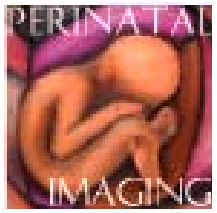

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MRI in neonatal hypoxic-ischaemic encephalopathy: predicting outcome and assessing interventions.

M A Rutherford

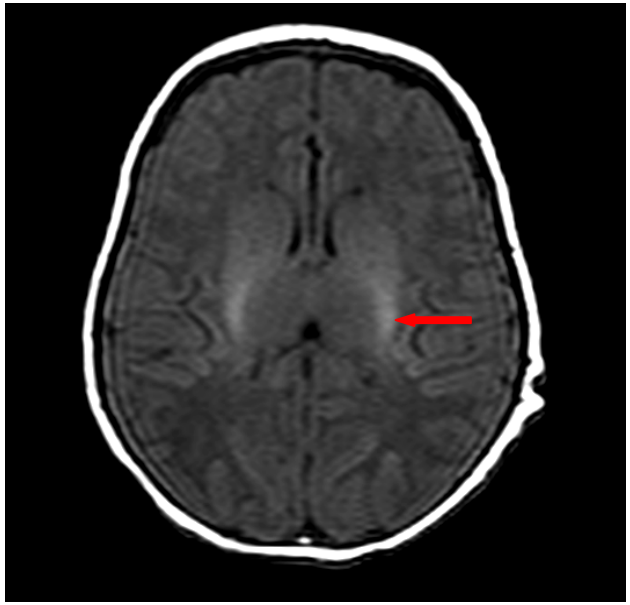
Centre for the Developing Brain

The role of neonatal MR imaging

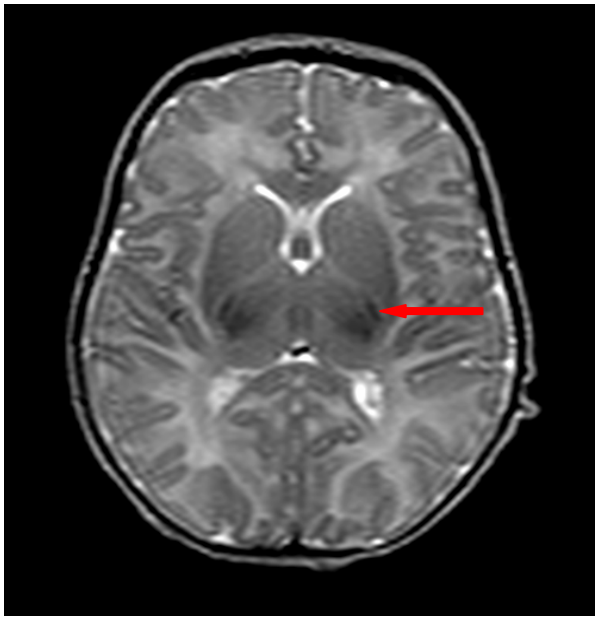
- Confirm a normally developed brain
- Assess severity and pattern of any injury
- Predict outcome form pattern of injury and clinical details
- Assess/ monitor the effect of any intervention

- Even with all diagnostic criteria
  - The spectrum of injury may be wide
  - The evolution of lesions variable

Term brain: normal appearances



T1 weighted

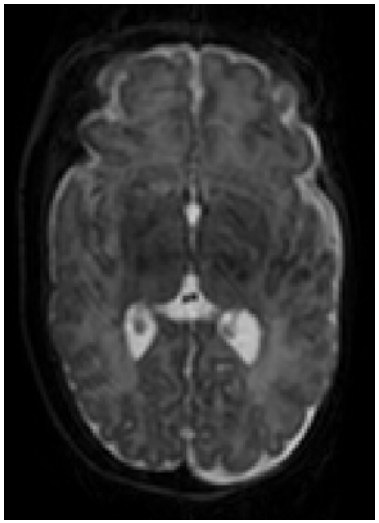


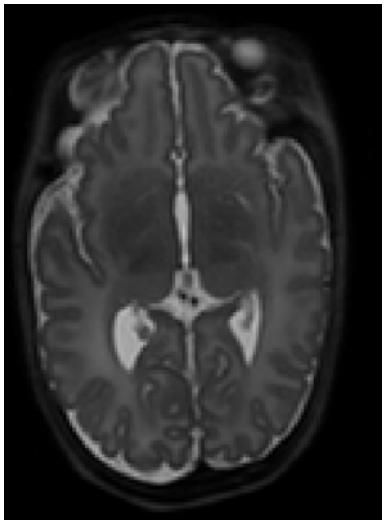
T2 weighted

- 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 artefacted 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 a an Apparent Diffusion Coefficient (**ADC**)

- ADC is reduced in acute infarction.
- Diffusion is the most sensitive sequence to detect early ischaemic lesions

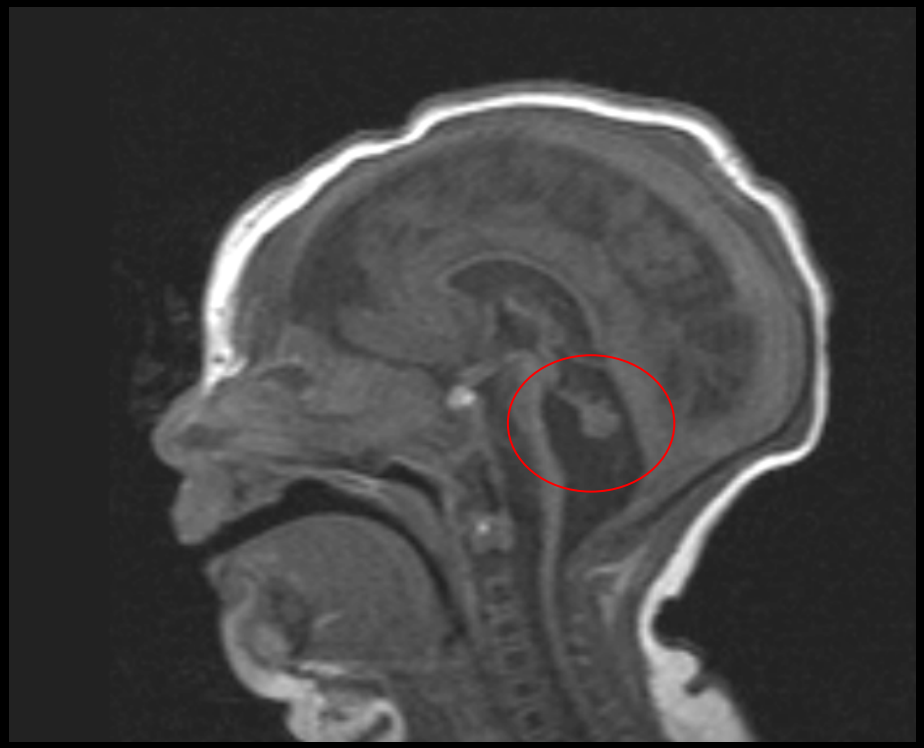
Hypoxic- ischaemic encephalopathy:diagnostsic criteria

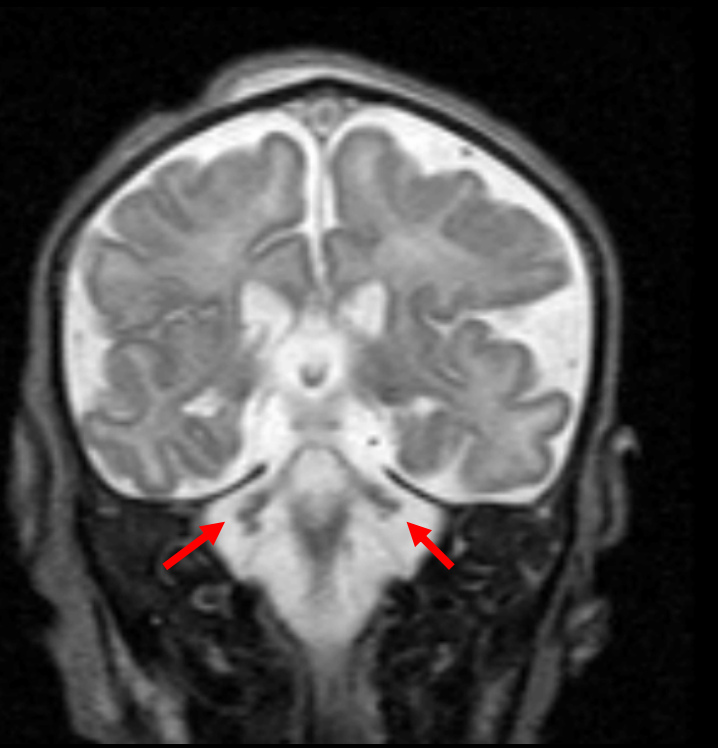
- Term born neonate >37 weeks gestation
- Evidence of fetal distress (abnormal CTG,MSL)
- Low Apgar Scores
- Low umbilical cord pH <7.1
- Necessity for resuscitation
- Neurological signs

