Neonatal Encephalopathy: Perspectives from the ACOG AAP Revision

Mary E. D’Alton, M.D.
Willard C. Rappleye Professor and Chair, Department of Obstetrics & Gynecology
Columbia University College of Physicians & Surgeons

Objectives

• Identify neonatal signs consistent with an acute peripartum or intrapartum event

• Identify type and timing of contributing factors consistent with an acute peripartum or intrapartum event

• Discuss root cause analysis that will assist teams in the evaluation of newborns with encephalopathy and help define both the cause and timing of NE

• Identify advances in neuroimaging and differences between the 2003 and 2013 documents
Criteria Required to Define an Acute Intrapartum Hypoxic Event as Sufficient to Cause Cerebral Palsy (2003)

Essential criteria:
1. Evidence of a metabolic acidosis in fetal, umbilical cord arterial blood obtained at delivery (pH<7.00 and base deficit >12 mmol/L)
2. Early onset of severe or moderate NE in infants of 34 or more weeks of gestation
3. Cerebral palsy of the spastic quadriplegic or dyskinetic type
4. Exclusion of other identifiable etiologies such as trauma, coagulation disorders, infectious conditions, or genetic disorders

Criteria That Collectively Suggest an Intrapartum Timing but Are Nonspecific to Asphyxial Insults (2003)

- A sentinel (signal) hypoxic event
- A sudden and sustained fetal bradycardia or category 3* tracing following a previously normal FHR pattern
- Apgar scores of 0-3 beyond 5 minutes
- Evidence of multi-system involvement up to 72 hours
- Early imaging study showing evidence of acute nonfocal cerebral abnormality

* = 2008 definition NICHD
Antepartum Risk Factors for Newborn Encephalopathy: The Western Australian Case-Control Study

- Metropolitan Western Australia June 93-Sept 95
- All 164 term infants with moderate/severe encephalopathy
- Controls – 400 randomly selected
- Stats
  - Birth prevalence of moderate/severe newborn encephalopathy 3.8/1000 term live births
  - Neonatal Fatality 9.1%
- Conclusions
  - Causes of newborn encephalopathy are heterogeneous and many of the causal pathways start before birth


Distribution of Risk Factors for Newborn Encephalopathy

Conclusions of Task Force 2003

“Epidemiological studies suggest that in about 90% of cases of cerebral palsy intrapartum hypoxia could not be the cause of cerebral palsy . . .

and in the remaining 10% intrapartum signs compatible with damaging hypoxia may have had antenatal or intrapartum origins.”

MRI Findings in 245 Term Infants with Neonatal Encephalopathy and Perinatal Asphyxia

<table>
<thead>
<tr>
<th>MRI Findings</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Injury Pattern</td>
<td>197/245 (80%)</td>
</tr>
<tr>
<td>Normal</td>
<td>40/245 (16%)</td>
</tr>
<tr>
<td>Findings not compatible with hypoxia</td>
<td>8/245 (3%)</td>
</tr>
<tr>
<td>Acute hypoxic damage with other disorders</td>
<td>9/245 (4%)</td>
</tr>
</tbody>
</table>

NE defined by abnormal tone pattern, feeding difficulties, altered alertness.

Perinatal Asphyxia defined by at least 3 of the following:

- Late decelerations or MSAF
- Delayed onset respirations
- Arterial cord blood pH < 7.1
- Apgar <7 at 5 minutes
- Multi organ failure

Cowan, F., et. al., The Lancet, 2003; vol 361:736-742
### Clinical Characteristics MRI Pattern in 173 infants with NE

<table>
<thead>
<tr>
<th></th>
<th>Normal 51(30%)</th>
<th>Watershed predominant 78 (45%)</th>
<th>Basal ganglia/predominant 44 (25%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Perinatal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal distress</td>
<td>33 (66%)</td>
<td>51 (66%)</td>
<td>23 (56%)</td>
<td>.5</td>
</tr>
<tr>
<td>Complicated vaginal delivery</td>
<td>8 (16%)</td>
<td>17 (18%)</td>
<td>10 (23%)</td>
<td>.7</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>Emergent Cesarean delivery</td>
<td>24 (47%)</td>
<td>42 (54%)</td>
<td>22 (50%)</td>
</tr>
<tr>
<td>Placenta/cord insult</td>
<td>16 (31%)</td>
<td>21 (27%)</td>
<td>15 (34%)</td>
<td>.7</td>
</tr>
</tbody>
</table>

