MRI in neonatal hypoxic-ischaemic encephalopathy: predicting outcome and assessing interventions.

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The role of neonatal MR imaging

- Confirm a normally developed brain
- Assess severity and pattern of any injury
- Predict outcome form pattern of injury and clinical details
- Assess/monitor the effect of any intervention

- Even with all diagnostic criteria
  - The spectrum of injury may be wide
  - The evolution of lesions variable
The arrows point to the myelinated posterior limb of the internal capsule.

It is essential to appreciate the normal imaging appearances for term.
Imaging recommendations

- Obtain good quality non motion artefact images
- Sedate and monitor (no need to anaesthetise)
- Use neonatally optimised sequences
- Use motion resistant sequences*

* Malamateniou et al AJNR 2012
Imaging recommendations

- Image between 5 and 14 days from delivery
- T1 and T2 weighted sequences in axial plane
- T1 weighted in sagittal plane thinner slices
- Diffusion weighted or tensor imaging axial plane
  - Generate ADC map.
- MR Venogram to exclude sinus venous thrombosis
- MR proton spectroscopy. Measure Lactate/Naa ratio
Diffusion tensor imaging

- This sequence exploits random motion of water within a tissue.
- Alterations in signal intensity relate to freedom of motion termed **Diffusivity**, measured as an Apparent Diffusion Coefficient (ADC).
- ADC is reduced in acute infarction.
- Diffusion is the most sensitive sequence to detect early ischaemic lesions.
Hypoxic-ischaemic encephalopathy: diagnostic criteria

- Term born neonate >37 weeks gestation
- Evidence of fetal distress (abnormal CTG, MSL)
- Low Apgar Scores
- Low umbilical cord pH <7.1
- Necessity for resuscitation
- Neurological signs

Exclude metabolic, infective disorders, congenital malformations

NB: Always consider dual pathology
Alternative aetiology in HIE

- Pontocerebellar hypoplasia. Diagnosis made on MRI.
- Normal OFC- this neonate fulfilled all criteria for a cooling trial
Spectrum of injury: antenatal history

- Decreased fetal movements
  - Common, 4-16% pregnancies
  - Over-represented in neonates with HIE, 15-25%

- Imaging findings*
  - 24 out of 70 neonates with HIE referred over 15 month period
    - Basal ganglia and thalamic injury in 12%
    - White matter and cortex injury in 75%
      - Consistent with more prolonged insult

Personal data
Case: Decreased fetal movements for 48 hours. Born at 37+3 weeks GA. Unreactive CTG. EMCS performed. Seizures. Imaged day 2

Diffusion imaging excellent for early detection of WM injury - Note abnormal high signal throughout the white matter on DWI and corresponding low signal in the ADC map

Decreased fetal movements associated with WM injury
Sentinel events

- Acute severe hypoxic-ischaemic insult may occur with a sentinel event e.g. uterine rupture, cord prolapse, placental abruption

- However only a minority (10%*) of HIE cases have a sentinel event

* Okereaforo et al 2008
Acute hypoxic-ischaemic insult sites of abnormality

- basal ganglia and thalami
- internal capsule
- cortex
- subcortical white matter
- medial temporal lobe
- brainstem

These sites are susceptible because they have:

- Increased metabolic rate
- Actively myelinating
- Increased glutamate receptors
Sites of injury associated with an acute hypoxic ischaemic event

Lesions seen as low signal intensity on the early ADC map and abnormal high signal intensity on the later T1 weighted images are predominantly in grey matter.
Acute hypoxic-ischaemic insult: sites of abnormality

- basal ganglia and thalami (BGT)

- BGT lesions give rise to cerebral palsy
- BGT lesions can be graded as mild, moderate and severe
- The severity of neonatal BGT lesion dictates severity of impairment

- Mild; Focal with normal PLIC
- Moderate; multifocal equivocal or abnormal PLIC
- Severe; widespread with abnormal PLIC
Acute hypoxic-ischaemic insult

sites of abnormality

- basal ganglia and thalami
- posterior limb of the internal capsule (PLIC)

Abnormal signal intensity within the PLIC (arrow) predicts abnormal motor outcome

Sensitivity = 0.9  Specificity = 1.0 *

* Rutherford et al Pediatrics 1998
Range of abnormal PLIC appearances: use both T1 and T2 weighted sequences to assess
Injury patterns

- Determined by
  - Nature of insult; chronic, acute

- Imaging appearances are influenced by
  - Sequences used
  - Time of imaging from injury
Optimal timing conventional imaging

- Between 7 and 21 days to ascertain maximum extent of lesions
BGT lesions that were subtle at 4 days are very obvious at 18 days.
- T1 and T2 weighted sequences aged 14 days
- Late scanning underestimates severity
- T1 weighted 6 weeks
Early diffusion imaging

- Early conventional imaging may underestimate extent of injury
- Need to use diffusion imaging
- Excellent for white matter infarction
- Less predictable in serial early imaging of BGT injury
Low signal intensity regions on these ADC maps are consistent with hypoxic-ischaemic injury. By day 11 the reduced ADC has normalised everywhere. However the low signal intensity in the globus pallidus has become more obvious.
The day 3 low signal intensity on the ADC map is less marked than the eventual injury on T2W image at day 22.