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

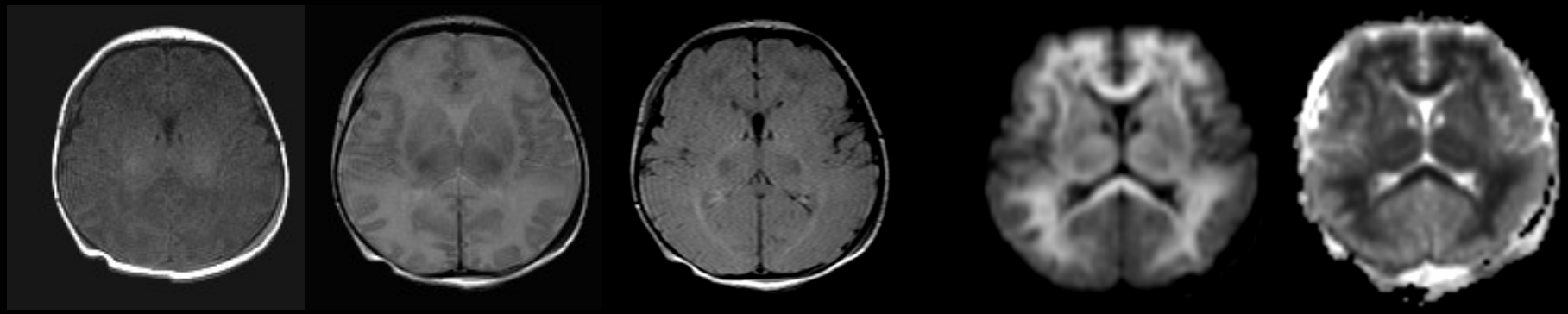
- Decreased fetal movements
  - Common, 4-16% pregnancies
  - Over-represented in neonates with HIE, 15-25%

- 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



T1 T2 FLAIR DWI ADC

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

* Okereafor et al 2008

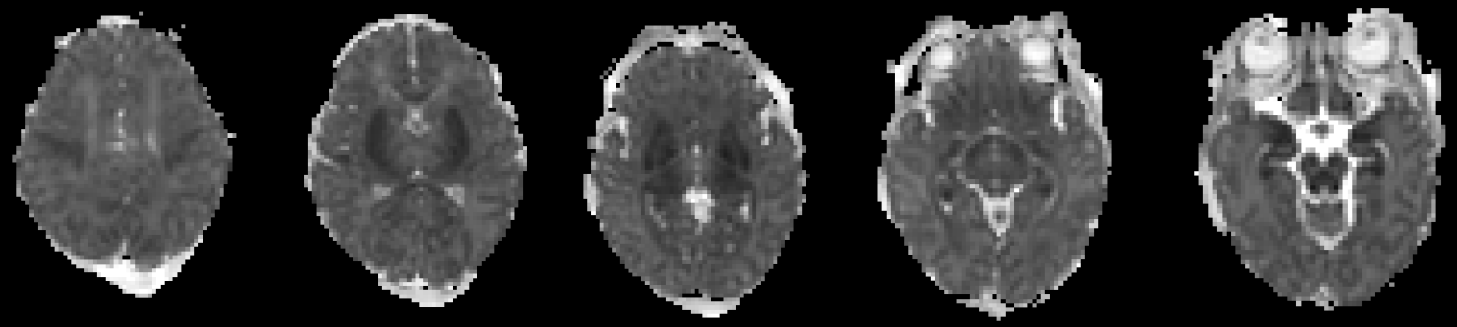
Acute hypoxic-ischaemic insult sites of abnormality

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

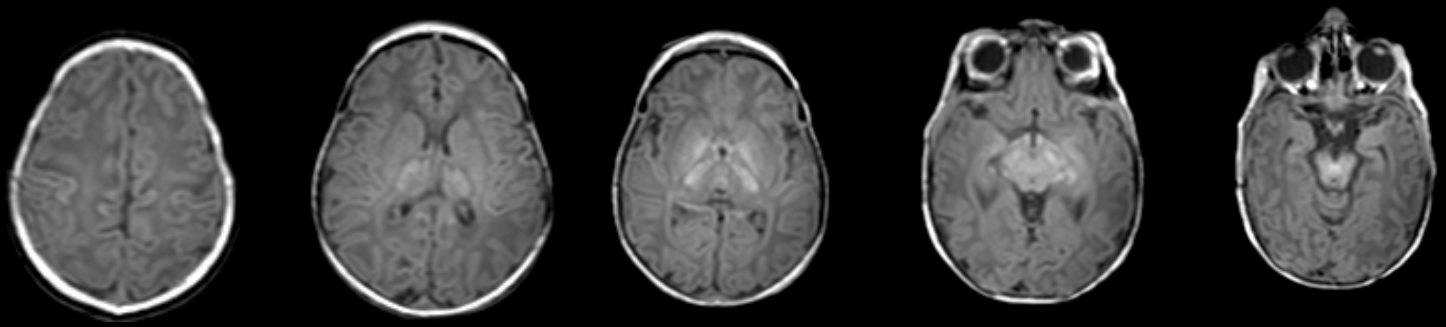
- These sites are susceptible because they have:

