Prognosis in Hypoxic-Ischemic Encephalopathy

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Major problems we have to face while caring infants with HIE are;

- to provide families with reliable information about outcome.
- to decide how long we will pursue treatment in infants who may have a very poor prognosis.

How can we predict outcome?

- **Clinical predictors**
- **Biomarkers** (markers of BBB integrity and neuroinflammation
- **Neurophysiologic monitoring** (cEEG, aEEG,EP, NIRS)
- **Imaging studies**

✓Combination of different strategies is more helpfull!

✓Therapeutic hypothermia can change or modify the prognostic value of these markers!

Clinical predictors of outcome

Sarnat & Sarnat described a grading system for HIE in 1976 to estimate the risk of adverse outcome

Bohr and Greisen used modified Sarnat & Sarnat grading and collected outcome data of 16 studies:

- ✓With mild HIE, 98% of infants have normal outcome
- ✓With severe HIE, 96% of infants die or have severe neurologic sequelae.
- ✓With moderate HIE, which infants will recover??

Modified Sarnat & Sarnat Staging for HIE and Outcome

Grade	Mental status	Need for ventilation	Feeding problems	Tone	Seizures	Probability of severe handicap or death
Mild (Sarnat 1)	Hyperalert	No	Mild	Jittery	No	<1%
Moderate (Sarnat 2)	Lethargy	No	Moderate	High	Yes	25%
Moderate to severe	Lethargy	Yes	Moderate	High	Yes	50%
Severe (Sarnat 3)	Coma	Yes	Severe	Flaccid	Yes	75%

Levene MI et al. Lancet 1986

Clinical predictors of outcome

- On serial neurological examinations, improvement in stage of HIE was associated with cooling.
- Persistence of **severe HIE at 72 hours** and **abnormal neurological exam at discharge** were associated with a greater risk of death or disability.

(Shankaran S et al, J Pediatr. 2012)

Clinical predictors of outcome

Impact of clinical seizures: When adjustment was made for severity of encephalopathy, seizures were not associated with death, or moderate to severe disability at 18 months of life.

(Kwon JM et al, J Child Neurol. 2011)

Clinical predictors of outcome

- **10 min Apgar score** is independently associated with death despite therapeutic cooling in infants with HIE.
- Infants who remain asystolic at 10 min and beyond are unlikely to survive despite cooling, and the rare survivor is likely to have severe disability.

(Sarkar S et al, Arch Dis Child Fetal Neonatal Ed 2010)

