IMAGING OF HYPOXIC ISCHEMIC INJURY IN A NEONATE

NICU GRAND ROUNDS

02/02/17

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PURPOSE:

- 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
- To discuss the patterns of HI injury in term versus premature infants
Table 1. Classification of Prematurity

<table>
<thead>
<tr>
<th>Classification</th>
<th>Gestational Age</th>
<th>Birthweight</th>
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</thead>
<tbody>
<tr>
<td>EPT</td>
<td>≤28 weeks</td>
<td>LBW: &lt;2,500 g (5 lb, 8 oz.)</td>
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<tr>
<td>VPT</td>
<td>≤32 weeks</td>
<td>VLBW: &lt;1,500 g (3 lb, 4 oz.)</td>
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<tr>
<td>Preterm</td>
<td>34-36 weeks + 6 days</td>
<td>ELBW: &lt;1,000 g (2 lb, 3 oz.)</td>
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<tr>
<td>Term</td>
<td>37-40 weeks</td>
<td></td>
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<tr>
<td>Postmature</td>
<td>41 weeks + 6 days</td>
<td></td>
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</table>

ELBW: extremely low birthweight; EPT: extremely preterm; LBW: low birthweight; LPT: late preterm; VLBW: very low birthweight; VPT: very preterm.
Source: Reference 1.
DEFINITIONS

- **Hypoxic-ischemic injury**: to designate any brain impairment caused by insufficient oxygenation and blood flow.

- **Hypoxic-ischemic encephalopathy**: a condition that is diagnosed on the basis of specific clinical findings of profound acidosis, a poor Apgar score (0–3) at birth, seizure, coma, hypotonia, and multiorgan dysfunction.

- **Brain ischemia leads to a shift in metabolism from oxidative phosphorylation to anaerobic oxidation**.
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
Serial cranial ultrasonography or early MRI for detecting preterm brain injury?

Annemarie Plaisier,1,2 Marlou M A Raets,1 Ginette M Ecuyr-Goossen,1
Paul Govaert,1,3 Monique Feijen-Roon,1,2 Irwin K M Reiss,1 Liesbeth S Smit,1,4
Maarten H Lequin,2 Jeroen Dudink1,2

What is already known on this topic?

► MRI is considered the optimal imaging method to identify preterm brain injury, but clinical circumstances may preclude its use.
► Cranial ultrasonography (CUS) allows serial scanning at bedside and technical developments are improving detection of injury.

What this study adds?

► Combined use of advanced serial CUS and MRI improves detection of common patterns of preterm brain injury.
► Compared to MRI, CUS seems more sensitive for recognising acute intraventricular haemorrhage, perforator stroke and sinovenous thrombosis, but less for small cerebellar haemorrhages.
► Clinical feasibility of MRI is limited for critically ill preterm infants.

The risks associated with erythropoietin (Epo):
Increased blood pressure (*reported in adults*), Increased clotting (*reported in adults*), Seizures (*reported in adults*), High red blood cell count, Increased iron utilization

**A cranial ultrasound** will be obtained prior to drug administration to document whether an IVH is present prior to dosing
HEAD US: TECHNIQUE

- Transducers - 7-13 MHz for extraaxial fluid, dura, meninges, convexities
  - 3.5-6 MHz 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)
Premature brain-normal

- < 32 weeks - smooth surface
- 36 weeks - reaches adult configuration
- Subarachnoid space should be < 5 mm in premature infants; less in term
- Cavum septum pellucidum – usually closes by 2-6 months
- Normal cisterna magna height 3-8 mm
Premature brain-normal

Undersulcation

Ventricular prominence, prominent extraaxial spaces, open sylvian cistern

Cavum septum pellucidum
INTRACRANIAL HEMORRHAGE

- Premature Infants:
  - Incidence: 20-25%
  - Risks: < 30 wks / < 1500 g

- Germinal matrix

- 67% of premature infant less than 32 weeks have ICH versus 5% for term

- 25-50%-clinically silent, 50%-Day 1, 90% Day 3
INTRACRANIAL HEMORRHAGE

- Predisposing factors
- Increased systemic BP - Increased pCO2, increased IV vol, decreased Hb
- Increased CNS venous pressure - Tension pneumothorax, asphyxia, CHF, mechanical ventilation
- Decreased CNS perfusion - Hypotension, decreased pO2, Hb
Germinal matrix

• Proliferating cells which give rise to neuroblast that migrate peripherally to form neurons of the cerebral cortex and basal ganglia

• Highly vascular-Ependyma of the lateral ventricle and caudate nucleus, roof of the 3rd and the 4th ventricles