Increased metabolic rate
Actively myelinating
Increased glutamate receptors

Sites of injury associated with an acute hypoxic ischaemic event



Day 5
diffusion

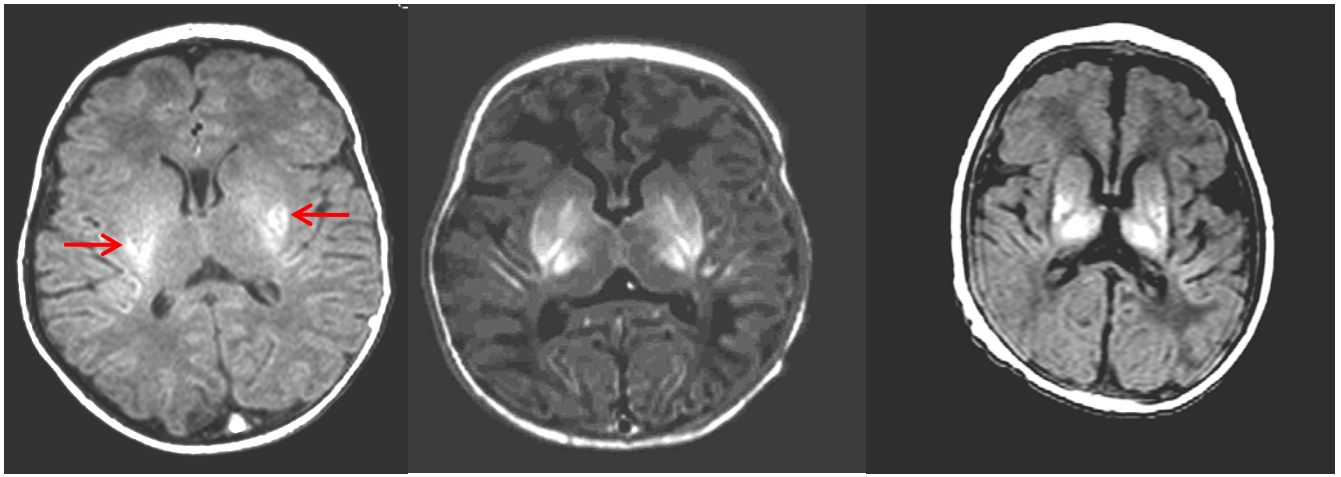


Day 11
T1w

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)**



Mild;
Focal with
normal PLIC

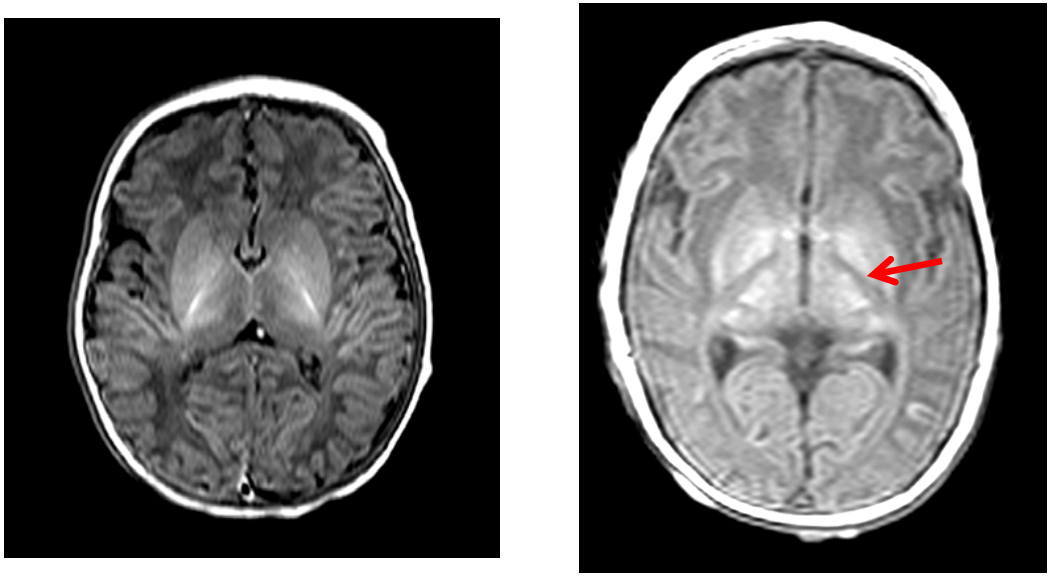
Moderate;
multifocal equivocal
or abnormal PLIC

Severe; widespread
with abnormal PLIC

- 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

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

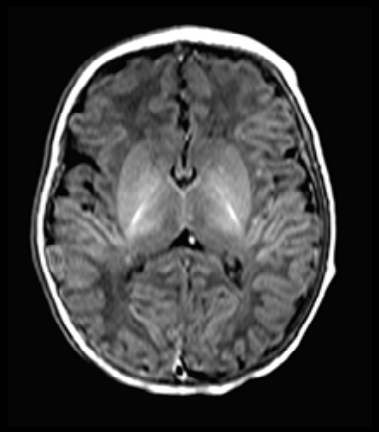
Sensitivity= 0.9 Specificity = 1.0 *

* Rutherford et al Pediatrics 1998

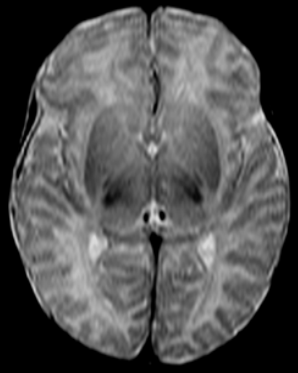
Range of abnormal PLIC appearances:
use both T1 and T2 weighted sequences to assess