- Diffusion imaging at one time point may underestimate BGT injury
Early imaging < 7 days

- Early conventional imaging may underestimate extent of injury
- Need to use diffusion imaging
- Excellent for white matter infarction
- Evolves in serial early imaging of BGT injury*
- Diffusion imaging may underestimate BGT injury

* Barkovich et al AJNR 2006
Pattern of injury in neonatal HIE

- Pattern of brain injury dictated by nature of insult.
- Take a careful history
- Exclude infection
- Exclude metabolic and congenital abnormalities
Predicting Outcome

- Pattern of injury dictates neurodevelopmental outcome
- Basal ganglia and thalamic (BGT) lesions associated with cerebral palsy
- Abnormal PLIC associated with abnormal motor outcome
Patients

555 infants included in our 1993-2007 neonatal encephalopathy database

- 186 infants did not have BGT injury
- 20 infants were < 35 wks
- 10 infants were lost to follow-up
- 64 infants had metabolic disorders, congenital malformations or infections
- 59 infants had an MRI scan after 6 weeks
- 41 infants were cooled

175 infants included
Neurodevelopmental Outcome

175 infants with BGT injury

49 died (28%)

126 survived (72%)

- 89 (71%) cerebral palsy (CP)
- 37 (29%) no CP

- abnormal exam 14 (38%)
- normal exam 23
MRI and motor outcome at 2 years

- **Severe CP** (levels IV & V)
- **Moderate CP** (levels II & III)
- **No CP / mild CP** (level I)

Spearman’s correlation coefficient = 0.773

* Gross motor function score
All children with normal signal intensity in the posterior limb of the internal capsule (PLIC) were walking independently by 2 years.

<table>
<thead>
<tr>
<th>PLIC</th>
<th>Not walking</th>
<th>Walking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal</td>
<td>73</td>
<td>10</td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
<td>23</td>
</tr>
</tbody>
</table>

Sensitivity = 1.0  
Specificity = 0.70  
PPV = 0.88  
NPV = 1.0

Martinez Biarge Neurology 2011
Acute hypoxic-ischaemic insult
sites of abnormality

- basal ganglia and thalami
- internal capsule

- brainstem
  - swollen pons
  - loss of corticospinal tracts
  - ponto subicular necrosis
Brainstem lesions and outcome in HIE (n=175)

No brainstem injury (32%)
No deaths

Moderate brainstem injury (23%)
25% died

Severe brainstem injury (45%)
49% died

Martinez Biarge Neurology 2011
Brain stem lesions in HIE

In surviving infants with BGT lesions:

- mesencephalic injury was associated with prolonged feeding difficulties ($p<0.001$)

- pontine injury was associated with gastrostomy ($p<0.001$).

* Martinez Biarge *Neurology* 2011
Isolated white matter injury

- Uncommon in HIE
- More common if history of decreased fetal movements
- More common if infection
- Associated with hypoglycaemia
Scoring system for white matter injury

Normal WM

Mild WM
Exaggerated long T1/T2 in the PV WM only

Moderate WM
Long T1/T2 extending to the subcortical WM, or focal punctate lesions or focal area of infarction

Severe WM
Widespread abnormalities including overt infarction, haemorrhage and loss of grey matter/WM differentiation

Martinez Biarge et al  J Pediatrics 2012 in press
67 children were evaluated with Griffiths at a median age of 29 months (range 12-56)

<table>
<thead>
<tr>
<th></th>
<th>Normal and mild WM n = 22</th>
<th>Moderate WM n = 28</th>
<th>Severe WM n = 18</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Total DQ</td>
<td>112</td>
<td>104.7</td>
<td>85.4</td>
<td>&lt;0.001</td>
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<tr>
<td>Motor</td>
<td>108.4</td>
<td>107.3</td>
<td>91.4</td>
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<tr>
<td>Social</td>
<td>114.3</td>
<td>108.5</td>
<td>94.6</td>
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<tr>
<td>Language</td>
<td>111.7</td>
<td>106</td>
<td>79.2</td>
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<tr>
<td>Eye and Hand Coordination</td>
<td>109.4</td>
<td>99.3</td>
<td>82.3</td>
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<td>Performance</td>
<td>115.6</td>
<td>103.5</td>
<td>81.1</td>
<td>&lt;0.001</td>
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The role of MR imaging in HIE

- Confirm normally developed brain
- Assess severity and pattern of injury
  - Influenced by nature of insult
- Predict outcome
  - Associated with pattern of injury
- Assess/monitor effect of intervention
MRI to assess the effect of interventions in HIE.

