Hypoxic Ischemic Encephalopathy
and Neonatal Seizures

NOT Synonyms

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HIE Definition- vs “NEONATAL Encephalopathy”

- Reduced oxygen delivery to the cells in the brain causing death or damage, temporary or permanent
  - hypoxia, anemia
  - Ischemia- decreased blood flow
    - Most important
NEONATAL ENCEPHALOPATHY

- Seizures in newborn
- Abnormal neurologic exam
- Questionable outcome
- NOT necessarily caused by HIE
- Many causes
Acute Perinatal HIE versus Neonatal encephalopathy

• Many babies recover without permanent disability
• Diseases NOT caused by HIE
  – Mental Retardation
  – Epilepsy
• Must have CP since motor areas more vulnerable
• Rare exceptions
Don't Put Square Peg
In Round Hole-
“Neonatal Encephalopathy”
Case

- 2 kg infant SVD Apgars 1/1
- Decelerations shortly before delivery
- Seizures shortly after delivery
- Now comatose in your nursery
- Cord pH 7.30
- Initial baby pH 7.4
- Diagnosis in chart “asphyxia”
Myotonic Dystrophy NOT HIE
HIE 1-2/1000

calculate your numbers

- Criteria for Diagnosis of HIE
- Usually **ALL** necessary
  - Abnormal tracing-flat or severe bradycardia
  - Low apgars 1, 5, and 10 minutes
  - Cord pH < 7.00
  - Seizures within 12 hours
  - Hypotonia lasting 48 hours
  - Multiorgan system dysfunction
- 1-2/1000 = 4000 infants each year in U.S.
Apgar Scores not sufficient for HIE

- One Minute $\leq 3$
  - 4.8% of all infants
  - 1.7% CP eight times normal
  - BUT - 0% CP if 5 minute $\geq 4$
  - Kids with CP only 26% had one minute $\leq 3$

- ONE MINUTE SCORE NOT PREDICTIVE
- DO NOT TREAT DUE TO ONE MINUTE SCORE !!!
Apgar Scores 5 min?

• Five Minute $\leq 3$
  – 1% of all normal (longterm) infants
  – If next apgar $\geq 4$ “only” 1% CP incidence
  – Kids with CP only 15% had five minute $\leq 3$

• FIVE MINUTE NOT PREDICTIVE DO NOT TREAT FOR FIVE MINUTE SCORE !!!
Apgar Scores

• 10 Minute < =3
  – <.5% of all infants
  – 34% died
  – 16.7% CP in survivors 80 time normal
  – If normal at 15 minutes risk is 4.7%

• **CONSIDER TREATMENT FOR TEN MINUTE SCORE !!!**
Apgar Scores

- 15-20 Minute < =3
  - <.1% of all infants
  - Over 50% died
  - 36% and 57% CP
- TREAT VIRTUALLY ALL.
Cord pH not sufficient

- .6% of all deliveries pH less than 7
- 50% of these had one minute apgar ≤6
- 17% had five minute ≤3
- Only those with both low apgar and low pH had risk of permanent injury
Seizures

- Abnormal firing of neurons
- Can cause brain injury
- Many causes
- Recognition:
  - Start/Stop
  - Quality of movement
  - VS and state of baby
  - Eye movements
Seizures

- Incidence of seizures
- Recognition of seizures
- Differential diagnosis of etiology
- Prognosis
- Evaluation
- Treatment
Incidence and importance

- 0.8% of newborns
- 5% of NICU babies
- 95% of the time successfully identify pathologic cause
Recognizing neonatal seizures—listen to the nurses

- Abnormal movements in an at risk infant
  - Asleep movements can be misinterpreted
- Quality of movements
  - tremor versus seizure
- Start and stop movements
- Vital sign changes
- Eye movements
History most important
take it yourself
Physical / Neurological Exam
EEG is it a seizure??
LP
Laboratory evaluation
Seizure is a sign not diagnosis

- Differential diagnosis
  - Hypoxia acute versus old
  - Metabolic
  - Hemorrhagic and vascular
  - Drugs
  - Structural
  - Infectious
  - Familial
  - Idiopathic
Causes of seizures in the newborn

- O2
- Meta
- Blood
- Drug
- Struc
- Bug
- Folk
- ??
History - To Diagnose Asphyxia

1. Evidence of Abnormal Fetal Heart Rate
2. Low Cord pH <7.20
3. Low Apgar
4. Seizures
5. Evidence of Other System Dysfunction
6. No Other Disease
OLD UNDERSTANDING

- Everyone
- normal

Intrapartum → Abnormal baby insult

- Antenatal “events” in 48% of all term infants
  - Blue
  - Meconium
  - Deceleration
  - Jaundice
  - Etc etc
NEW UNDERSTANDING