Normal

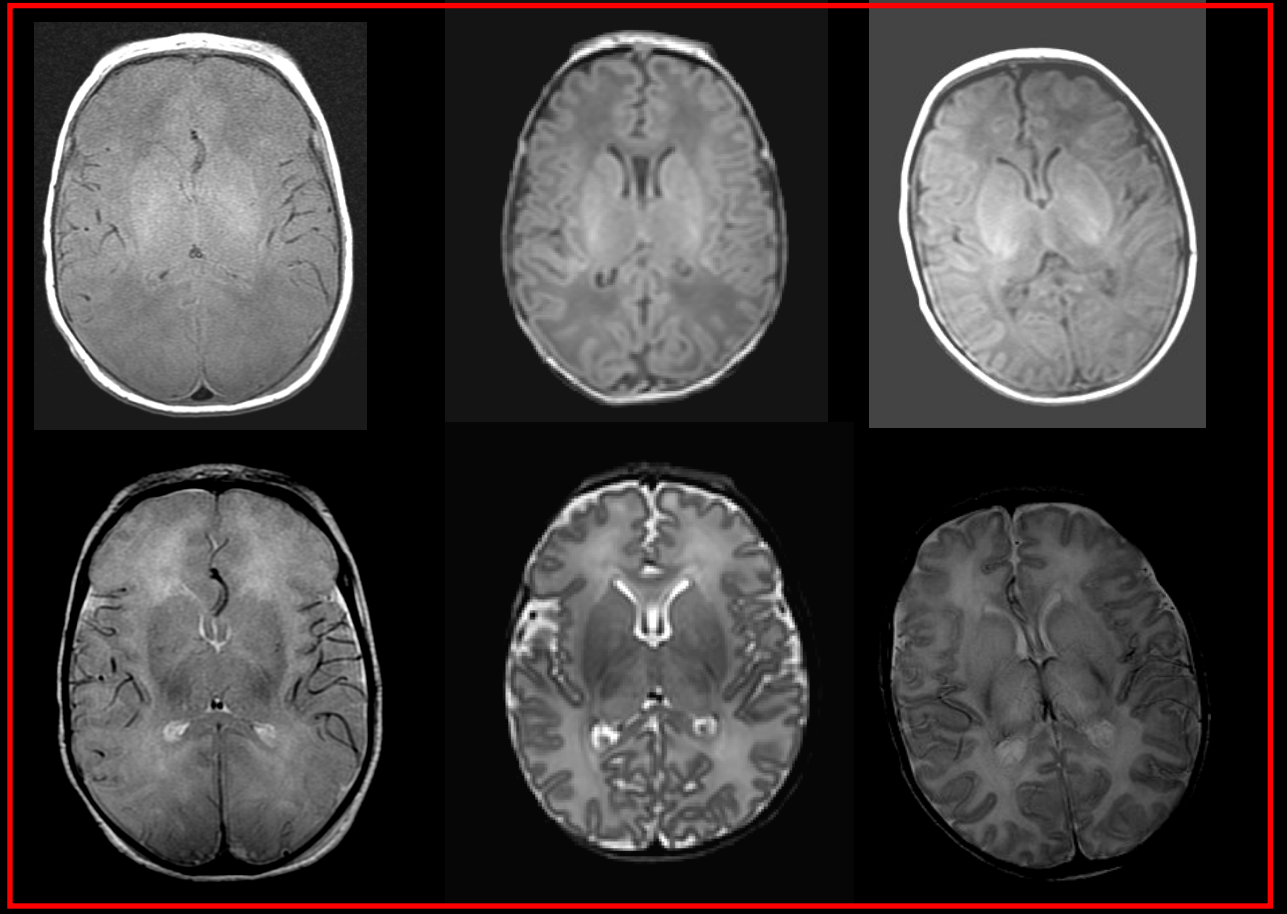
Abnormal



T1



T2



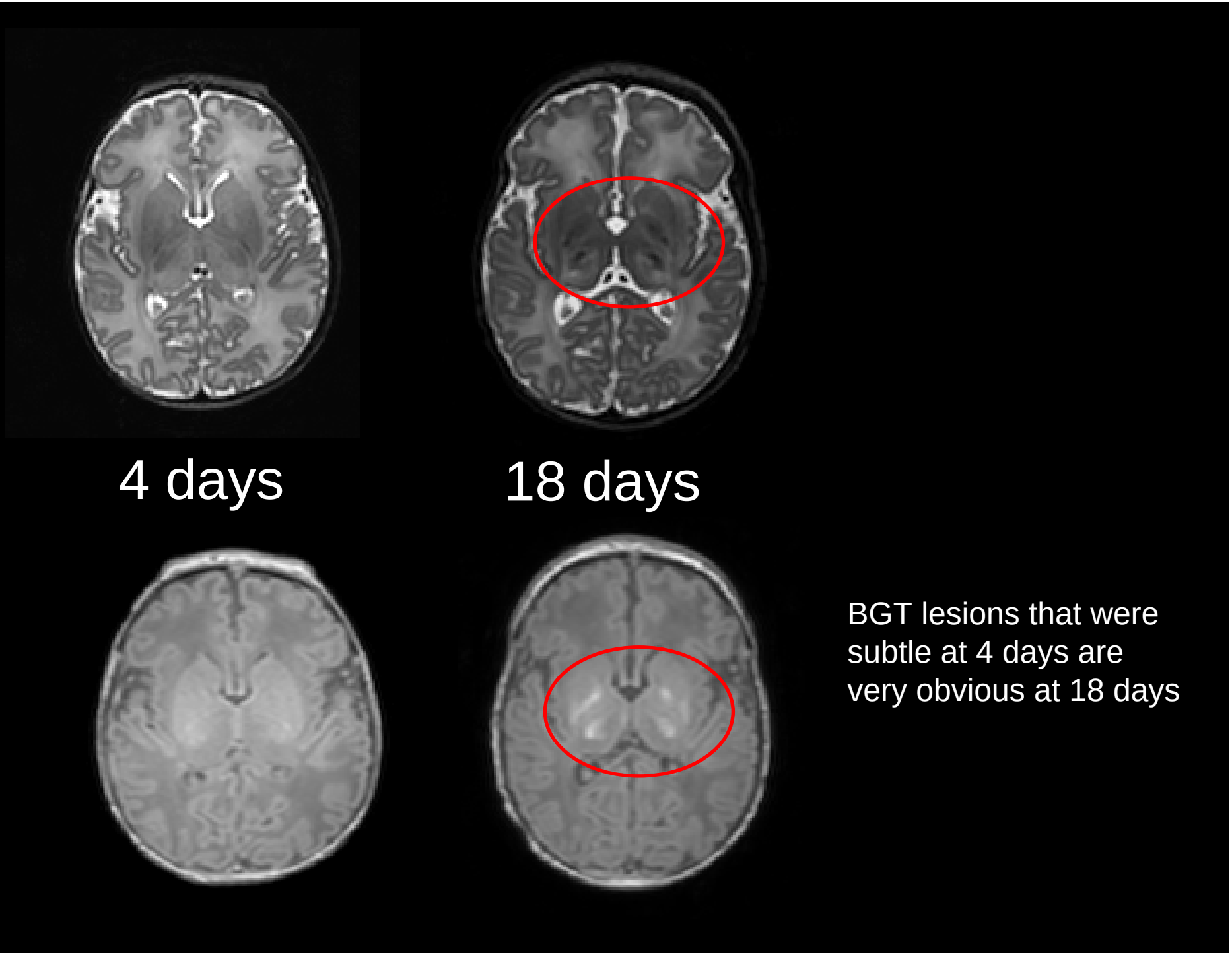
Injury patterns

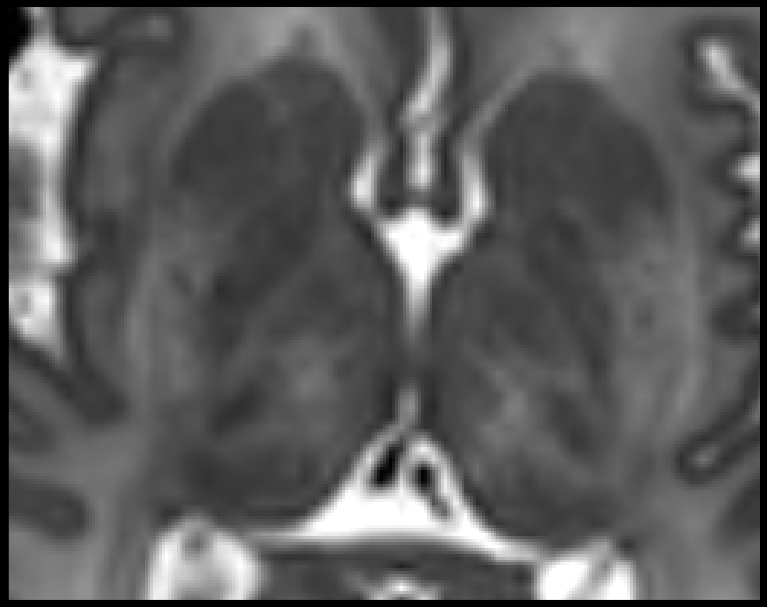
- Determined by
  - Nature of insult; chronic, acute

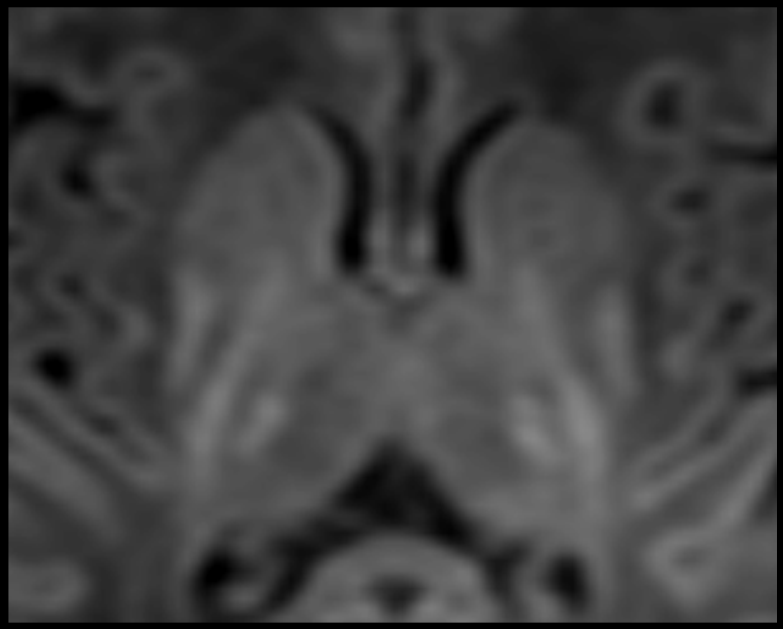
- Imaging appearances are influenced by
  - Sequences used
  - Time of imaging from injury

Optimal timing conventional imaging

- Between 7 and 21 days to ascertain maximum extent of lesions

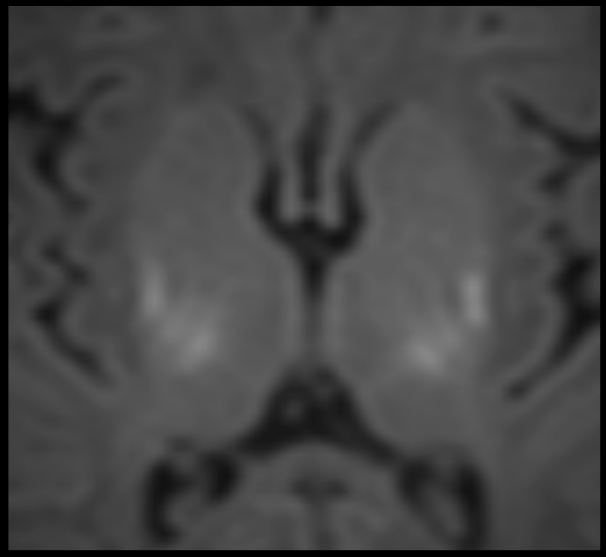

4 days
18 days
BGT lesions that were subtle at 4 days are very obvious at 18 days





