Cerebral Injury in the Term Infant

Jeff Neil, MD, PhD

Departments of Neurology, Radiology and Pediatrics
1. Patterns of injury
2. Hypothermia
3. Seizures
4. Odds and ends
Major neuropathologies in the term encephalopathic infant

- Basal ganglia/thalamus injury
- Watershed injury
- Stroke
- Venous sinus thrombosis
BG/thalamus
+ watershed
Patterns of “acute” cerebral injury


Intrapartum Hypoxic-Ischemic Brain Injury

- Acute Injury
- Sentinel Event
- Cord pH < 7.00
- Resuscitation
- Low Apgar scores
- Encephalopathy
- Renal dysfunction
- Neuroimaging +

- Subacute Injury
- Normal Labor
- Cord pH > 7.00
- Minimal resuscitation
- Good Apgar scores
- Encephalopathy
- Neuroimaging +
Basal Ganglia Injury
McKinstry RC et al.
Watershed Injury with Wallerian Degeneration
Watershed Injury with Wallerian Degeneration

Nine months
Clinico-pathological correlate

Isolated basal ganglia injury

Neonatal period – hypotonia

Later – High risk for adverse outcome
spastic quadriplegic, movement disorders
( may have spared intellect and language)
Clinico-pathological correlate

Selective cortical neuronal injury - parasagittal

Neonatal period – proximal axial weakness

Later – Lower risk for adverse outcome
- Specific intellectual impairments including memory, visuospatial & language
Arterial stroke
+ venous thrombosis
Encephalopathy in term infants (stroke)
Perinatal stroke – risk factors

- About 50% are symptomatic of an established risk factor
- Cardiac (structural, rhythm disturbance)
- Inflammatory (maternal infection, meningitis, TORCH infection)
- Prothrombotic

Neonatal arterial ischemic stroke

- The newborn period is a time of high risk for stroke
- Rate of 1 in 2300 live births
- More than half present acutely, typically with seizures
- Focal deficits or encephalopathy seem rare (2/3 missed based on follow up studies)
Neonatal arterial ischemic stroke
Perinatal sinovenous thrombosis

- The newborn period is again a time of high risk
- About half the incidence of arterial ischemic stroke
- Superficial venous structures more commonly involved
- Half associated with stroke
- One third associated with IVH
- Thrombus propagation may occur in 25% during the first week (anticoagulation?) – Deveber et al.
Perinatal sinovenous thrombosis
Perinatal stroke – outcome

- 30-60% of children with arterial ischemic and sinovenous thrombosis stroke have a motor deficit
- Neurologic deficits or epilepsy occur in up to 75% of survivors with perinatal ischemic strokes
- Deficits in language, cognition and vision occur in 20-60%
- Lesions sparing the cortex have much lower risk of cognitive, behavioral, language or seizure disorders
Posterior Limb of the Internal Capsule
Abnormal PLIC in relation to outcome
Rutherford et al; *Pediatrics 1998*

<table>
<thead>
<tr>
<th>PLIC</th>
<th>Outcome Abnormal</th>
<th>Outcome Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0</td>
<td>28</td>
</tr>
<tr>
<td>Abnormal</td>
<td>41</td>
<td>4*</td>
</tr>
</tbody>
</table>

* these infants had extensive white matter damage; sensitivity 0.90; specificity 1; PPV 1; NPV 0.87
Posterior limb of the internal capsule and outcome

Outcome for survivors

F=5.60, 2df, p=0.02

Lowest PLIC ADC Value (um²/ms)

<table>
<thead>
<tr>
<th>Normal</th>
<th>Mid/Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>0.6</td>
<td>0.7</td>
</tr>
<tr>
<td>0.8</td>
<td>0.9</td>
<td>1.0</td>
</tr>
<tr>
<td>1.0</td>
<td>1.1</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Glutamine/glutamate

Choline:
Membrane constituent

Lactate:
Marker of failed oxidative phosphorylation or increased glycolysis
Produced in astrocytes and shuttled to neurons to use as fuel