• Thin walled vessels are extremely fragile, single endothelial lining
Germinal matrix

- Involution-3mth-9mths of gestation
- 28-32 weeks: only small amount left in caudothalamic groove
- By 36 weeks: involution is complete
- Premature-Lack of autoregulation-High risk of bleed-Capillary-Venous level hemorrhage
Burstein and Papile grading system

• Grade 1
  - Subependymal hemorrhage only

• Grade 2
  - Subependymal hemorrhage with blood in nondilated ventricles

• Grade 3 -35%
  - Subependymal hemorrhage with blood in dilated lateral ventricles

• Grade 4
  - Subependymal, blood in dilated ventricles, intraparenchymal blood
Grade 1 Hemorrhage

• Coronal image:
  • Echogenic mass inferior and lateral to floor of frontal horns

• Parasagittal image:
  • Echogenicity anterior to caudothalamic groove

• Clot liquefies over days to weeks, may form small 3-5 mm subependymal cysts
Grade 2 Hemorrhage

• Most difficult to diagnose

• Germinal matrix hemorrhage ruptures through ependyma, entering lateral ventricle

• No choroid plexus in occipital horns or frontal horns, so echogenicity anterior to foramen of monroe is clot

• Clot avascular / choroid plexus is not

• Can develop hydrocephalus
Intraventricular extension
Grade 3 Hemorrhage

- Expands the lateral ventricles, 3rd, 4th ventricle
- Resolves over 5-6 weeks
  - Low level echoes, CSF/blood levels
- Hydrocephalus – Arrest/resolve-75%
- 10% require shunting
Grade 4 Hemorrhage

- Intraparenchymal hemorrhage
- Causes mass effect (vs PVL)
- Hemorrhagic venous infarct resulting from germinal matrix bleed compressing / thrombosis of periventricular veins
- Liquefies and retracts over several weeks
  - Hypoechogenic center
    - Large porencephalic cysts (vs PVL) 2-3 months
Cystic encephalomalacia
### Prognosis

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mortality</th>
<th>Neuro Sequelae</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>5 %</td>
<td>5 %</td>
</tr>
<tr>
<td>2</td>
<td>10 %</td>
<td>15 %</td>
</tr>
<tr>
<td>3</td>
<td>20 %</td>
<td>35 %</td>
</tr>
<tr>
<td>4</td>
<td>50 %</td>
<td>90 %</td>
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</table>

**Neurologic Sequelae** – Mental retardation, visual impairment, spastic diplegia or quadriplegia
Cerebellar hemorrhage

- Cerebellar hemorrhages occur in approximately 25% of preterm infants with very low birth weight
- External granular layer of cerebellum is also a germinal zone
- Best imaged through post/post-lateral fontanelle
- Can result in brainstem compression, increased ICP, cerebellar atrophy
- US: echogenic SOL in cerebellar hemisphere
WHITE MATTER INJURY /HIEOF PREMATURITY

- Old term “periventricular leukomalacia”
- Lack of autoregulation
- Periventricular white matter adjacent to trigones and frontal horns; Deep or subcortical WM
- Secondary gray matter - thalami, BG, cortex, cerebellum
- US not sensitive to noncavitary white matter injury and underestimates
- Increased echogenicity of periventricular white matter > choroid plexus
- Definitive diagnosis: cystic necrosis
SUMMARY USG

- Ultrasound fast and convenient for unstable infants
- Better at detecting hemorrhage than ischemia/hypoxia
- Initial evaluation in term infants - ischemia/hypoxia, congenital malformations, infection
MRI
PATIENT IMAGING-MRI

- Right preparation
- Imaging parameters
- Safety - Team, Suction pump, O2 supply, Laryngoscope, Monitoring devices
- Examination on the day of the study
- Swaddling
- 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.
## 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>
<th>8</th>
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<tr>
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<td>Sagittal</td>
<td>Axial</td>
<td>Axial</td>
<td>Axial</td>
<td>Axial</td>
<td>Axial</td>
<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>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>
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<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*
**Indications**
Periventricular leukomalacia (PVL)
Intraventricular hemorrhage (IVH)
Prematurity
Neonatal hypoxic ischemic encephalopathy (HEI)
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></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</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>1.5 mm</td>
<td>2 mm</td>
<td>N/A</td>
</tr>
<tr>
<td>FOV</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>
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</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 MYELINATION/GENERAL MRI PATTERNS

• Need to know what is normal to know what is not normal.
  • Fully myelinated: T1 hyper   T2 hypo
  • T1 signal increases with increasing cholesterol and galactocerebroside
  • T2 signal decreases with decreasing amount of brain water
    • displaced by myelin
    • Increased length hydrocarbons and double bonds
• T2 changes lag behind T1 changes
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
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**
NORMAL MRS IN A TERM INFANT  

NORMAL MRS IN AN ADULT

Premie MR Spectroscopy

Varies
Preterm may contain lactate
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
HIE IN PRETERM

- **Severe** hypoxic-ischemic insults to the premature brain typically injure the thalamus, anterior part of the vermis, and dorsal brainstem. Involvement of the basal ganglia, hippocampus, cerebellum, and corticospinal tracts also may be seen.