- T1 and T2 weighted sequences aged 14 days

- T1 weighted 6 weeks

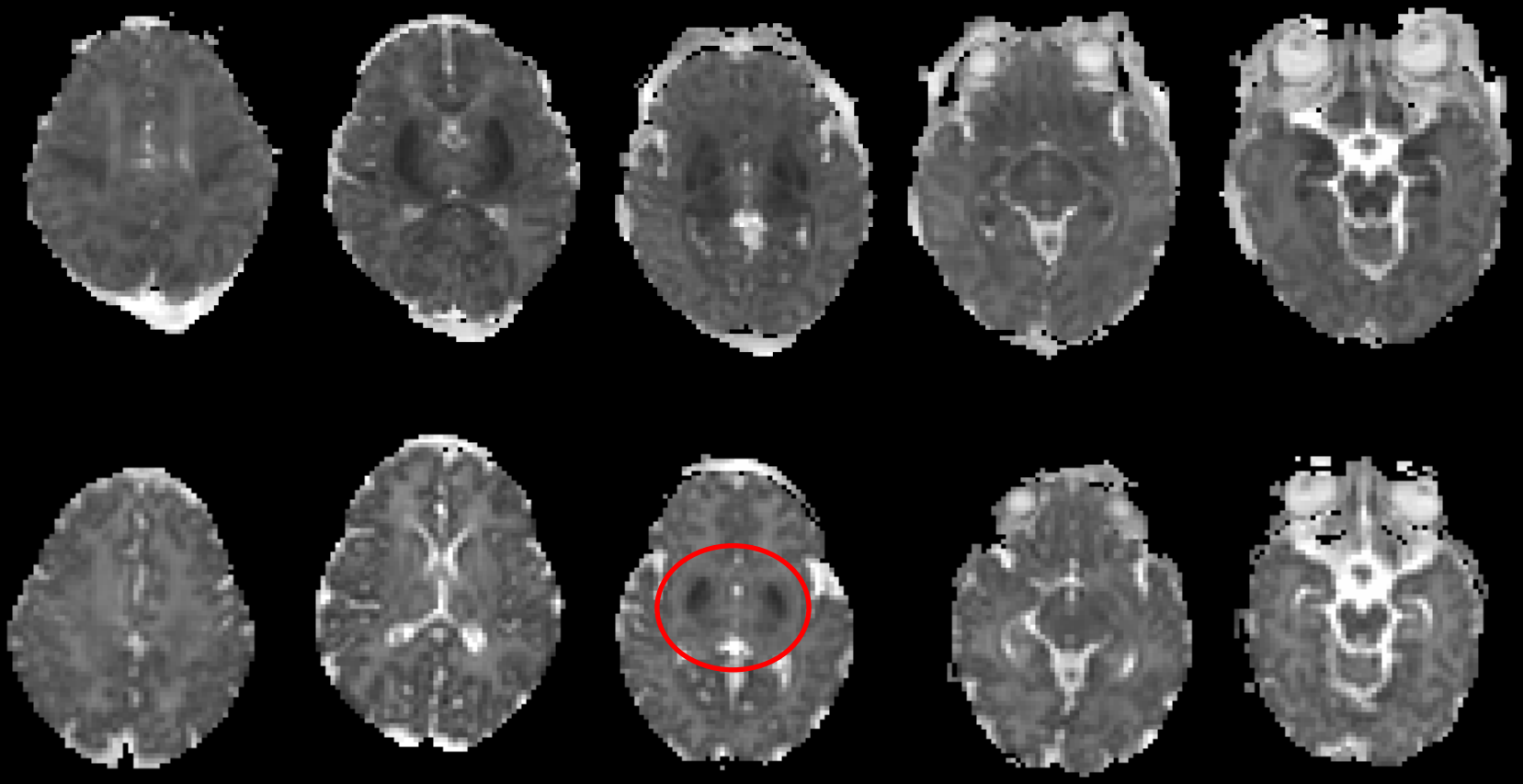


- Late scanning underestimates severity

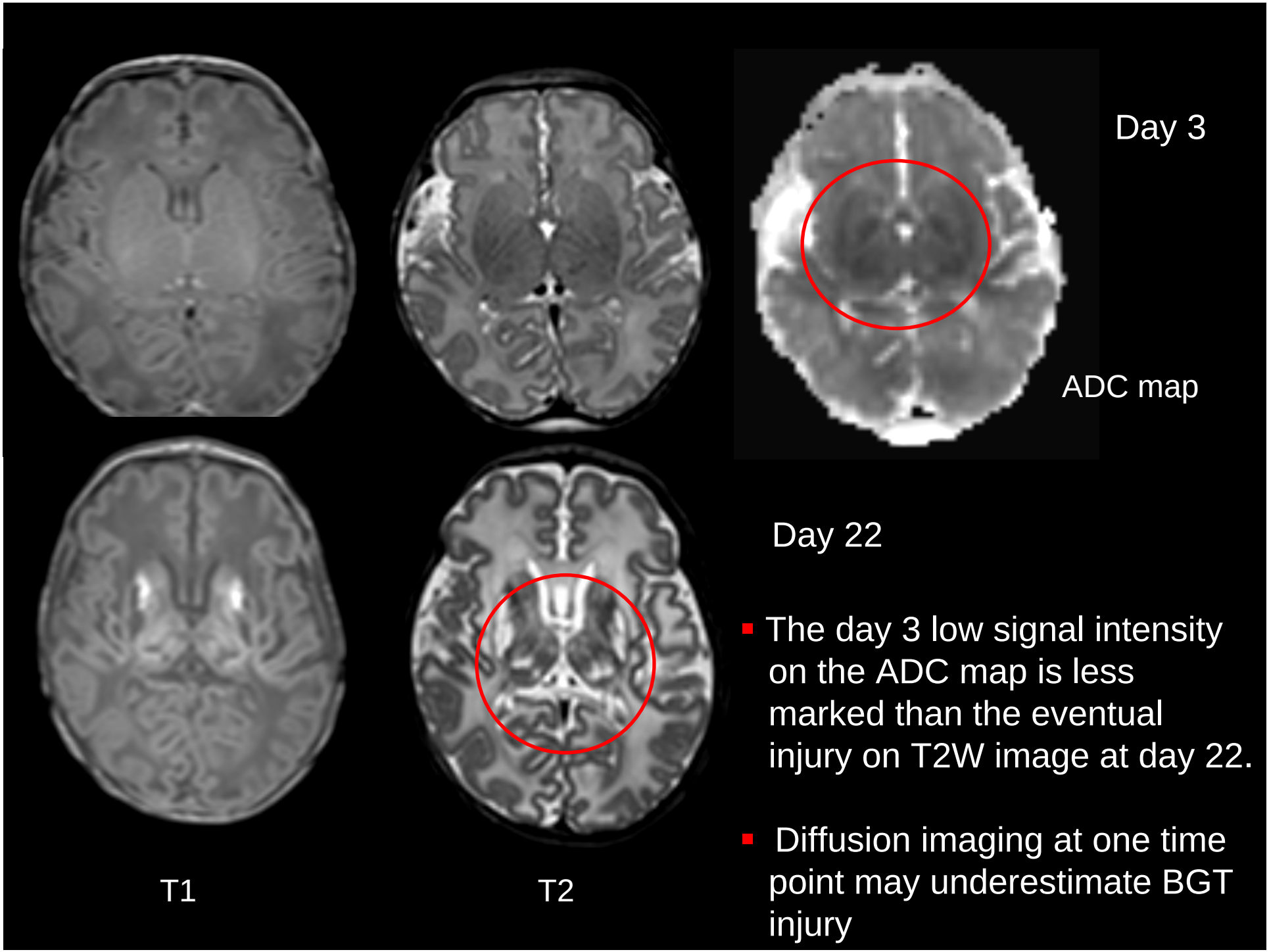
Early diffusion imaging

- 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

Evolution of diffusion changes



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