- In-utero
  - injury
    - Intrapartum
      - Abnormal baby

- At least 25% and as many as 80% abnormal before labor

- Isolated intrapartum injury occurs and is not common

- Injury does not equal malpractice - life is dangerous and fatal.
Hemorrhage

Premie
Term with trauma
Not malpractice
Term with asphyxia
Term with malformation
<table>
<thead>
<tr>
<th>Disability</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No sequelae</td>
<td>15 (33)</td>
</tr>
<tr>
<td>CP</td>
<td>22 (48)</td>
</tr>
<tr>
<td>Right hemiplegia (n = 10)</td>
<td></td>
</tr>
<tr>
<td>Left hemiplegia (n = 3)</td>
<td></td>
</tr>
<tr>
<td>Spastic quadriplegia (n = 8)</td>
<td></td>
</tr>
<tr>
<td>Spastic diplegia (n = 1)</td>
<td></td>
</tr>
<tr>
<td>MDI &lt;70</td>
<td>19 (41)</td>
</tr>
<tr>
<td>MDI &lt;50</td>
<td>14 (30)</td>
</tr>
<tr>
<td>CP and MDI &lt;70</td>
<td>12 (26)</td>
</tr>
<tr>
<td>CP and MDI &lt;50</td>
<td>8 (17)</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>7 (15)</td>
</tr>
<tr>
<td>Seizure disorder*</td>
<td>21 (46)</td>
</tr>
<tr>
<td>Single disability</td>
<td>8 (17)</td>
</tr>
<tr>
<td>Multiple disabilities</td>
<td>23 (50)</td>
</tr>
</tbody>
</table>

*CP, Cerebral palsy; MDI, mental development index.

*Seizure disorder after the neonatal period requiring the re-institution of anti-epileptic medication.
Drugs or toxins

- Withdrawal from maternal abuse especially after Narcan
- Isoniazid, propoxyphene
- Xylocaine
- Bilirubin encephalopathy
Metabolic urgent

Glucose only have 30 minutes
Ketones think FA oxidation
Calcium important good longterm

Ammonia- low BUN
2 days of age
Metabolic important and “rare”

• Early intractable seizures
  Non-ketotic hyperglycinemia—hiccups and seizures
  Pyridoxine dependent seizures—give B6 with EEG
Structural causes
Infections only 2%

- Viral TORCH infections - SGA, HSM
- HSV treatable but not good outcome
- Bacteria GBS, E.Coli, GNR
  - 25% of sepsis has associated meningitis
  - 18% of meningitis negative Blood culture
  - CRP very useful
- LP indicated if fontanel not bulging. IICP?
Familial

- Neurocutaneous syndromes

- Familial seizures- “fifth day fits” both benign and severely abnormal outcome have been reported.
Evaluation

• History most important DX 60%
• PE sometimes essential usually not diagnostic- 5%
• Imaging- CT for hemorrhage, MRI for structure-15%
• Lab evaluation-15%
  – LP, CBC, glucose, Calcium and electrolytes, ammonia, AA profile
• Pyridoxine infusion
Outcome of seizures in the newborn
Treatment

- Treat underlying cause glucose, pyridoxine deficiency
- Phenobarbital treatment of choice 1st order kinetics 20mg/kg/dose until effect. Maintain 3-4 mg/kg/day.
- Keppra new drug
- Phenytoin 15-20 mg/kg/dose not in very sick infants. Not oral.
- Benzodiazapines- short effect.
Keppra

• Levitiracetam

• The precise mechanism(s) by which levetiracetam exerts its antiepileptic effect is unknown.

• Safe down to age two- but fewer side effects and better animal outcomes have encouraged use.
Treatment of Asphyxia

- Vanderbilt University doing selective head cooling for asphyxiated newborns to decrease brain damage.
- Treatment must be started within 5 hours.
- Please call if baby has any ONE of the following: Apgar <6 at 10 minutes, pH<7, base deficit>16, resuscitation at 10 minutes.
Treatment of HIE ??
Pathogenesis of encephalopathy

- Decrease ATP = decrease ENERGY
- One half of all energy used maintains membrane ionic gradients
- Membranes fail to function cells leak and die
cell death from energy loss
Cooling whose idea??
Humans only animals born wet and hairless
Warmth and Resuscitation

• Silverman 1958
• Survival of Premies = 83% if warmed
• 68% if not warmed
Hypothermia Risks

- Peripheral Vasoconstriction
- Diuresis
- Cardiac Dysfunction
- Arrythmias
- Coagulopathy
- Leukocyte dysfunction
Keep the baby warm!
Reduction in death and disability by whole body hypothermia

- 204 infants followed
- Death/disability: 45% vs 62% (RR: 0.55-0.93), adjusted: 0.60-0.98
- Death: 24% vs 36% not “significant”
A priori defined group excluding infants with severely abnormal aEEG with seizure

<table>
<thead>
<tr>
<th></th>
<th>Cooled</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>84</td>
<td>88</td>
</tr>
<tr>
<td>Favorable</td>
<td>44 (52%)</td>
<td>30 (34%)</td>
</tr>
<tr>
<td>Unfavorable</td>
<td>40 (48%)</td>
<td>58 (66%)</td>
</tr>
</tbody>
</table>

Fisher’s exact p=0.02: logistic regression, OR: 0.42 (0.22, 0.80), p=0.01
Conclusion-hypothermia works

• Hypothermia is effective in decreasing long term morbidity in some infants.
• Impossible to compare efficacy at this time.
• Hypothermia of some form should be applied to infants with moderate HIE as soon after birth as possible.
NOT STANDARD OF CARE !!

• Presentations at AAP meeting in San Francisco Oct 2007

• Commentary in Pediatrics Nov 2007
  – Bias- fewer deaths because of hope for cooled?
  – Hyperthermia BAD maybe just avoid hyperthermia- 20-30% controls hot ( cause or effect)
  – Subgroup analysis questionable p=.1 in Head Cool trial
  – Number needed 692 number reported in two trials 442
Everything depends upon the diagnosis

- Pursue the diagnosis; it will determine the treatment and the prognosis