Myo-inositol:
Osmolyte
Glial marker

NAA:
Marker of neuronal/axonal density and viability

Creatine:
Cell energetics

Choline:
Membrane constituent

Lactate:
Marker of failed oxidative phosphorylation or increased glycolysis
Produced in astrocytes and shuttled to neurons to use as fuel

NAA: Marker of neuronal/axonal density and viability

Choline: Membrane constituent

Lactate: Marker of failed oxidative phosphorylation or increased glycolysis
Produced in astrocytes and shuttled to neurons to use as fuel

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Number of Studies</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lac/NAA</td>
<td>10</td>
<td>82%</td>
<td>95%</td>
</tr>
<tr>
<td>NAA/Cr</td>
<td>9</td>
<td>61%</td>
<td>94%</td>
</tr>
<tr>
<td>cMRI</td>
<td>19</td>
<td>91%</td>
<td>51%</td>
</tr>
<tr>
<td>PLIC</td>
<td>6</td>
<td>71%</td>
<td>86%</td>
</tr>
<tr>
<td>ADC</td>
<td>5</td>
<td>66%</td>
<td>64%</td>
</tr>
</tbody>
</table>

NB: Lac=Lactate, NAA=N-acetyl aspartate, Cr= creatine, cMRI=conventional MR imaging, PLIC=loss of normal high signal intensity in posterior limb of internal capsule; ADC=apparent diffusion coefficient.

$^1$H Spectroscopy – Normal infant
$^1$H Spectroscopy – Day 1 after injury
Take home message

• Stroke is often unrecognized (should have high index of suspicion with seizure, encephalopathy, abnormal neurologic exam).

• Early imaging is useful to confirm presence of stroke by diffusion imaging (don’t forget to include MR venography).

• Pattern of injury present on MRI is predictive of outcome (basal ganglia/thalamus and stroke involving cortex worst).

• Abnormalities of PLIC strongly associated with hemiparesis.
1. Patterns of injury
2. Hypothermia
3. Seizures
4. Odds and ends
Therapeutic hypothermia


<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hypothermia n/N</th>
<th>Standard care n/N</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td></td>
<td>M-H, Fixed 95% CI</td>
<td></td>
<td>M-H, Fixed 95% CI</td>
</tr>
<tr>
<td>I High quality follow-up at 18–22 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gunn 1998</td>
<td>7/18</td>
<td>4/13</td>
<td>2.9 %</td>
<td>1.26 [0.46, 3.44]</td>
<td></td>
</tr>
<tr>
<td>Gluckman 2005</td>
<td>59/108</td>
<td>73/110</td>
<td>4.45 %</td>
<td>0.82 [0.66, 1.02]</td>
<td></td>
</tr>
<tr>
<td>Shankaran 2005</td>
<td>45/102</td>
<td>64/103</td>
<td>39.2 %</td>
<td>0.71 [0.54, 0.93]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>228</strong></td>
<td><strong>226</strong></td>
<td><strong>86.6 %</strong></td>
<td><strong>0.79 [0.67, 0.93]</strong></td>
<td></td>
</tr>
<tr>
<td>Total events: 111 (Hypothermia), 141 (Standard care)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 1.60$, df = 2 ($P = 0.45$); $I^2 = 0.00$%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: $Z = 2.82$ ($P = 0.0048$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Lower quality follow-up at 12 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eicher 2005</td>
<td>14/27</td>
<td>21/25</td>
<td>13.4 %</td>
<td>0.62 [0.41, 0.92]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>27</strong></td>
<td><strong>25</strong></td>
<td><strong>13.4 %</strong></td>
<td><strong>0.62 [0.41, 0.92]</strong></td>
<td></td>
</tr>
<tr>
<td>Total events: 14 (Hypothermia), 21 (Standard care)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 2.35$ ($P = 0.019$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>255</strong></td>
<td><strong>251</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.76 [0.65, 0.89]</strong></td>
<td></td>
</tr>
</tbody>
</table>
Hypothermia

• Therapeutic hypothermia reduced the combined outcome of mortality or major neurodevelopmental disability at 18 – 22 months of age [typical RR 0.76 (95% CI 0.65, 0.89), typical RD -0.15 (95% CI -0.24, -0.07), NNT 7 (95% CI 4, 14), p = 0.0006].