Clinical predictors of outcome

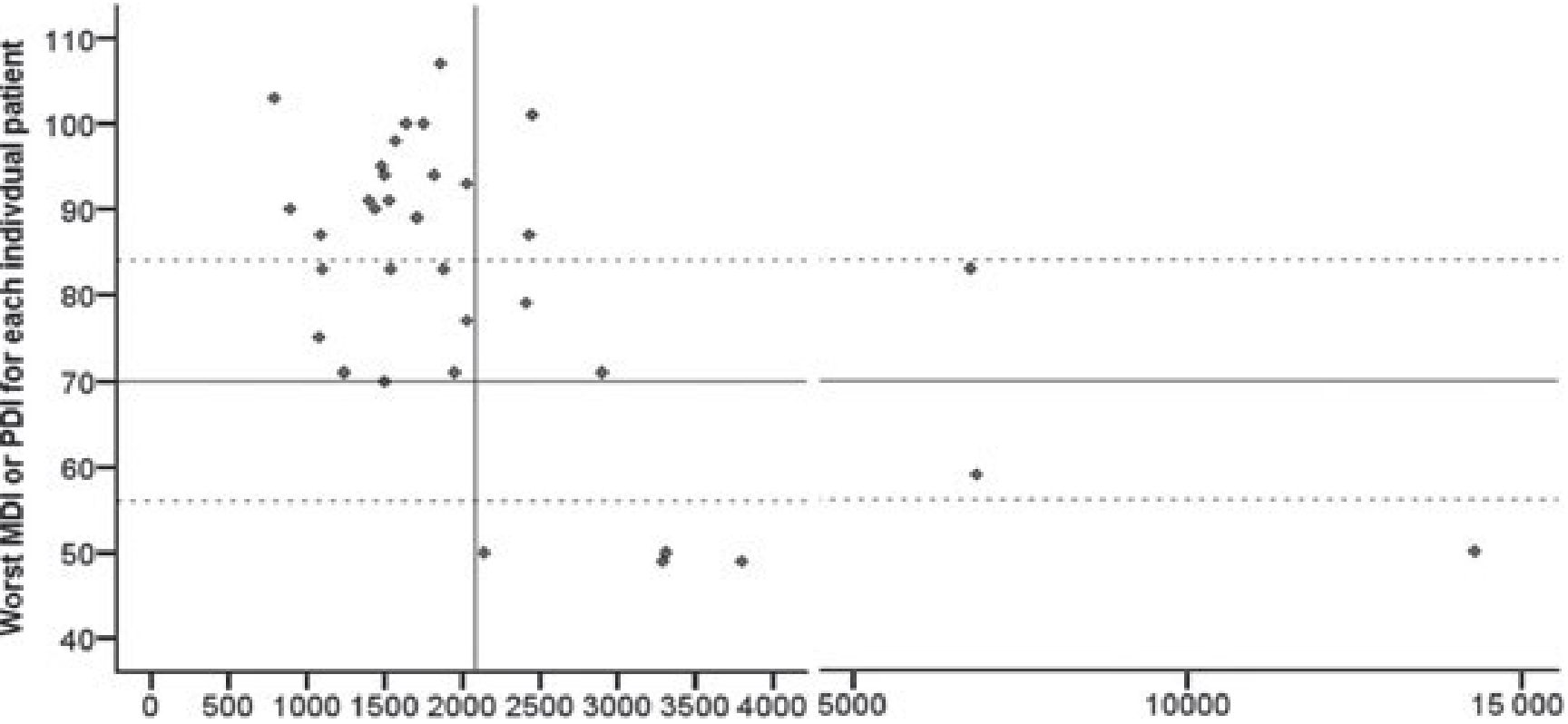
- In term infants with HIE, the site and severity of brain lesions seen on early MRI are highly correlated with **general movements**. Central gray matter damage leads to cramped-synchronized general movements and poor motor outcome.
- Early MRI scans and general movements are complementary tools for predicting motor outcome.

Biomarkers of HIE

- **Early hypoglycaemia** (0-6 hours of life) was associated with severe HIE, and thereby; adverse outcome. (*Nadeem M. et al, BMC Pediatrics 2011)*
- **Profound acidosis** (BD >18 mmol/L at 30 min of life) was associated with moderate–severe encephalopathy in nearly 80% of patients, and no cases occurred with BD <10–12 mmol/L. Between these extremes outcomes are rather variable. (*Wayenberg JL. J Matern Fetal Neonatal Med 2005)*

LDH > 2085 U/L (within 6 h of birth) was associated with adverse outcome in hypothermia-treated term infants with moderate/severe HIE.

(*Thoresen M et al, Acta Pædiatrica 2012)*



Biomarkers of HIE

Strong ion gap (SIG) with base excess (BE) and lactate revealed correlations with MRI abnormalities in infants not treated with cooling.

SIG at 24 hours of life had the largest AUC and PPV of 84%. *(Mann C. Et al, Am J Perinatol 20*

$$SIG = \{[Na^+] + [K^+] + [Mg^{2+}] + [Ca^{2+}] - [Cl^-] - [lactate^-]\}$$
$$- \{(1000 \times 2.46 \times 10^{-11} \times (pCO_2/10^{-pH}) + [albumin^-](g/dL)$$
$$\times (0.123 \times pH - 0.631) + [phosphate^-](mg/dL) \times (0.309 \times pH - 0.469)\}$$

Biomarkers of HIE

Protein S-100 β

Synthesized by astrocytes and released into the blood when BBB is disturbed.

