOD

- Amino/organic acidopathies:
  - Nonketotic hyperglycinemia
  - Glutaric aciduria I and II
  - Sulfite oxidase deficiency
  - Maple syrup urine disease
  - Proprionic Acidemia
    - Urea Cycle disorders
    - Mitochondrial/respiratory chain abnormalities
    - Peroxisomal biogenesis disorders
11 day old w/encephalopathy and high ammonia:

Compare with normal term neonate...
IMPORTANT CLINICAL CORRELATES

- Long-term studies of the outcome of very prematurely born infants - significant motor, cognitive, and behavioral deficits
- More prone to develop encephalopathies
- In comparison to the term-born infants, the premature infants at term demonstrated prominent reductions in cerebral cortical and deep GM volume
- The major predictors of altered cerebral volumes were gestational age at birth and the presence of cerebral WM injury
**IMPORTANT CLINICAL CORRELATES**

- Infants with significantly reduced cortical GM and deep nuclear GM volumes and increased CSF volume volumes exhibited moderate to severe neurodevelopmental disability at 1 year of age.

- The nature of the cerebral abnormalities that underlie these common and serious developmental disabilities is not entirely understood.

- Postulated - WM injury and delayed WM and GM gyral development.
CONCLUSIONS:

- Hypoxic ischemic injury manifests differently in a full term than in a premature on MRI
- USG of head serves as a baseline examination to enroll a patient in the PENUT trial AND a routine baseline scan on day 7 of a premature baby
- Imaging of the patients who have undergone cooling demonstrate lesser extent of brain injury
A four-day reduction in hospital stay, multiplied by the number of preemies born each year, would result in a $2.4 billion annual cost savings for the national healthcare system.