Miller, SP et. al., J Pediatr, April 2005; 453-460

### Neurodevelopmental Outcome of Newborns Observed to 30 months of Age by MRI

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Watershed predominant</th>
<th>Basal ganglia / thalamus predominant</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>20</td>
<td>48</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Died*</td>
<td>0</td>
<td>3</td>
<td>5</td>
<td>.01</td>
</tr>
<tr>
<td>30-month MDI</td>
<td>101 (77-121)</td>
<td>84 (50-116)</td>
<td>62.5 (50-104)</td>
<td>.0007</td>
</tr>
<tr>
<td>12-month MDI</td>
<td>93 (53-109)</td>
<td>91.5 (50-120)</td>
<td>58 (50-109)</td>
<td>.006</td>
</tr>
<tr>
<td>30-month NMS</td>
<td>0 (0-2)</td>
<td>1 (0-5)</td>
<td>5 (0-5)</td>
<td>.0001</td>
</tr>
<tr>
<td>12-month NMS</td>
<td>0 (0-3)</td>
<td>1 (0-5)</td>
<td>5 (0-5)</td>
<td>.0008</td>
</tr>
</tbody>
</table>

*All infants died before 12 months of age.

MDI = Mental Development Index   NMS = Neuromotor score

Miller SP, et. al., J Pediatr, April 2005; 453-460
Conclusion by Dr. Steven Miller et al. 2005

“Brain injury in most newborns with encephalopathy occurs at or near the time of birth . . .”

Miller SP, et. al., J Pediatr, April 2005; 453-460

Process for 2014 Report

- Dr. Richard Waldman’s presidential initiative
- Task Force convened in 2010
- Met 4 times over span of 3 years
- Task Force identified clinicians and scientists from multiple disciplines
- 88 international consultants
- Reviewed and edited draft manuscripts and deliberated to achieve consensus
Major Changes Since 2003 Report

- Classification of EFM patterns
- MRI studies conflict with epidemiological data
- Landmark introduction of hypothermia for neonatal treatment
- New chapters on neuroimaging, patient safety, placental pathology, neonatal interventions, and fetal physiology
- Significantly expanded document

Vermont Oxford NE Registry

- 4,171 infants ≥ 36 weeks from 95 centers met encephalopathy criteria in first 3 days of life 2006-2010
- 3,493 infants (84%) underwent some form of neuroimaging evaluation (MRI, HUS, CT)
- Infants who died more commonly had no neuroimaging compared to surviving infants (23.3% vs. 15.5%)
- 15% living term NE infants had NO neuroimaging

Barnette AR, et al. Pediatrics 2014 133; e1508
### Imaging Findings

<table>
<thead>
<tr>
<th></th>
<th>Ultrasound</th>
<th>CT Scan</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of exams</strong></td>
<td>2006/4111</td>
<td>933/4107</td>
<td>2690/4109</td>
</tr>
<tr>
<td>(48.8%)</td>
<td>(22.7%)</td>
<td>(65.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Day of life at first scan</strong></td>
<td>2 (1-3)</td>
<td>2 (2-3)</td>
<td>6 (4-8)</td>
</tr>
<tr>
<td><strong>Abnormal</strong></td>
<td>642 (32.3%)</td>
<td>552 (59.4%)</td>
<td>1798 (67.2%)</td>
</tr>
<tr>
<td><strong>DNGM</strong></td>
<td>140 (7%)</td>
<td>65 (7%)</td>
<td>603 (22.6%)</td>
</tr>
<tr>
<td><strong>Diffuse WM Injury</strong></td>
<td>-</td>
<td>-</td>
<td>628 (23.5%)</td>
</tr>
<tr>
<td><strong>Diffuse cortical signal abnormality</strong></td>
<td>-</td>
<td>-</td>
<td>572/2673 (21.4%)</td>
</tr>
<tr>
<td><strong>Parasagittal watershed injury</strong></td>
<td>-</td>
<td>-</td>
<td>285/2665 (10.7%)</td>
</tr>
<tr>
<td><strong>Absent PLIC</strong></td>
<td></td>
<td></td>
<td>114/2659 (21.9%)</td>
</tr>
</tbody>
</table>

Barnette AR, *et al.* Pediatrics 2014 133; e1508

### Efficacy of Hypothermia: Cochrane Analysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Relative Risk</th>
<th>Confidence Interval (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality or Major Disability (18 months)</td>
<td>0.75</td>
<td>0.68 - 0.83</td>
</tr>
<tr>
<td>Cerebral Palsy</td>
<td>0.65</td>
<td>0.46 – 0.94</td>
</tr>
<tr>
<td>Neuromotor delay</td>
<td>0.75</td>
<td>0.59 – 0.94</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>0.74</td>
<td>0.58 – 0.94</td>
</tr>
<tr>
<td>Blindness</td>
<td>0.62</td>
<td>0.38 – 1.01</td>
</tr>
<tr>
<td>Deafness</td>
<td>0.66</td>
<td>0.35 – 1.26</td>
</tr>
</tbody>
</table>

11 randomized clinical trials including 1505 patients counted in analysis

How to cool?