Reference ranges are available for newborns.

Can be detected in urine, blood, CSF and saliva.

Urinary S-100β concentrations >1 mcg/L predicts neonatal death with 100% senstivity and specificity. (not effected by renal failure)

Biomarkers of HIE

Glial Fibrillary Acidic Protein (GFAB):

Cytoskeletal protein of the astrocytes.

Serum GFAP ≥0.15ng/mL at NICU admission was predictive of abnormal brain MRI

Neuron-Specific Enolase:

Detected in serum only after both neuronal death and distrubtion of BBB.

Serum NSE >45 mcg/L distinguish infants who will have poor outcomes.

Biomarkers of HIE

Brain-Derived Neurotrophic Factor (BDNF):

A neurotrophin that supports survival of existing neurons as well as growth and differentiation of new neurons and synapses.

Cord plasma levels are higher in infants with HIE and reflects brain cell recovery.

Biomarkers of HIE

Serum cytokines

- Elevated **IL-6** and monocyte chemotactic protein-1 (**MCP-1**) within 9 hours after birth and low macrophage inflammatory protein 1a (**MIP-1a**) at 60 to 70 hours of age were associated with death or severely abnormal neurodevelopment at 12 months of age.
- In hypothermia treated neonates with better outcomes, down modulation of **IL-6, IL-8**, and **IL-10** from their peak levels at 24 hours to their nadir at 36 hours was observed.

(*Jenkins DD et al, Journal of Cerebral Blood Flow & Metabolism 2012)*

Neurophysiologic monitoring

Conventional EEG:

Usefullness of EEG in infants with HIE has been confirmed by multiple studies.

Background patterns and paroxysmal activity

Severe EEG abnormalities:

- Low-voltage tracing
- Electrocerebral inactivity
- Burst-suppression pattern

EEG

Combinations of **clinical grading+EEG findings** offer improved prediction of outcome.

In infants with moderate HIE,

- severely abnormal EEG changes the probability of death or severe disability from 25% to 73%.
- İf EEG is marginally abnormal or normal, death or severe disability is 3%.

EEG

In infants with moderate to severe HIE,

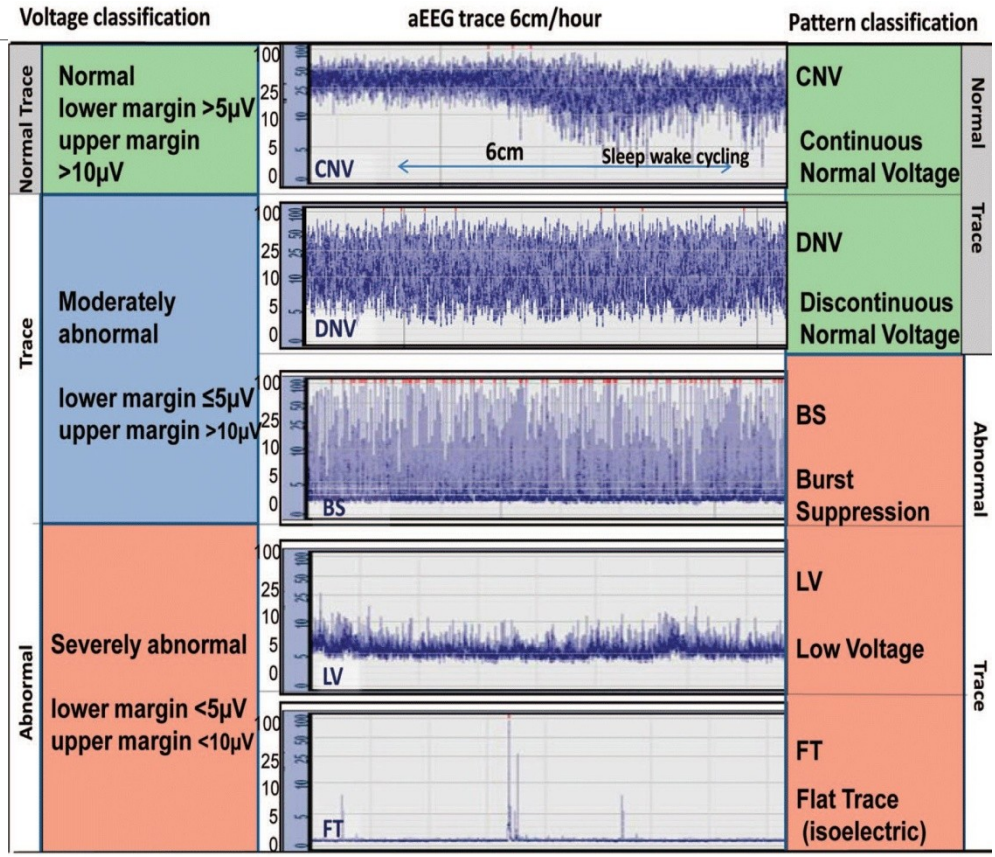
- severely abnormal EEG changes the probability of adverse outcome from 50% to 89%.
- If EEG is marginally abnormal or normal, risk of adverse outcome is 9%.

