Medico-Legal Implications of Hypoxic-Ischemic Encephalopathy

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“The fact is, that there was considerable difficulty in inducing Oliver to take upon himself the office of respiration, a troublesome practice, but one which custom has rendered necessary to our easy existence; and for some time he lay gasping on a little flock mattress, rather unequally poised between this world and the next, the balance being decidedly in favour of the latter. Now, if during this brief period, Oliver had been surrounded by careful grandmothers, anxious aunts, experienced nurses, and doctors of profound wisdom, he would most inevitably and indubitably have been killed in no time.”

Charles Dickens

*Oliver Twist*

1837
The fetus, who is adapted to life inside the womb, must be capable of survival in a totally different environment at birth.
Adaptation to Extrauterine Life

- First few breaths
- Establishment of regular breathing
- Establishment of “adult” circulation
- Thermoregulation
- Metabolic adjustments
Cardiorespiratory Changes

- Placental flow ceases
- SVR $\uparrow$ after clamping cord
- Lung expansion (FRC)
- Absorption of lung fluid
- Improved oxygenation $\downarrow$ PVR
- Closure of PFO
- L to R shunt through the PDA
HIE: The Paradigm
Asphyxia

• **Functional:** Failure of the organ of respiration

• **Biochemical:**
  - Hypoxia (low PaO$_2$)
  - Hypercapnia (high PaCO$_2$)
  - Acidosis (low pH)
Neonatal Hypoxic-Ischemic Encephalopathy (HIE)

• 2-3/1,000 full-term live births in developed countries
• 15-20% neonatal mortality
• Overall, 25% of survivors have permanent clinical deficits (motor and cognitive)

HIE and CP

- Animal data
- Epidemiology
- Folklore and history
Spastic Diplegia: Little’s Disease

- William John Little, British orthopedic surgeon
- Observation of relationship between spastic diplegic cerebral palsy and “difficult” birth
- Devised heel cord lengthening procedure
- Compilation of cases
- Obstetrical Society of London presentation:
  Proposed an association between difficult delivery, prematurity, asphyxia, and CP
Spastic Diplegia: Little’s Disease

“Most infants presenting with asphyxia at birth are not affected.”

- W. J. Little, MD

1861
• 1891-1897 monographs

“Since the same abnormal processes of birth frequently produce no effects...diplegia still may be of congenital origin. Difficult birth...may be merely a symptom of deeper effects which influenced the development of the fetus.”
“Proxies” for Fetal Hypoxemia

- Non-reassuring FHR
- Low scalp pH
- Decreased fetal movement
Insult vs. Damage

- Causative or trigger event
- Hypoxemia vs. Brain injury
- Therapeutic window
  (Brain or body cooling)
Asphyxia

- Prolonged, partial
- Total
Prolonged Partial Asphyxia

- Partial reduction in oxygen delivery
- Shunting of blood away from organs of lesser importance (e.g., lungs, kidneys, liver, spleen, gut, muscle, skin) to maintain oxygen delivery to BRAIN, HEART, and ADRENAL GLANDS
- Systemic injuries precede brain damage
- Primary site of injury in the brain is the parasagittal gray matter, resulting in spastic quadriplegic cerebral palsy
Parasagittal Cerebral Injury
Total Asphyxia

- Catastrophic conditions (e.g., total placental abruption, umbilical cord avulsion, maternal arrest, etc.) cut off oxygen supply to fetus
- No time for compensation
- “All or none” phenomenon
- Primary site of injury in the brain is the basal ganglia, resulting in athetoid cerebral palsy
Basal Ganglia Injury
Asphyxia

Prolonged, Partial

Total/Near Total
**TOTAL vs. PARTIAL Asphyxia Rhesus monkey model (Myers)**

**Total**
- 13 minutes
- pH 6.9
- Profound hypotension
- No seizures or cerebral edema
- Brainstem, thalamus, and basal ganglia

**Prolonged Partial**
- 3-4 hours
- pH 6.9
- BP normal or sl. low
- Seizures and brain swelling
- Cortical gray matter
Ante- vs. Intrapartum Hypoxia

• Antepartum is far more common
• Clinical correlates are helpful
  - Maternal illness
  - IUGR
  - Antepartum bleeding
  - Abnormal fetal well-being tests
Antepartum Asphyxia