• Cooling reduced neurodevelopmental disability in survivors [typical RR 0.68 (95% CI 0.51, 0.92), typical RD -0.13 (95% CI -0.23, -0.03), NNT 8 (95% CI 4, 33), p = 0.01].

• Adverse effects of hypothermia included an increase in thrombocytopenia and in the need for inotrope support.
The Art of Hypothermia

• Method of cooling
  – Brain injured infants will drop their body temperature
  – Resuscitation under overheads can increase body and brain temperature to inadvertent hyperthermia
  – No attention to temperature can lead to profound hypothermia
Inadvertent hypothermia

**Chart Description:**
- **Rectal Temperature (°C):** The graph shows the rectal temperature over time, with a marked change in temperature following uncontrolled cooling and rewarming.
- **Hours since birth:** The time scale is marked from 0 to 96 hours since birth, showing the temperature changes over time.

**Clinical Details:**
- 42 wk GA, Apgar 0,0,0,4, HR by 16 min, lactate 24 at birth, cord pH 6.84
- Meconium aspirated, Hb 9.0, antepartum hemorrhage.
- 100% O₂, N₂O during transport. Low PCO₂
Impact of overhead heater on brain temperature

Regional brain temperature changes in 12 h-old piglet during normothermia when overhead heater is turned on and off.
The Art of Hypothermia

• Method of cooling
  – Take home message is monitor the temperature by rectal probe. Avoid overhead radiant warmers
  – Method of therapeutic hypothermia influences stability of temperature
  – Avoid hyperthermia
The Art of Hypothermia

- Drug metabolism is altered and prolonged for drugs metabolized in the liver
- Bradycardia - sinus
- Sedation and stress – Morphine infusion at reduced rate after the first 6 hours
- With-holding feeding or non-nutritive feeding
- Maintain adequate blood pressure
- Rewarming slowly – risk of seizures and alterations in mental status
1. Patterns of injury
2. Hypothermia
3. Seizures
4. Odds and ends
Seizures on rewarming

Thoresen M. Clinics Perinatology 2008;35:749-63
Evaluating the high risk infant - neonatal seizures

• Should we monitor at high risk infants for neonatal seizures?
  – 30-90% of the seizures are subclinical – 2/3rds of abnormal movements do not have an EEG correlate
    – Mizrahi and Kellaway 1987
    – Murray DM Archives of Dis Childhood 2007
  – Electromechanical dissociation with anticonvulsant therapy
    – Boylan GB. Et al Archives of Dis in Childhood 2002 86(3):F165-70
Considerations in neonatal seizures

Murray DM et al Archives Dis Childhood 2007

- 51 infants encephalopathy and/or risk HIE
  - 12 infants with seizures and/or treated for seizures
  - Overall 48/526 EEG seizures (9%) clinically recognized (19% on video EEG)

- 3 infants “aggressively treated” for up to 31 clinical events with NO EEG seizures
- 2 infants did not receive any anticonvulsant therapy and had 38 & 56 EEG seizures.
- 5/12 infants (42%) received incorrect therapy
Neuro-protective strategies

• Does seizure detection and therapy improve outcomes?
  – Retrospective study of intensive aEEG monitoring and therapy for “subclinical” seizures showed reduction in post-neonatal epilepsy
  – Seizure therapy
    • Phenobarbitol 40mg/kg between 1-6hours (Hall et al J Pediatr 1998;132:345-8)
Consent

Limited channel EEG (72 h)  
cEEG monitoring (12 h)  
MRI, Developmental follow-up

Blinded Seizure Group (BSG)
- Limited channel EEG monitor blinded
- Standard clinical care
- 1 hour cEEG report

Monitored Seizure Group (MSG)
- Able to observe aEEG monitor
- Seizure detection software loaded

Standard of Care AEDs:
- Phenobarb (up to 40 mg/kg load)
- Fosphenytoin (20 mg/kg load)
- Midazolam infusion

Algorithm goes off

Clinical decision initiating/enhancing AED
How good are we clinically, on limited channel and with a “seizure alert”?