Evoked potentials

- Can be used to assess multiple anotomic levels of the CNS
- Visual Evoked Potential (VEP), Brainstem Evoked Potential (BAEP), Somatosensory Evoked Potential (SSEP) and Event-Related Potential (ERP)
- **Somotosensory evoked potentials** are the most sensitive and specific and have similar predictive power to EEG.
- Difficult to obtain at the bedside
- Lack of experience in neonates

Amplitude-integrated EEG

- Simplified, continuous EEG with a limited number of electrodes
- Provides an overall impression of cerebral activity
- Background activity
- Sleep-wake cycles (SWC)
- Neonatal seizures



From Thoresen M, et al. Effect of hypothermia on amplitude-integrated electroencephalogram in infants with asphyxia. Pediatrics. 2010 Jul;126(1):e131-9. PMID:9563847 Reprinted with permission of The American Academy of Pediatrics

aEEG

- Severely abnormal tracing predicts poor outcome with 91% senstivity.
- Burst suppression on flat tracing or continuous low-voltage patterns without recovery at 24 hours are predictive of a poor outcome with 91-95% senstivity, 86-88% positive predictive value, 91-96% negative predictive value.

aEEG

- Some infants with severely abnormal EEG recover to normal voltage patterns

  (earlier the recovery, better the prognosis)

- **Onset of SWC** correlates with severity of HIE

  (milder the injury, earlier the onset of SWC)

- In neonates with moderate to severe HIE treated with hypothermia, approximately 65% with acquisition of cycling have a normal outcome *(Takenouchi T et al, J Pediatr 2011)*

Near-infrared spectroscopy

- Noninvasive method of monitoring brain tissue oxygenation at a depth of 2.5-3cm (**frontal cortex only**)
- Regional cerebral oxygen saturation (**rSO2**), hemoglobin difference signal (**HbD**), cerebral blood volume (**CBV**) , fractional tissue O2 extraction (**FTOE**)

Most useful for monitoring changes over time in an individual patient!

Near-infrared spectroscopy

↑**FTOE** → higher O2 consumption in relation to oxygen delivery to brain

↓**FTOE** → less utilization of O2 by brain tissue

Infants with adverse NDO had nearly 50% decrease in FTOE

Increased **CBV** or unusually high **rSO2** during the first days after birth were associated with adverse NDO at 1-2 years of age.

Increased **CBV** had a senstivity of 86% for predicting death or disability.

Imaging studies

Cranial ultrasonography:

Easiest study to perform, readily available

Poor predictor of outcome with high false positive rate

Cerebral blood velocity can be measured by doppler

Severe **basal ganglia (BG)** and **thalamic (T)** echo densities suggest poor prognosis.