Images courtesy of Terrie Inder, MD

Cool Cap

Whole Body Cooling

Reduction in cerebral lesions on MRI with therapeutic hypothermia (TOBY trial)

<table>
<thead>
<tr>
<th>Lesion Site</th>
<th>Adjusted odds ratio (95% confidence intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal ganglia and thalami</td>
<td>0.36 (0.15-0.84) P=0.02</td>
</tr>
<tr>
<td>Posterior limb of internal capsule</td>
<td>0.38 (0.17-0.85) P=0.02</td>
</tr>
<tr>
<td>White matter</td>
<td>0.30 (0.12-0.77) P=0.01</td>
</tr>
<tr>
<td>Cortex</td>
<td>0.62 (0.27-1.41) P=0.25</td>
</tr>
</tbody>
</table>

131 of 325 had MRI

2014 Report

- AAP - Co-Author
- ACOG - Co-Author
- CREOG
- RCOG
- SMFM
- SOGC

Federal agencies can no longer endorse but were represented
- CDC
- NICHD

Neonatal Encephalopathy and Neurologic Outcome

- Task Force prefers term “neonatal encephalopathy” [NE] to “hypoxic ischemic encephalopathy” [HIE]

- HIE is a cause-specific subset of NE

- Continued absence of precise terminology in the literature since 2003 document

- An array of developmental outcomes may arise following NE in addition to CP
Neonatal Encephalopathy & Neurologic Outcome (2014)

Pre- and Perinatal Causal Pathways to CP in Term Infants

- A broader perspective is taken
- Knowledge gaps still preclude a definitive test
  or
- set of markers

that accurately identifies with high sensitivity and specificity, an infant whose NE is attributable to an acute intrapartum event

ACOG/AAP 2014
Piecing it together…

Comprehensive Evaluation of NE

- Maternal medical history
- Obstetric antecedents
- Intrapartum factors
- Placental pathology
- Newborn course
  - Labs
  - EEG
  - Neuroimaging

Ob and Neonatal Checklist examples provided in the publication appendix.
Purpose of identifying the cause(s) which have contributed to NE

- Guide treatment
- Judge prognosis
- Appropriate family counseling
- Improving clinical practice
- Guide research efforts

Comprehensive Evaluation of NE

I. Case Definition

II. Neonatal Signs Consistent with an Acute Peripartum or Intrapartum Event

III. Type & Timing of Contributing Factors

IV. Developmental Outcome Is Spastic Quadriplegia or Dyskinetic Cerebral Palsy
I. Case Definition

Neonatal Encephalopathy

• “A syndrome of disturbed neurological function
• in the earliest days of life in the infant at or beyond 35 weeks gestation,
• manifested by subnormal levels of consciousness or seizures,
• and often accompanied by difficulty with initiating and maintaining respirations and depression of tone and reflexes.”

ACOG/AAP 2014

Comprehensive Evaluation

I. Case Definition

II. Neonatal Signs Consistent with an Acute Peripartum or Intrapartum Event

III. Type & Timing of Contributing Factors

IV. Developmental Outcome Is Spastic Quadriplegia or Dyskinetic Cerebral Palsy
II. Neonatal Signs Consistent with an Acute Peripartum or Intrapartum Event

Apgar Score of <5 at 5 and 10 Minutes

- Low Apgar scores at 5 and 10 minutes significantly increase the risk of long-term neurologic impairment
- Degree of Apgar abnormality at 5 and 10 minutes correlates with the risk of CP
- If the Apgar score at 5 minutes is ≥ 7, it is unlikely that peripartum hypoxia–ischemia played a major role in causing NE