- **Subjects**
  - 27/40 (68%) infants with seizures
  - 1039 seizures over 2708 hr

- **Conventional EEG**
  - 385 seizure events detected on cEEG (94% were subclinical on video)
  - 317/385 (82%) picked up on limited channel EEG

- **Algorithm**
  - 606/1038 detected (58%)
    - For the alarms in 3 infants the nursing staff did not notify the physician
  - False Positive Rate 1 FP/11 hours
## Results – raw 2 channel EEG (n=1038)

<table>
<thead>
<tr>
<th>Seizure Length</th>
<th>Missed</th>
<th>Detected</th>
<th>% Detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-30 s</td>
<td>271</td>
<td>71</td>
<td>21%</td>
</tr>
<tr>
<td>30-60s</td>
<td>115</td>
<td>182</td>
<td>61%</td>
</tr>
<tr>
<td>1-10 min</td>
<td>46</td>
<td>338</td>
<td>88%</td>
</tr>
<tr>
<td>&gt; 10 min</td>
<td>0</td>
<td>15</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Overall Detection Rate:** 77%
# Seizure Burden

<table>
<thead>
<tr>
<th></th>
<th>Blinded N=20</th>
<th>Monitored N=20</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number with seizures</td>
<td>13</td>
<td>12</td>
<td>-</td>
</tr>
<tr>
<td>Total seizure burden (s)</td>
<td>66,189</td>
<td>30,770</td>
<td>0.144</td>
</tr>
<tr>
<td>Sz burden/patient (s)</td>
<td>5,091</td>
<td>2,564</td>
<td>-</td>
</tr>
</tbody>
</table>
Motor Outcomes

Group Median Score

<table>
<thead>
<tr>
<th>Group</th>
<th>Median Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinded (N=10)</td>
<td>61 (46 - 100)</td>
</tr>
<tr>
<td>Monitored (N=11)</td>
<td>97 (49-124)</td>
</tr>
</tbody>
</table>
**Language Outcomes**

<table>
<thead>
<tr>
<th>Group</th>
<th>Median Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinded (N=10)</td>
<td>75 (47-106)</td>
</tr>
<tr>
<td>Monitored (N=11)</td>
<td>94 (79-100)</td>
</tr>
</tbody>
</table>

*p* = 0.099

*by Mann-Whitney*
Take home message

• Limited channel aEEG is associated with a trend toward reduced seizure burden in encephalopathic neonates
• This reduction in seizure burden may correlate with improved motor outcome at 12-24 months
• More data.....
1. Patterns of injury
2. Hypothermia
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4. Odds and ends
Neuronal Cell Death

- Necrosis (hit by bus)
  - Dissolution of tissue
- Apoptosis (suicide)
  - Orderly cell death
  - Associated with caspase activation
  - More prominent in immature brain
  - Potential target for therapeutic intervention
- Aponecrosis
Agents thought to induce apoptosis in neonates

- NMDA antagonists (PCP, ketamine, Xe)
- GABA_A agonists
- AED’s (phenobarbital, phenytoin, valporate, clonazepam, diazepam, vigabatrin)
- Prolonged narcotic exposure (fentanyl)
- Ethanol
- Anesthetic cocktail
  - midazolam/isoﬂurane/N_2O

Apoptosis and anesthesia

Apoptosis and anesthesia

National Institute of Health - NICHD R01HD042872; R01HD058056; P30HD062171; Green Chair in Pediatric Neurology; Doris Duke Foundation Distinguished Clinical Scientist Award