- **Mild to moderate** hypoxic-ischemic injury may result in a germinal matrix hemorrhage, periventricular leukomalacia, or both.
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
2 PATIENTS WITH CYSTIC TYPE INJURY
CEREBELLAR GM HEMORRHAGE

HEMORRHAGIC HIE OF PREMATURE-WM INJURY
Thinning of the corpus callosum, particularly in the posterior body and splenium, is a characteristic late feature of periventricular leukomalacia.
PREMATURE- SEVERE INJURY

Died on day 16
Diffusion in the cortex is more restricted because of the higher ratio of cells to extracellular space.
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
FULL TERM INFANTS

- Severe, basal ganglia pattern
- Severe, total hypoxia
- Mixed pattern
4 day old term boy

T1 shows normally increased signal intensity of posterior limb of internal capsule relative to basal ganglia and thalamus.

T2 shows foci of normal hypointense signal in posterior limb of internal capsule relative to adjacent basal ganglia and thalamus.
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.
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

Blurring of GW differentiation more evident on B=0 than conventional T2-weighted images.
CURRENT THERAPIES

• Modest reductions in brain temperature-2º to 4º C, neuroprotective

• STANDARD OF CARE

• The aim is to cool infants with moderate or severe HIE within 6 h of birth to a body temperature between 33.5ºC and 34.5ºC and maintain this degree of cooling without interruption for 72 h

• Slow re-warming over at least 4 h at a rate of 0.5ºC per hour until their rectal temperature reaches the desired range (36.5-37°C)
Reduction in glutamate release

Decrease in intracellular acidosis and lactic acid accumulation

Preservation of endogenous antioxidants

Reduction of leukotriene production

Prevention of blood-brain barrier disruption and brain edema

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.
In 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
PRETERM

- 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

TERM

- 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
Fig 1. Tissue segmentation (A) from the coronal T2-weighted (B) and coronal SPGR (C) MR images. The tissues are segmented into cortical GM (gray), unmyelinated WM (red), myelinated WM (yellow), deep nuclear GM (white), and CSF (blue).
A New Ultrasound Marker for Bedside Monitoring of Preterm Brain Growth.

Roelants JA¹, Koning IV¹, Raets MM¹, Willemsen SP¹, Leguin MH¹, Steegers-Theunissen RP¹, Reiss IK¹, Vermeulen MJ¹, Govaert P¹, Dudink J².

Abstract

BACKGROUND AND PURPOSE: Preterm neonates are at risk for neurodevelopmental impairment, but reliable, bedside-available markers to monitor preterm brain growth during hospital stay are still lacking. The aim of this study was to assess the feasibility of corpus callosum-fastigium length as a new cranial sonography marker for monitoring of preterm brain growth.

MATERIALS AND METHODS: In this longitudinal prospective cohort study, cranial ultrasound was planned on the day of birth, days 1, 2, 3, and 7 of life; and then weekly until discharge in preterm infants born before 29 weeks of gestational age. Reproducibility and associations between clinical variables and corpus callosum-fastigium growth trajectories were studied.

RESULTS: A series of 1-8 cranial ultrasounds was performed in 140 infants (median gestational age at birth, 27⁺² weeks (interquartile range, 26⁻¹ to 28⁺¹; 57.9% male infants). Corpus callosum-fastigium measurements showed good-to-excellent agreement for inter- and intraobserver reproducibility (intraclass correlation coefficient >0.89). Growth charts for preterm infants between 24 and 32 weeks of gestation were developed. Male sex and birth weight SD score were positively associated with corpus callosum-fastigium growth rate.

CONCLUSIONS: Corpus callosum-fastigium length measurement is a new reproducible marker applicable for bedside monitoring of preterm brain growth during neonatal intensive care stay.
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
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.
IMPORTANT CLINICAL CORRELATES

- No influence of immaturity on cerebral myelinated or unmyelinated WM volumes
- Deep nuclear GM volumes and the number of days of ventilator support alteration of axonal fiber development
- High-dose postnatal dexamethasone therapy has been shown to be associated with significantly reduced cortical GM and cerebral tissue volumes
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.