ACOG/AAP 2014

II. Neonatal Signs

Fetal Umbilical Artery Acidemia

**pH less than < 7  or  BD ≥12mmol/L**

- Commonly accepted as indicative of pathologic fetal acidemia
- Continuum of increasing risk of NE with worsening acidemia
- Even in the presence of significant acidemia, the majority of newborns will be neurologically normal
- If the cord arterial gas pH levels are 7.20 or greater, it is unlikely that peripartum hypoxia played a role in causing NE
- The presence of metabolic acidemia does **not** define the timing of the onset of a hypoxic–ischemic event

ACOG/AAP 2014
II. Neuroimaging Evidence of Acute Brain Injury

- MRI is the neuroimaging modality of choice
- Distinct patterns of neuroimaging abnormalities recognized in HIE injury in infants
- Have prognostic value for predicting neurodevelopmental impairment
- A normal MRI/MRS obtained after the first 24 hours of life makes intrapartum hypoxia unlikely

ACOG/AAP 2014

Patterns of “Acute” Cerebral Injury

Intrapartum Hypoxic-Ischemic Brain Injury

- Sentinel Event Identified
- Cord pH < 7.00
- Resuscitation
- Low Apgar scores
- More Severe Encephalopathy and Seizures
- Mechanism frequently not as clear
- Cord pH < 7.00
- Variable Resuscitation requirement
- Apgar scores usually higher
- Milder or Delayed Onset Encephalopathy
- Neuroimaging +

Images courtesy of Terrie Inder, MD
Posterior Limb of the Internal Capsule (PLIC)


Deep Nuclear Gray Matter Injury

Mild Basal Ganglia/Thalamic

Cerebral palsy 10-15%
(only mild-moderate impairment)

- Normal PLIC
  - Walking at 2 yrs

- Equivocal PLIC
  - 2/3 walking at 2 yrs, some may start late

Feeding
- 10%

Speech & language
- 25%

Vision
- No Impairment

DQ
- >84 in 80%
- >70 in 90%

Seizures


Moderate Basal Ganglia/Thalamic

Look at the PLIC

- Equivocal PLIC
  - Cerebral palsy 60%
    - Mostly mild (75%)
    - 2/3 will be walking, may start late

- Abnormal PLIC
  - Cerebral palsy 75%
    - Moderate (50%) or Severe (40%)
    - 70-80% will not walk at 2 yrs

Feeding
- 40-50%
  - Most, with severe in 25%

Speech & language
- 20-55%
  - 50-75% assessable

Vision
- 35% DQ <70

DQ
- Normal/Mild: 3-6%
- Moderate: 11%
- Severe: 19%

Seizures

II. Neuroimaging Evidence of Acute Brain Injury Summary

- MRI is the neuroimaging modality of choice
- Distinct patterns of neuroimaging abnormalities recognized in HIE injury in infants
- These patterns have prognostic value for predicting neurodevelopmental impairment
II. Presence of Multisystem Involvement Consistent With HIE

- Multisystem involvement includes:
  - renal, hepatic, cardiac, gastrointestinal injury, or hematologic abnormalities

- Although presence of organ dysfunction increases the chance of HIE in the setting of NE, severity of brain injury seen on imaging does not always correlate with injuries to other organ systems

Comprehensive Evaluation of NE

I. Case Definition

II. Neonatal Signs Consistent with an Acute Peripartum or Intrapartum Event

III. Type & Timing of Contributing Factors

IV. Developmental Outcome Is Spastic Quadriplegia or Dyskinetic Cerebral Palsy

COLUMBIA UNIVERSITY MEDICAL CENTER
III. Type and Timing of Contributing Factors Consistent with an Acute Peripartum or Intrapartum Event

- A sentinel hypoxic or ischemic event occurring immediately before or during labor and delivery
  - Uterine rupture
  - Placental abruption
  - Umbilical cord prolapse
  - Amniotic fluid embolus
  - Maternal cardiac arrest

ACOG/AAP 2014

III. Fetal Heart Rate Patterns

- Fetal heart rate monitor patterns consistent with an acute peripartum or intrapartum event
- A category 1 or category 2 FHR tracing associated with
  - Apgar scores ≥7 at 5 minutes
  - Normal arterial cord gases [+/- 1 standard deviation (SD)]
  is not consistent with an acute hypoxic–ischemic event
- Great distinction needs to be made between
  - a patient who initially presents with an abnormal fetal heart rate pattern
  - one who presents with a normal pattern and develops an abnormal fetal heart rate pattern during labor

ACOG/AAP 2014
III. Fetal Heart Rate Patterns

- An FHR pattern in a fetus who presents with
  - persistent minimal or absent variability and no accels
  - lasting ≥ 60 minutes (even in the absence of decels)
  is suggestive of a previously compromised or injured fetus