- Fetal Depression
- Encephalopathy
- “Chicken/Egg” scenario
Condition at Birth

• State of depression?
• Resuscitatable?
• Acid-Base balance?
Umbilical Cord Blood pH

- pH < 7 may be “presumptive”
- Neonatal blood pH helpful
- “Working backwards”
- Reperfusion state
Prolonged Resuscitation

• Birth as a “relief” event
• Need for a “jump start”
• Documentation issues
Neonatal Encephalopathy

- Altered level of consciousness
- Abnormal reflex status
- Disturbed Tone
- Seizures (50%)
Seizures

- Often difficult to diagnose
- Clinical v. Electrical seizures
- Timing
- Role of “prophylactic” anticonvulsants
Neonatal Encephalopathy

- HIE
  - Antepartum
  - Postpartum
- Other
  - Metabolic
  - Developmental
  - Infectious
Intrapartum HIE

- Intrapartum event
- Neonatal depression
- Acidosis
- Injury to other organs
- Neurologic syndrome
Other Confounders

- Traumatic injury
- Perinatal infection and FIRS
Etiology and Timing of CP

The timing of events causing cerebral palsy

- **Conception**
  - Chromosomal abnormalities
  - Cerebral dysgenesis

- **Pregnancy**
  - Fetal hypoxia–ischaemia
  - Intrapartum hypoxia–ischaemia

- **Labour**
  - Neonatal complications

- **Postnatal**
  - Postneonatal trauma or infection

**Cerebral palsy**
Causal Link Between Intrapartum Asphyxia and Later Motoric Disability

1. “Evidence” of severe hypoxia:
   - Sentinel event (e.g., prolapsed cord, abruption, uterine rupture, etc.)
   - Clinical signs of “fetal distress”
   - Abnormal FHR tracing

2. Severe depression of vital signs at birth requiring resuscitation

3. Cord blood pH ≤ 7.0 with BD > -12
Causal Link Between Intrapartum Asphyxia and Later Motoric Disability

4. Neonatal encephalopathy with no cause more likely than cerebral hypoxia-ischemia
5. Features of ischemic injury to other organs, e.g., renal impairment
6. Dominant disability is spastic cerebral palsy, usually affecting all four limbs
Obstetric Factors

1. Failure to take into account past obstetric history
2. Failure to predict cephalo-pelvic disproportion
3. Failure to act when admission findings suggested an already compromised fetus
Obstetric Factors

4. Injudicious use of Oxytocin
5. Failure to recognize lack of progress during labor
6. Failure to correctly diagnose malpresentation or malposition of the head
Obstetric Factors

7. Delay or failure to diagnose fetal distress while under observation
8. Delay in carrying out cesarean section or operative delivery
9. Substandard operative delivery technique
Resuscitation at Birth

1. Failure to arrange for pediatrician to be present at birth
2. Late arrival of the pediatrician
3. Faulty equipment
4. Substandard resuscitation technique
Post-Resuscitation Care

1. Failure to transfer baby immediately to neonatal unit
2. Failure to be vigilant for seizures
3. Failure to recognize hypoglycemia
4. Failure to be vigilant for infection
Documentation of Resuscitation at Birth

1. Time of attendance at resuscitation
2. Any resuscitation care given by others prior to arrival
3. Description of vital signs (don’t simply rely on Apgar scores)
4. Time of onset of any positive pressure ventilation even if only by bag and mask
5. Time of intubation; comment on ease of intubation
6. Movement of chest wall and auscultation findings in response to positive pressure ventilation
7. Timed sequence of changes in heart rate, spontaneous breathing, and color change in response to resuscitation
8. If re-intubation is needed, give reason
What’s New?
Current Therapies for Neonatal HIE

• Supportive intensive care
  ▪ Resuscitation
  ▪ Attention to glucose, PaCO$_2$, fluid and electrolytes
  ▪ Correction of hypotension
  ▪ Treatment of seizures
Novel Therapies for Neonatal HIE

• Brain specific therapies
  ▪ Modest reduction in brain temperature
  ▪ Receptor agonists of excitatory neurotransmitters
  ▪ Reduction in oxygen free radicals
  ▪ Blockage of inflammatory mediators and inhibition of apoptotic pathways
Novel Therapies for Neonatal HIE

- Brain specific therapies
  - *Modest reduction in brain temperature*
Mechanisms of Action of Hypothermia