Computed tomography:

Do not become abnormal for several days after birth

Only slightly better than cranial USG

Imaging studies

Magnetic Resonans Imaging:

- More sensitive
- Predictive power similar to EEG and EP
- Good correlation exists between results of the EEG within the first 3 days and MRI after 1 week (7-28 days) and outcome prediction.
- Lesions can be graded, and the pattern of involvement is related to the outcome.

MRI

- In infants with a global HI insult, the most frequent site of injury is the **central gray matter**
- Bilateral **BG** and **T lesions** are strongly associated with the development of motor impairment.
- **Bilateral loss of signal in the posterior limb of the internal capsule (PLIC)** was used to predict severe adverse outcome at 1 year. (detection rate of 100%, a false positive rate of 10%)

3 main MRI patterns of HIE lesions:

1. *Periventricular leukomalacia– PVL,*
2. *Basal ganglia and/or thalamus lesions – BGTL,*
3. *Multicystic encephalopathy – MCE accompanied by injury to the basal ganglia, thalamus and/or cerebral cortex*

MRI

PVL → *preterm infants with chronic hypoxia*

- In late preterm newborns the injury involves the subcortical white matter as well.
- Typically the lesions are symmetrical, though less often can be asymmetric

Clinical correlate: Spastic CP (diplegia, quadriplegia or hemiplegia with more severe involvement of the lower limbs), epilepsy

The prognosis is worse when the **subcortical white matter** is also affected (spastic tetraplegia, severe mental retardation, epilepsy, and often impaired vision)

MRI

BGLT → Acute and severe hypoxia in term infants

Selective neuronal necrosis: usually bilateral, extend depends on the severity and duration of the HI event

- Mild: Normal signal from the PLIC and focal lesions in BG
- Moderate: Altered signal from the PLIC and the focal changes in BG and lateral part of the talamus.
- Severe: Altered signal from the PLIC , diffuse changes in the BG and can extend to mesencephalon.

Clinical correlate: Extrapyramidal CP and normal intellectual development.

MRI

MCE → The severe form of selective neuronal necrosis

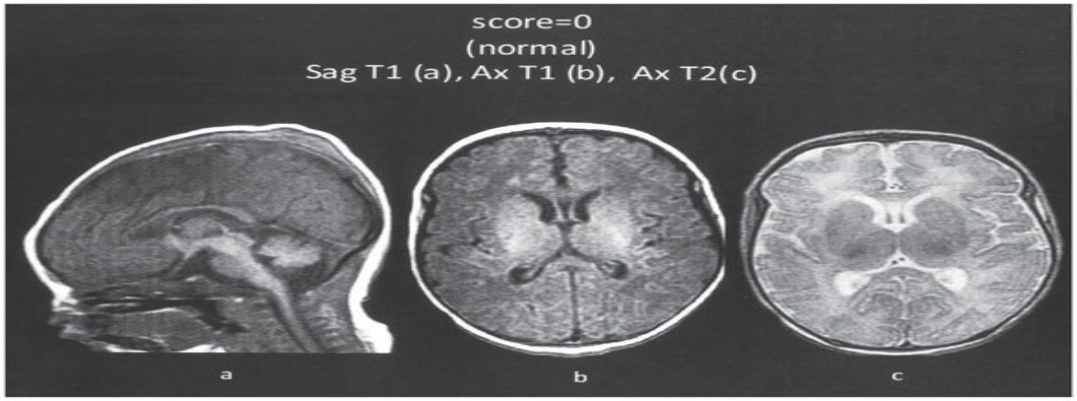
A cavity within the WM with the involvement of BG, thalamus and/or cerebral cortex.