- Conventional imaging
  - Visual analysis of lesions with grading

- Diffusion tensor imaging
  - Tract Based Spatial Statistics (TBSS)
Visual analysis: Hypothermia

- Does hypothermia alter pattern of lesions?
- Does it decrease the number of lesions?
- Does it delay the onset or evolution of lesions?
- Does it impair the ability of MR to predict outcome?
TOBY trial

- Multi centre 42 hospitals between 2002-2006
- Term neonates >36 weeks GA
  - Fetal distress
  - Encephalopathy
  - Abnormal aEEG
- Recruit prior to 6 hours
- Moderate total body hypothermia 33-34° C for 72 hours
- Outcome at 18 months
- Imaging between 1-3 weeks
  - T1 and T2 weighted sequences in transverse and sagittal planes

Azzopardi et al NEJM 2009
TOBY trial

- 151 infants of 325 underwent MR imaging
- 131 scans suitable for analysis
- Good quality
- No consistent diffusion imaging
Patterns of injury: Haemorrhage

- 47/131 infants had signs of haemorrhage
- 39 had subdural, 10 moderate and 29 mild
- 10 infants had haemorrhage in other sites
  - 3 IVH
  - 1 caudate head
  - 1 cerebellum
  - 5 parenchyma

  2 associated with venous sinus thrombosis
Haemorrhage in TOBY trial neonates

The majority of haemorrhages detected were small and not considered to be significant for long term outcome.
There was no increase in haemorrhagic lesions associated with cooling.
- 25 cooled v 22 non-cooled (p=0.46)
3/131 infants imaged had signs consistent with sinus thrombosis

- 2 non cooled and one cooled.
Hypothermia

- Does hypothermia alter pattern of lesions?  **NO**
- Does it decrease the number of lesions
- Does it delay the evolution of lesions?
- Does it impair the ability of MR to predict outcome?
Hypothermia reduces tissue injury *

- Therapeutic hypothermia was associated with a reduction in:
  - Basal ganglia or thalamus lesions (P=0.02)
  - White matter lesions (P=0.01)
  - Abnormal posterior limb of the internal capsule (P=0.02).

- Cooled infants:
  - had fewer scans predictive of later neuromotor abnormalities (P=0.03)
  - were more likely to have normal scans (P=0.03).

* Rutherford et al Lancet Neurol 2010
Hypothermia

- Does hypothermia alter pattern of lesions?  NO
- Does it decrease the number of lesions?  YES
- Does it alter the evolution of lesions?
- Does it impair the ability of MR to predict outcome?
Evolution of lesions

- Does hypothermia effect evolution of lesions?
  On conventional imaging
  - Needs looking at systematically- no obvious effect in TOBY infants or non Trial infants.
  
  On diffusion imaging
  - Evolution of diffusion in BGT is prolonged and patterns very different even without hypothermia
  - Needs looking at systematically with hypothermia. Suggestion that hypothermia may prolong diffusion abnormalities*
  
  - However any abnormality in BGT on diffusion clinically significant as one scan likely to underestimate

Hypothermia

- Does hypothermia alter pattern of lesions? NO
- Does it decrease the number of lesions? YES
- Does it alter the evolution of lesions? UNCLEAR
- Does it impair the ability of MR to predict outcome?
Prediction of outcome

- MRI performed at median of 8 days in both cooled and noncooled infants
- The accuracy of prediction by MRI of death or disability to 18 months of age was
  - 0.84, 95% CI, 0.74-0.94 in the cooled and
  - 0.81, 95% CI, 0.71-0.91 in the non cooled groups.

* Rutherford et al Lancet Neurol 2010
Hypothermia (n=131)

- Does hypothermia alter pattern of lesions?  NO
- Does it decrease the number of lesions  YES
- Does it delay the evolution of lesions?  UNCLEAR
- Does it impair the ability of MR to predict outcome?  NO

All these questions need to be asked as new interventions administered e.g. Xenon
Summary 1: MRI in HIE

- Pattern of brain injury determined by
  - Nature of insult

- Imaging appearances influenced by
  - Sequences used
  - Time from injury

- Pattern of injury dictates outcome
  - Sentinel events, acute injury – BGT lesions
  - Prolonged injury, infection, hypoglycaemia – WM lesions
Summary 2: MRI in HIE

- Neonatal MR imaging provides excellent surrogate outcome
- Hypothermia decreases lesions
- Not associated with atypical injury
- Does not alter ability to predict outcome
Recommendations in HIE

- Image between 5 and 14 days
- T1 and T2 weighted sequences in axial plane
- T1 weighted in sagittal plane thinner slices
- Diffusion weighted imaging axial plane
  - Generate ADC map.
- MR Venogram
- MR proton spectroscopy Lactate/Naa ratio

- MOTION renders image data uninterpretable.*

* Malamateniou et al AJNR 2012
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