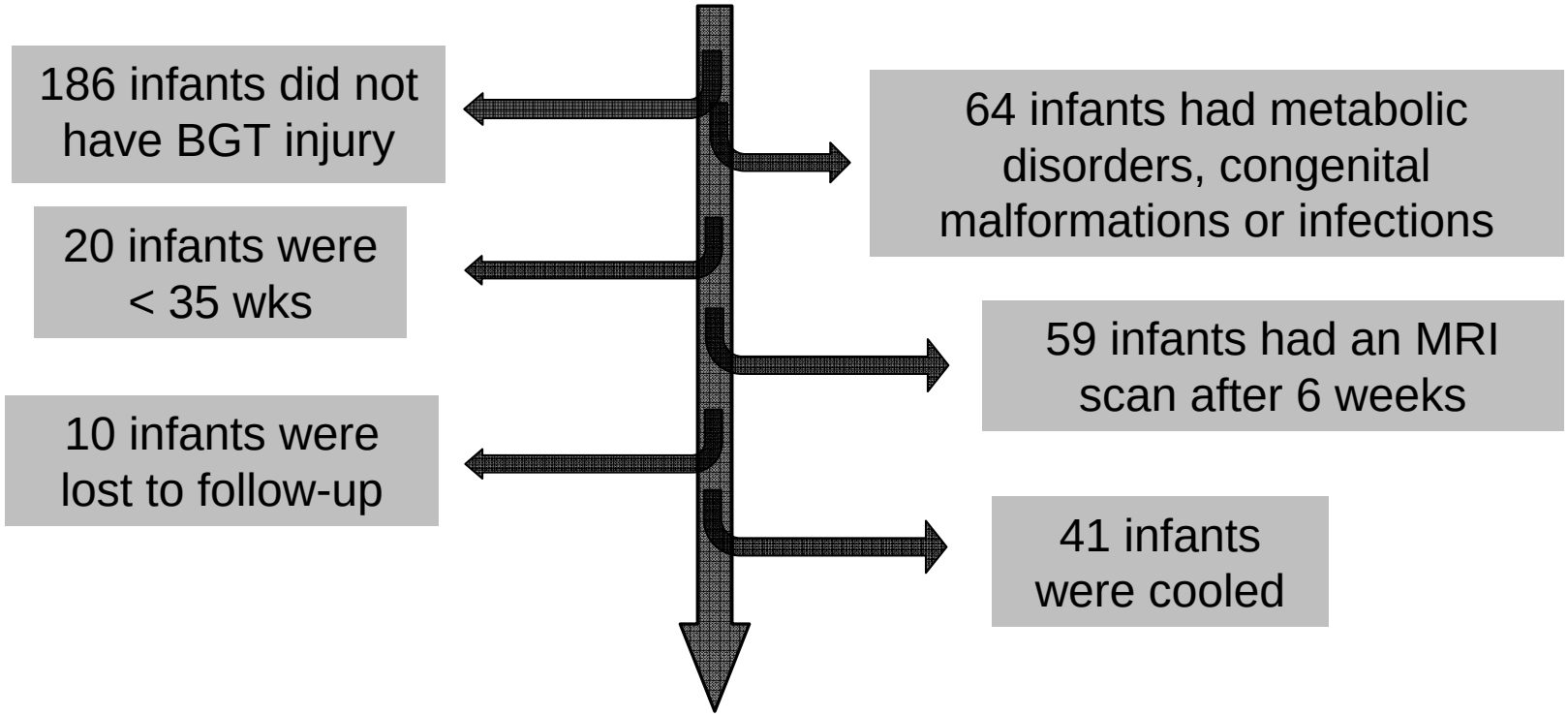
- Pattern of brain injury dictated by nature of insult.
- Take a careful history
- Exclude infection
- Exclude metabolic and congenital abnormalities

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

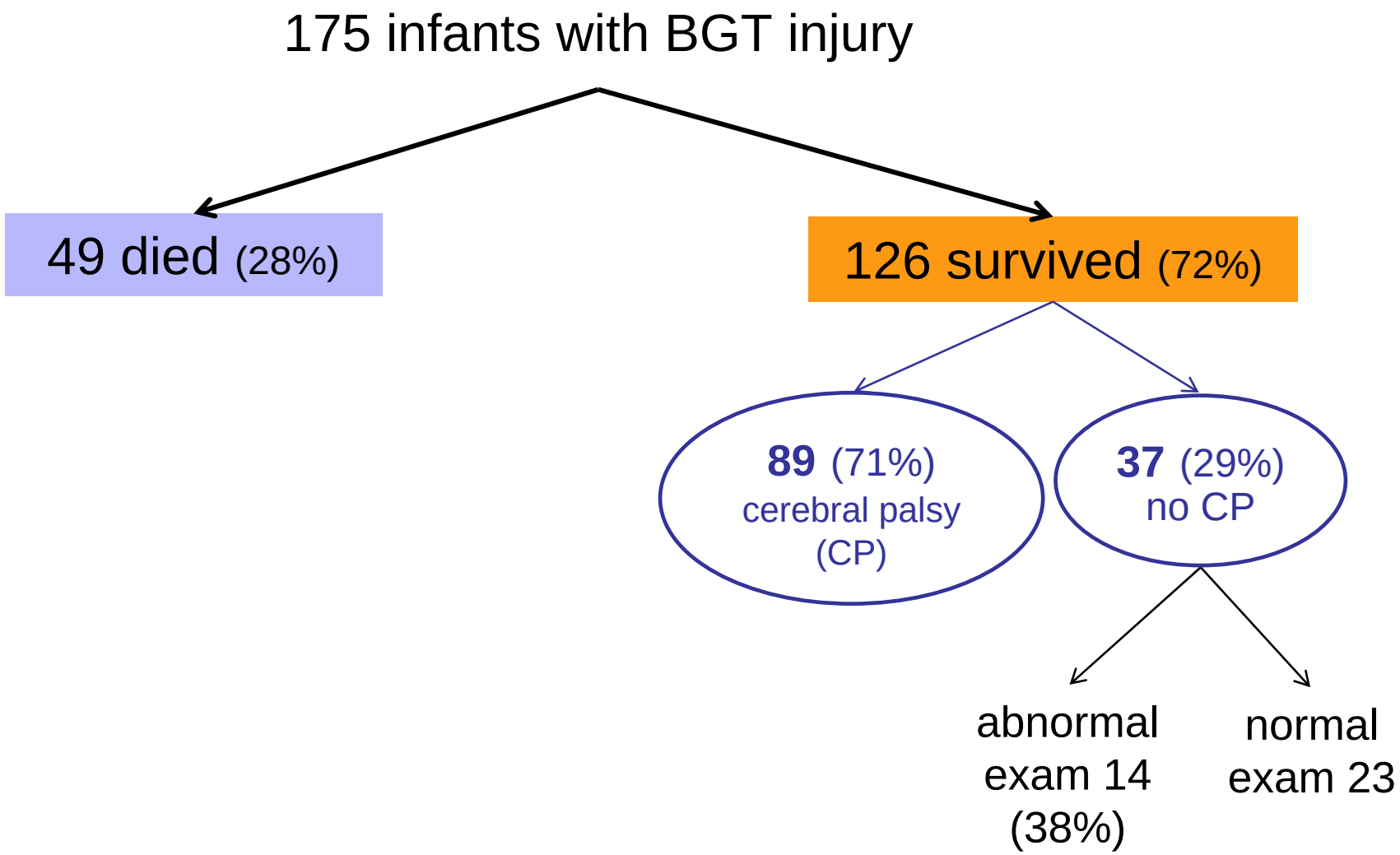
555 infants included in our 1993-2007 neonatal encephalopathy database



