Neonatal Medicine and brain injury in the Infant at term

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What do we mean by “birth asphyxia”

Interruption in oxygen delivery to the fetus severe enough to produce:
Metabolic acidosis
Bradycardia and decreased cardiac output
Impaired muscle tone and reflexes
Delayed onset of breathing
Some causes of intrapartum asphyxia (global cerebral hypoxia-ischemia)

1. Placental abruption.
2. Prolapsed umbilical cord
3. Prolonged/frequent uterine contraction
4. Fetal hemorrhage
5. Placental aging
6. Intrauterine growth restriction

7. Hypoxia combined with infection/inflammation/fever

The two types of asphyxia from Myers experimental work with pregnant monkeys:

1. Acute total asphyxia (clamping umbilical cord for 2–3 minutes. Damage to brain stem, basal ganglia.

2. Prolonged partial asphyxia (hypoxic gas mixture to the pregnant monkey for hours). Hemispheric damage with cerebral oedema.
What do we mean by neonatal encephalopathy?

1. Infants of 36 weeks or more.
2. Acute disturbance in tone and consciousness OR seizures

What do we mean by hypoxic-ischaemic encephalopathy (HIE)?

Neonatal encephalopathy with convincing evidence that birth asphyxia was the cause


Essential criteria:
1. Metabolic acidosis on cord blood or very early (1 hour) neonatal blood (pH 7.0 or base deficit ≥ 12 mmol/l).
2. Early onset of severe or moderate neonatal encephalopathy in infants of ≥ 34 weeks gestation.
3. Cerebral palsy of the spastic quadriplegic or dyskinetic type.

Criteria that together suggest an intrapartum timing but are non-specific:
4. A sentinel hypoxic event immediately before or during labour.
5. A sudden, rapid and sustained deterioration of fetal heart rate.
6. Apgar scores of 0-6 for longer than 5 minutes.
7. Early evidence of multisystem involvement.
8. Early imaging evidence of acute cerebral abnormality.

Prognosis after birth asphyxia

Apgar score < 5 at 10 minutes: nearly 50% death or disability (Leicester)
No spontaneous respiration after 20 min ca 60% disability in survivors (USA).
No spontaneous respiration after 30 minutes: nearly 100% disability in survivors (Newcastle).
Grade of post-hypoxic encephalopathy.
Moderate Hypoxic-ischaemic encephalopathy after Placental abruption

Grade 3 (severe) neonatal encephalopathy
Abnormal movement in hypoxic-ischaemic encephalopathy

Grade of encephalopathy and outcome

• Mild (grade 1) always recovers
• Moderate (grade 2) should be back to normal by 7 - 10 days if recovery is to be good. Overall 25 % disability
• Severe (grade 3) nearly 100% disability or death. Those that recover are showing it by 3 days.
The scale of the problem

How common is hypoxic-ischemic encephalopathy?

Moderate-severe HIE occurs in 1-2/1000 births

Approximately 0.5 to 1.0/1000 infants survive with cerebral palsy due to HIE.
In the UK, £ 3 million is the average compensation if negligence is shown.

Processes which continue to kill brain cells after re-oxygenation:

1. Free radical injury
2. Excitotoxic amino acids e.g. glutamate
3. Calcium entry
4. Inflammation
5. Apoptosis
6. Prolonged seizures?
7. Prolonged hypoglycemia
8. Prolonged hypotension
Cerebral function monitor

- Single channel portable EEG from bi-parietal electrodes
- Amplifies, filters (2-15 Hz)
- Compresses and rectifies
- Lower edge: non-rhythmic minimum level of cerebral activity
- Upper edge rhythmic and non-rhythmic maximum level of cerebral activity

Cerebral function monitor in the full term infant
Normal trace: Lower margin >5
Upper margin >10
Sleep-waking variability
Cerebral function monitor in the term infant
Seizure activity on a normal background

Cerebral function monitor in the term infant
Lower margin < 5 microvolts
Cerebral function monitor in the term infant
Lower margin < 5 microvolts
Upper margin < 10 microvolts. Burst suppression

Resistance Index

\[ RI = \frac{Systolic \ velocity \ - \ diastolic \ velocity}{Systolic \ velocity} \]

Advantages:
- Independent of angle of insonication
- Prognostic after 24 hours in HIE at term

Low RI, <0.55 predicts adverse outcome
Levene, 1989 \[ PPV \ 83\% \]
Example of low RI

Hypoxic-ischaemic Encephalopathy

MRI showing high T1 signal in the basal ganglia and thalamus
Interventions for hypoxic-ischaemic Encephalopathy at term

Interventions to reduce cerebral oedema
  Mannitol/corticosteroids
Anticonvulsants
Calcium channel blockers
Interventions aimed at glutamate receptors
  Magnesium sulphate
Interventions that reduce free radical damage
  Allupurinol
Hypothermia
Endorphin antagonists

Selective head cooling with mild systemic hypothermia
Whole body hypothermia by mattress
Cool Cap Trial

Multicentre US, UK, Canada, NZ (Bristol leading UK centre).