- Patient presenting with a Category I FHR pattern that converts to Category III is suggestive of intrapartum hypoxia

- Other patterns that develop following a Category I FHR pattern that may suggest intrapartum timing of HIE:
  - tachycardia with recurrent decelerations
  - persistent minimal variability with recurrent decelerations

III. Timing and Type of Brain Injury Patterns Consistent with an Acute Event

- Cranial ultrasound lacks sensitivity for common forms of brain injury in term NE
  - Echodensity seen 48 hours or longer following hypoxic-ischemic injury

- U/S may be the only neuroimaging modality available in a very unstable infant

- CT lacks sensitivity for brain injury

- MRI and MRS most sensitive (24-96 hours) to assist with the timing of a cerebral injury

- Using conventional MRI, cerebral abnormalities become most evident after 7 days following a cerebral injury
III. Timing and Type of Brain Injury Patterns Consistent with an Acute Event

- Diffusion abnormalities are most prominent between 24 and 96 hours of life

- Two MRI/MRS scans
  - First between 24 and 96 hours of life with emphasis on the evaluation of diffusion and spectroscopic abnormalities to assist in clinical management and evaluation of the timing of cerebral injury
  - Second at day 10 or later with an acceptable window of 7 to 21 days —will assist with full delineation of the nature and extent of cerebral injury

ACOG/AAP 2014

III. Timing and Type of Brain Injury Patterns Consistent with an Acute Event

Consistent with an Acute Event

If different patterns pursue an alternative diagnosis

- Focal arterial infarction
- Intraparenchymal or Intraventricular hemorrhage

suggest intrapartum hypoxia did **NOT** play a role in NE

ACOG/AAP 2014

III. Timing and Type of Brain Injury Patterns Consistent with an Acute Event

- Accurate interpretation of neuroimaging is key

- If limited expertise, an expert opinion is recommended

- Despite advances in neuroimaging ability to precisely time the occurrence of HIE is still limited (days rather than hours or minutes)

ACOG/AAP 2014
III. No Evidence of Other Contributing Factors

• In the presence of other significant risk factors:
  • abnormal fetal growth
  • maternal infection
  • fetomaternal hemorrhage
  • neonatal sepsis
  • chronic placental lesions

• An acute intrapartum event as the sole underlying cause of NE becomes much less likely.

ACOG/AAP 2014

Comprehensive Evaluation of NE

I. Case Definition

II. Neonatal Signs Consistent with an Acute Peripartum or Intrapartum Event

III. Type & Timing of Contributing Factors

IV. Developmental Outcome Is Spastic Quadriplegia or Dyskinetic Cerebral Palsy
IV. Developmental Outcome After HIE Due to Intrapartum Events

• Developmental Outcome is
  • Spastic Quadriplegia or Dyskinetic Cerebral Palsy
  • Other subtypes of cerebral palsy less likely to be associated with acute intrapartum hypoxia
  • Other developmental abnormalities may occur
    • Not specific to acute intrapartum HIE
    • May arise from a variety of other causes

ACOG/AAP 2014

In the decade since the 2003 “Green Book” was first published, considerable advances have been made in our knowledge and understanding of NE and long-term neurodevelopmental outcome.
Comprehensive Evaluation of NE

- Reflects the current state of scientific knowledge
- Acknowledges limitations in definitively distinguishing HIE from other forms of NE

This comprehensive assessment is key to recognizing:

- No one strategy to identify HIE at present is infallible
- No single strategy will achieve 100% certainty of determining the cause of NE in all cases

ACOG/AAP 2014

Task Force Members

Gary Hankins
Richard Berkowitz
Alessandro Ghidini
Karin Nelson
Yvonne Wu
Jay Goldsmith
Lu-Ann Papile
Diana Schendel
Jessica Bienstock
Donald Peebles
Roberto Romero
Cathy Spong
Thomas Moore
Renato Natale
Richard Waldman
Gerald Joseph Jr.
Rosemary Higgins

ACOG Staff:
Debra Hawks
Alyssa Politzer
Chuck Emig
Kelly Thomas
Endorsing Organizations

Neonatal Encephalopathy: Perspectives from the ACOG AAP Revision

Mary E. D’Alton, M.D.
Willard C. Rappleye Professor and Chair, Department of Obstetrics & Gynecology
Columbia University College of Physicians & Surgeons