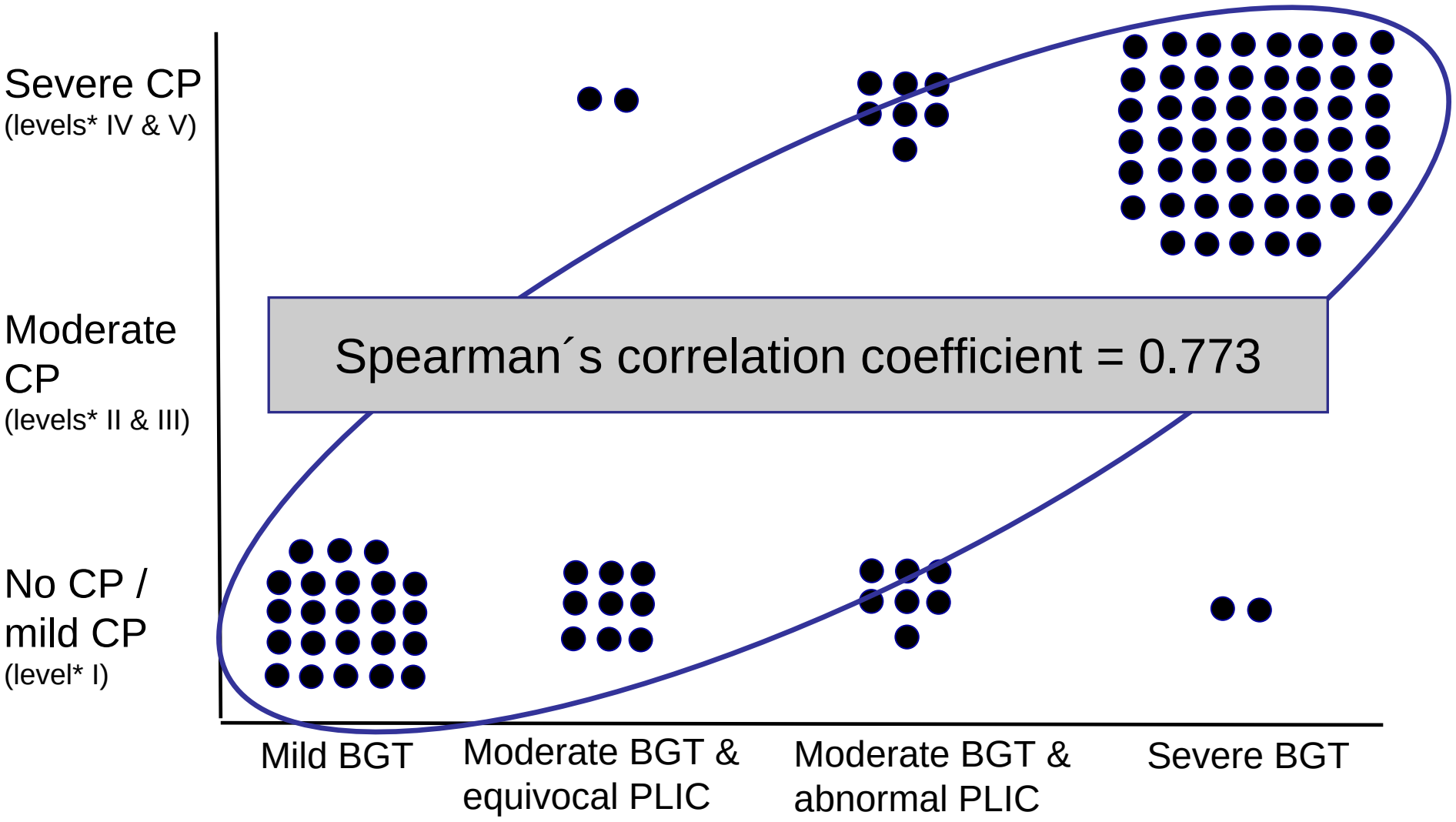
175 infants included

Martinez Biarge Neurology 2011

Neurodevelopmental Outcome



MRI and motor outcome at 2 years



* Gross motor function score

PLIC and ability to walk at age 2 years

All children with normal signal intensity in the posterior limb of the internal capsule (PLIC) were walking independently by 2 years

PLIC	Not walking	Walking
Abnormal	73	10
Normal	0	23

PPV = 0.88

NPV = 1.0

Sensitivity = 1.0

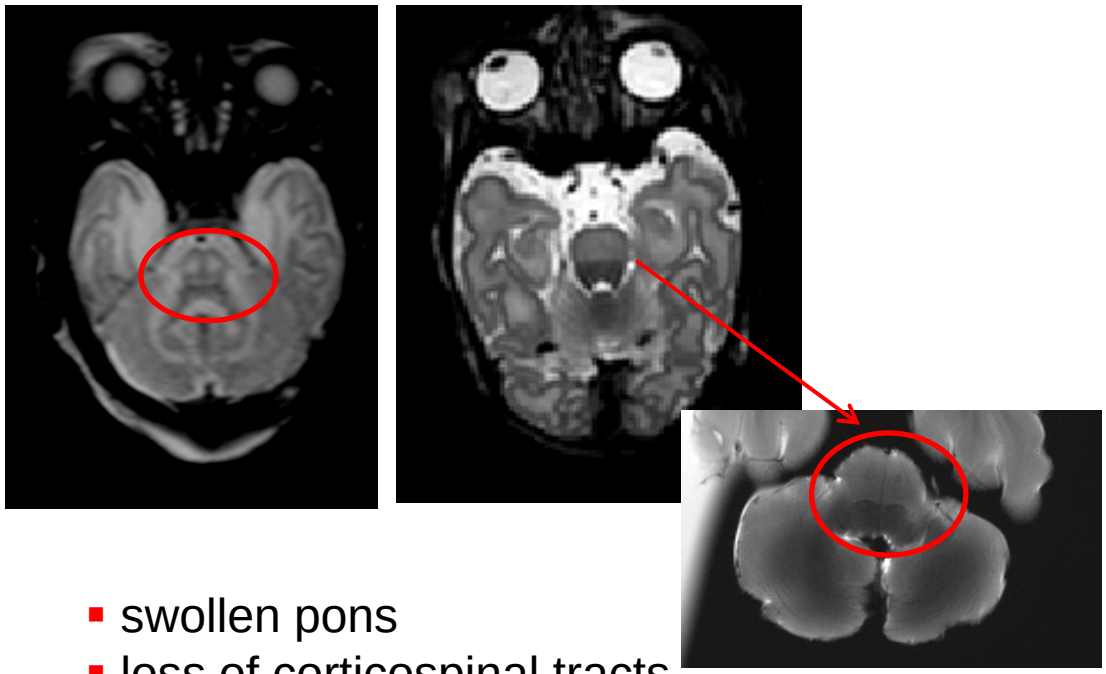
Specificity = 0.70

Martinez Biarge Neurology 2011

Acute hypoxic-ischaemic insult sites of abnormality

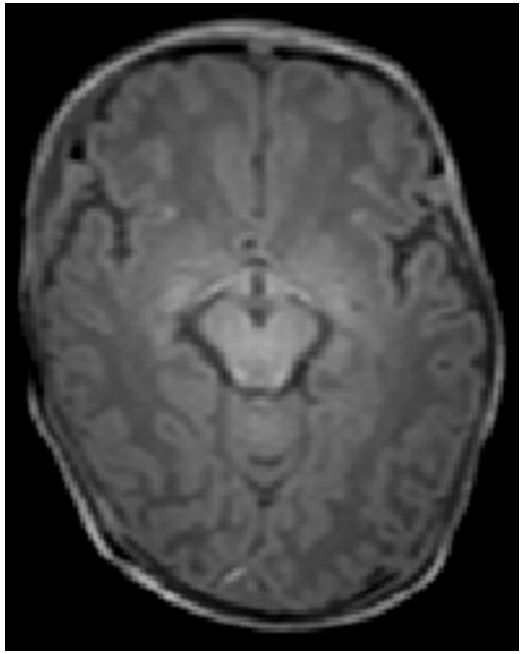
- basal ganglia and thalami
- internal capsule

- brainstem



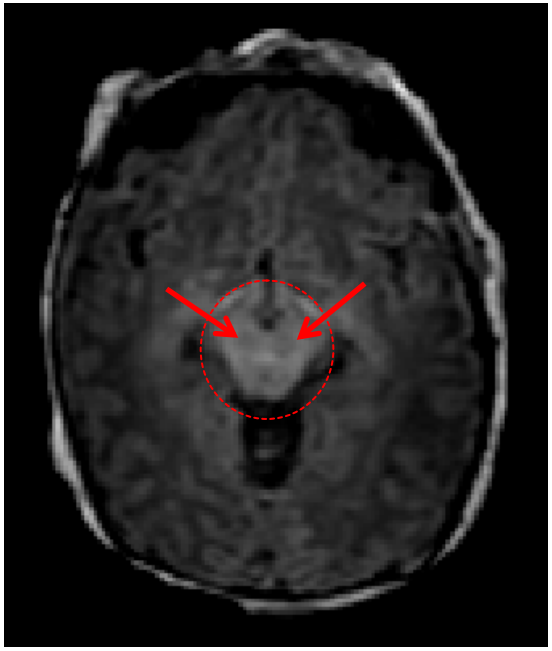
- swollen pons
- loss of corticospinal tracts
- ponto subicular necrosis