Asphyxia + neurological sign+ abnormal aEEG
Randomised by 5.5 hr. 72 head cooling with
Rectal temp 34.5 C for 72 hours v normo
N = 234. 218 followed up (93%)
66% of control group dead or disabled at 18 m
55% of hypothermia group dead/disabled

Cool Cap trial. Lancet 2005

Those who had the most advanced EEG changes
at entry had no advantage from cooling.
The 172 who had less advanced EEG changes
at entry showed a significant benefit from cooling.
Odds ratio for death or disability 0.42 (0.22 to 0.8

Number needed to treat 6
NICHD trial of whole body hypothermia
Shankaran et al   NEJM in press

Inclusion: Gestational age > 35 weeks
1. Birth asphyxia pH ≤7.0 or base deficit ≥16
2. Acute event or 10 min Apgar ≤5 or ventilation
   AND seizures or moderate/severe encephalopathy

Treatment: Blanket pre-cooled to 5°C
Oesophageal temperature 33.5°C for 72 hours.
Rewarm at 0.5°C/hour.

NICHD trial of whole body hypothermia
Shankaran et al       NEJM in press
709 screened
239 eligible
209 enrolled

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<th>Hypothermia</th>
<th>Normothermia</th>
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<tbody>
<tr>
<td>N</td>
<td>102</td>
<td>106</td>
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<tr>
<td>Age in hours</td>
<td>3.8</td>
<td>4.2</td>
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<tr>
<td>Outborn</td>
<td>48</td>
<td>45</td>
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<tr>
<td>Apgar ≤5 at 10 min</td>
<td>80</td>
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<tr>
<td>Temp</td>
<td>33.5 (32.7)</td>
<td>36.7 – 37.4</td>
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<td>Heart rate</td>
<td>110</td>
<td>147</td>
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NICHD trial of whole body hypothermia
Shankaran et al  NEJM in press 2005

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<th>Hypothermia</th>
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<tr>
<td>Death/disability</td>
<td>64 (62%)</td>
<td>45 (45%)</td>
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<tr>
<td>Odds ratio</td>
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<td>0.72 (0.55 to 0.93)</td>
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<tr>
<td>Number needed to treat</td>
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<tr>
<td>Bayley scales &gt;85</td>
<td>25 (42%)</td>
<td>39 (53%)</td>
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<tr>
<td>Bayley 70-84</td>
<td>13 (22%)</td>
<td>17 (23%)</td>
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<tr>
<td>Bayley &lt;70</td>
<td>22 (37%)</td>
<td>18 (24%)</td>
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<tr>
<td>Disabled CP</td>
<td>18 (29%)</td>
<td>15 (20%)</td>
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<tr>
<td>Death</td>
<td>38 (36%)</td>
<td>24 (24%)</td>
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Hypothemia
1. Eicher 2004 : Total body hypothermia 33 C
2. Gluckman 2005 Selective head cooling + 34.5 C
3. Shankaran 2005 Total body hypothermia 33.5 C

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<td>2. N</td>
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<td>3. N</td>
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<td>Dead or disabled</td>
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<td>Combined</td>
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<tr>
<td>Dead or disabled</td>
<td>118</td>
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<tr>
<td>Relative Risk</td>
<td>0.67 (0.54 to 0.84)</td>
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Left Middle cerebral artery infarct
Right sided motor impairment
Thought to be arterial thrombosis
or embolus from placenta
Not currently accepted as being
due to “birth asphyxia”

Differential diagnosis of neonatal
encephalopathy

Prenatal brain injury
Perinatal Infarct
Infection: bacterial/viral/protozoal
Trauma
Haemorrhage
Hypoglycaemia
Hyperbilirubinaemia
Cerebral malformations
Metabolic diseases
Questions to neuroiomaging

1. Differential diagnosis?
2. Timing of injury?
3. Prolonged partial v acute total asphyxia?
4. Severity of injury: prognosis

Withdrawal of life support in HIE

1. Severe HIE persisting > 48 hours. Clinical state not explained by drugs.
2. Corresponding EEG with low amplitude or burst suppression.
3. Low Resistance index < 0.55 after 24 hours
4. Corresponding imaging predictive of cerebral palsy: absence of myelin signal in PLIC and abnormal signal in basal ganglia/thalami.