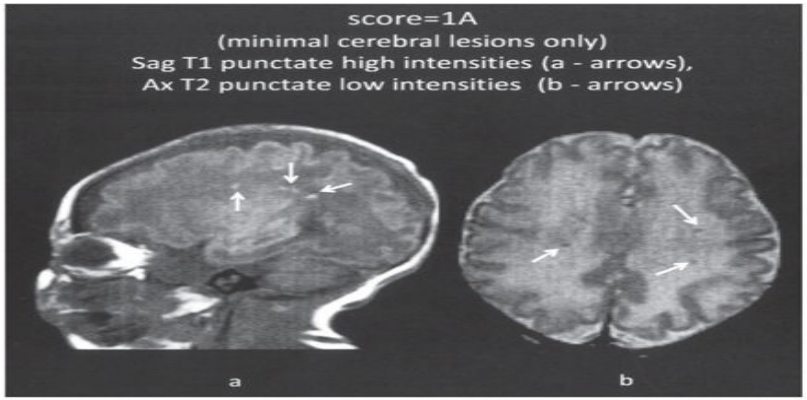
Typical for a prolonged and severe hypoxia.

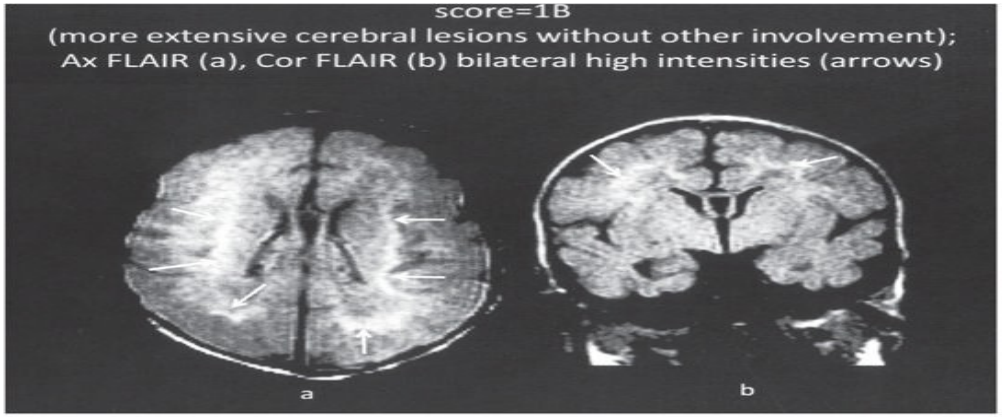
Prognosis is unfavourable.

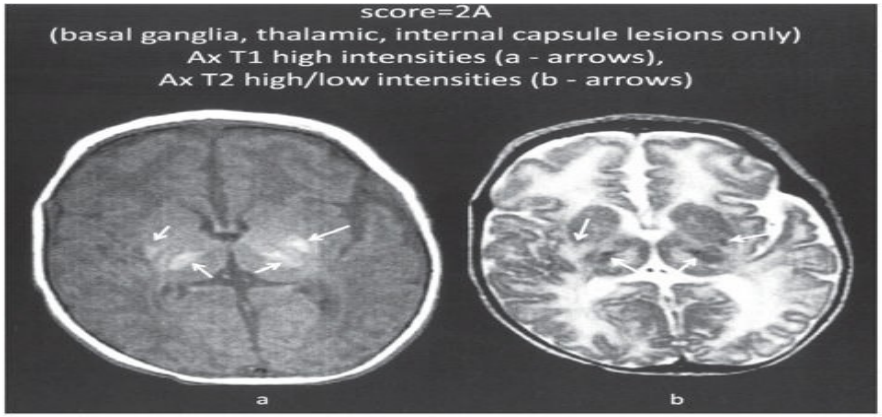
Clinical correlate: Severe quadriplegic CP with choreoathetotic symptoms, microcephaly, mental retardation, bulbar symptoms, and epilepsy