Brainstem lesions and outcome in HIE (n=175)



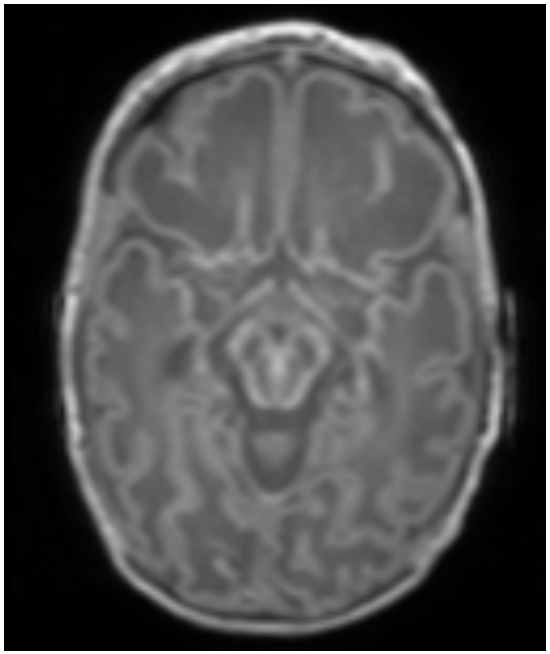
No brainstem injury (32%)

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 ($p<0.001$)

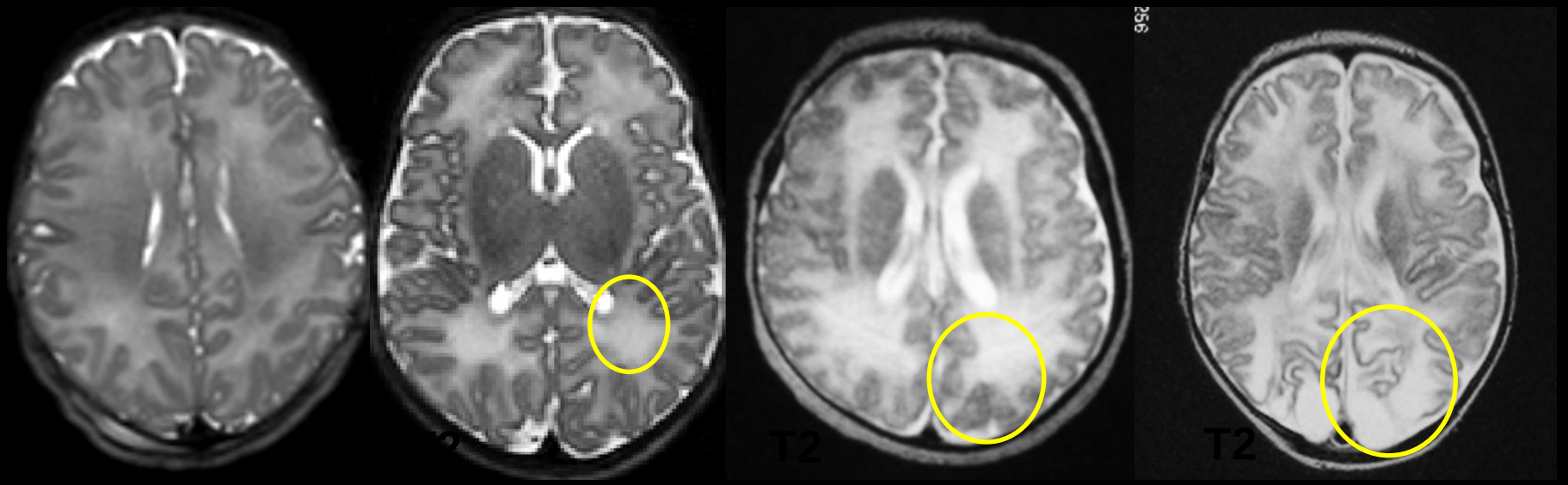
- pontine injury was associated with gastrostomy ($p<0.001$).

* 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	Moderate WM	Severe WM
	Exaggerated long T1/T2 in the PV WM only	Long T1/T2 extending to the subcortical WM, or focal punctate lesions or focal area of infarction	Widespread abnormalities including overt infarction, haemorrhage and loss of grey matter/WM differentiation

Martinez Biarge et al J Pediatrics 2012 *in press*

Outcomes in isolated WM injury in HIE

67 children were evaluated with Griffiths at a median age of 29 months (range 12-56)

	Normal and mild WM n = 22	Moderate WM n = 28	Severe WM n =18	P
Total DQ	**112**	**104.7**	**85.4**	**<0.001**
Motor	108.4	107.3	91.4	0.15
Social	114.3	108.5	94.6	0.018
Language	111.7	106	79.2	<0.001
Eye and Hand Coordination	109.4	99.3	82.3	<0.001
Performance	115.6	103.5	81.1	<0.001

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

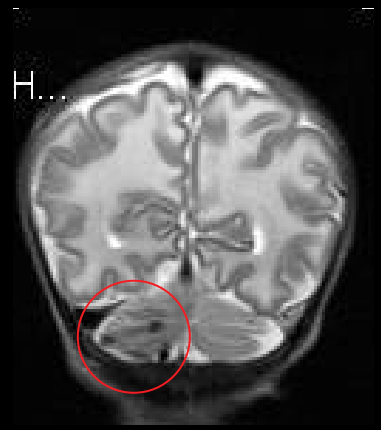
Patterns of injury: Haemorrhage

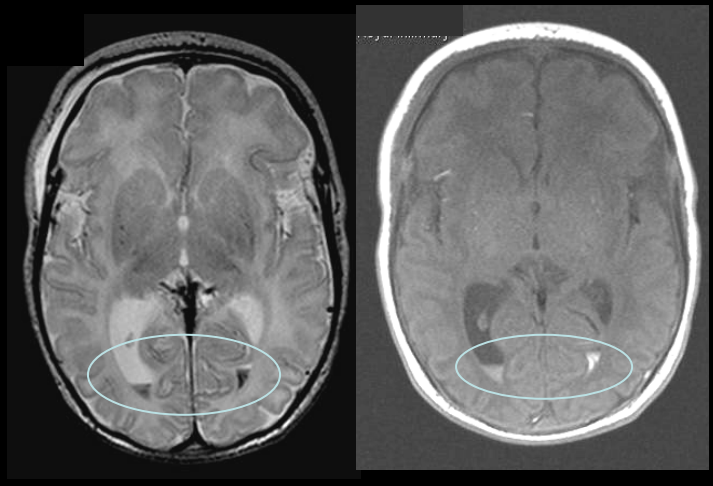
- 47/131 infants had signs of haemorrhage

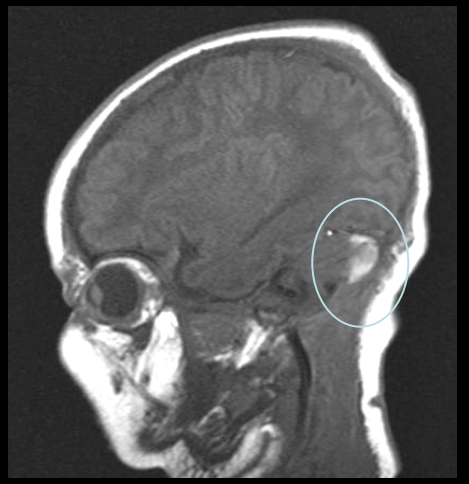
- 39 had subdural , 10 moderate and 29 mild
- 10 infants had haemorrhage in other sites
  - 3 IVH
  - 1 caudate head
  - 1 cerebellum
  - 5 parenchyma

    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

Haemorrhage

- There was no increase in haemorrhagic lesions associated with cooling
- 25 cooled v 22 non-cooled (p=0.46)

Sinus thrombosis

- 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

* Bednarek, et al. Neurology 2012

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

Summary1: 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

MRC Medical Research Council

Imperial College London

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