- Better maintenance of the cerebral energy state
- Attenuation of the release of excitatory neurotransmitters

Mechanisms of Action of Hypothermia

- Decreased caspase-3 activation and morphologic evidence of apoptosis
- Reduction of free radicals
- Modulation of microglial activation and cytokine production

Choices of Cooling

- Selective head cooling with mild systemic hypothermia (SHC)
  - Cool Cap protocol
- Whole body cooling (WBC)
  - NICHD protocol
  - Eicher (South Carolina) protocol
- Other protocols have been studied but lack published efficacy/safety
Selective Head Cooling (SHC)

- Cooling is achieved by surface cooling the head while actively warming the rest of the body
  - Cool Cap protocol ($T_{\text{rectal}}$ 34.5±0.5°C)
- Achieves adequate cerebral cooling with only a small reduction in core body temperature, thus minimizing the potential harmful systemic effects of cooling
Whole Body Cooling (WBC)

• Achieved by cooling the head and body together
  ▪ NICHD protocol \((T_{\text{esophageal}} 33.5 ^\circ \text{C})\)
  ▪ Eicher (South Carolina) protocol \((T_{\text{esophageal}} 33 ^\circ \text{C})\)

• Are there potentially more risks for adverse systemic effects of cooling?
Whole Body Cooling (WBC)

- Achieved by cooling the head and body together
  - NICHD protocol ($T_{esophageal}$ 33.5°C)
  - Eicher (South Carolina) protocol ($T_{esophageal}$ 33°C)
- Are there potentially more risks for adverse systemic effects of cooling? **NO!**

# Neuroprotection and Therapeutic Hypothermia - Clinical Trials

## Review
- Hypothermia

## Comparison
- Hypothermia versus normothermia

## Outcome
- Death or disability

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Hypothermia n/N</th>
<th>Control n/N</th>
<th>RR (fixed) 95% CI</th>
<th>Weight %</th>
<th>RR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coolcap</td>
<td>59/108</td>
<td>73/110</td>
<td></td>
<td>46.10</td>
<td>0.82 (0.66 to 1.02)</td>
</tr>
<tr>
<td>Eicher</td>
<td>14/27</td>
<td>21/25</td>
<td></td>
<td>13.90</td>
<td>0.62 (0.41 to 0.92)</td>
</tr>
<tr>
<td>NICHD</td>
<td>45/102</td>
<td>64/106</td>
<td></td>
<td>40.00</td>
<td>0.73 (0.56 to 0.95)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>237</td>
<td>241</td>
<td>0.76 (0.65 to 0.89)</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 118 (hypothermia), 158 (control)
Test for heterogeneity: $\chi^2 = 1.63$, df = 2 (p = 0.44), $I^2 = 0$
Test for overall effect: $z = 3.48$ (p = 0.0005)

## TOBY Trial - Similar results
- Reduction in risk - 24%
- NNT - 6

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Edwards AD, Azzopardi DV. Arch Dis Child 2006
Conclusions

• Hypothermia is thus far the only intervention that shows promise in improving neurologic outcome in infants with HIE

• 1 in 6 babies will gain some benefit

• More effective in milder HIE
Conclusions

• Severe HIE- outcome remains bleak despite cooling

• Either of the established whole body or selective head cooling protocols may be adopted to cool infants with HIE
Current Controversies and Unanswered Questions

• What is the most appropriate target temperature?
• How long should cooling be continued?
• Does hypothermia affect longer-term neurodevelopmental outcomes?
• Effective therapeutic window- how late is too late?
Current Controversies and Unanswered Questions

• How to select infants most likely to benefit? How to distinguish “treatable” from “untreatable?”

• Should hypothermia be combined with other novel neuroprotective interventions?

• *Has therapeutic hypothermia become the standard of care for newborns with intrapartum asphyxia?*
Question 1

- The bases for our current understanding of the relationship of intrapartum asphyxia and cerebral palsy stems from all of these except:

1. Epidemiology
2. Randomized, controlled human trials
3. Folklore
4. Animal-derived data
Question 2

• Important contributors to our understanding of HIE include:

1. Hippocrates
2. Sigmund Freud
3. Georg Semmelweis
4. Charles Darwin
Question 3

• Confounders in ascertaining the cause of a child’s CP include all of the following except:

1. Chorioamnionitis
2. Umbilical cord acidemia
3. Trauma
4. Decision to offer hypothermia