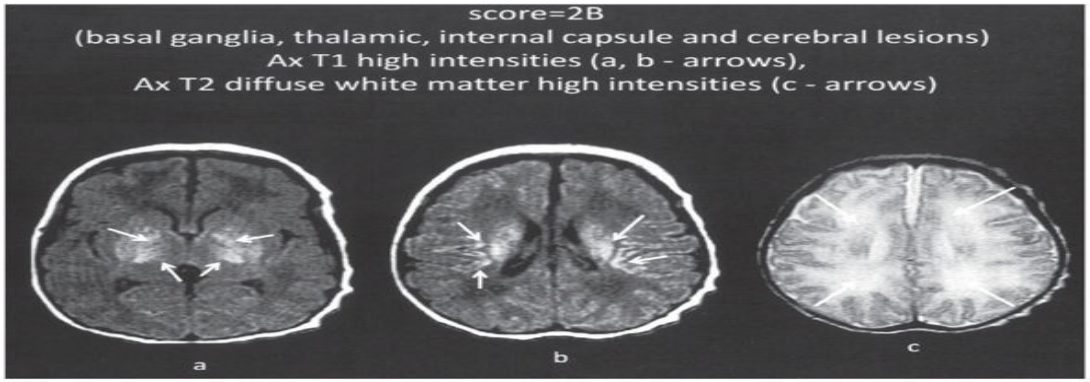
NICHD described a brain injury pattern on MRI
Each level reflects a greater involvement of the brain

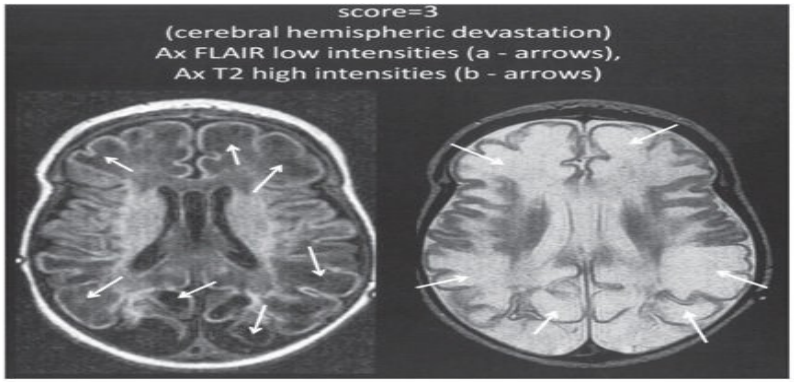












MRI

Each level increase was independently associated with a twofold increase in the odds of death or disability.

Fewer areas of infarction and a trend towards more normal scans were noted in brain MRI following whole-body hypothermia.

(Shankaran S et al, Arch Dis Child Fetal Neonatal Ed 2013)

Diffusion-weighted imaging

- Abnormalities can be detected several days after the insult with cMRI.
- DWI assesses tissue integrity early after injury.
- Apparent diffusion coefficient (ADC) values detects ischemia.
- Infants with poor outcome had significantly lower ADC values at early imaging in several regions including thalamus, putamen, Rolandic cortex, hippocampus, and PLIC.
- **Low ADC value in the PLIC** is the best predictor of poor motor outcome.

Magnetic Resonance Spectroscopy

- Basal ganglia or thalamic lactate/N-acetyl aspartate is a marker for the prediction of adverse long-term neurodevelopmental outcome or death.
- There is yet insufficient evidence to advise either positively or negatively about the use of MRS.

Systematic review of prognostic tests HIE:

Neurophysiologic tests (1st week)	Imaging (1st-2nd week)
aEEG (sensitivity 93%, specificity 90%)	**Diffusion weighted MRI** (specificity 89%)
CEEG (sensitivity 92%, specificity 83%)	**T1/T2-weighted MRI** (sensitivity 98%)
VEP (sensitivity 90%, specificity 92%)	**MR spectroscopy** (sensitivity of 75%, specificity %58)

van Laerhoven H et al. Pediatrics 2013. Prognostic tests in term neonates with hypoxic-ischemic encephalopathy: a systematic review.

Summary

- Combination of prognostic test results will perform better than individual tests. Best combination of prognostic tests?
- cEEG and aEEG both perform well in predicting outcome even in the first week of life.
- Normal/mildly abnormal EEG correlated with favorable outcome, particularly if neuroimaging is normal.
- When EEG is severely abnormal withdrawal of support can be considered because probability of severe disability is very high.
- MRI is generally advised between the fourth and