Neonatal Hypoxic-Ischemic Encephalopathy
ACNS Winter Course 2021
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Disclosures
• None

Objectives
• Review the criteria and modalities utilized in the diagnosis of neonatal hypoxic-ischemic encephalopathy (HIE)
• Discuss the current and emerging therapeutic approaches
• Understand the prognostic role of biomarkers and neuromonitoring tools (specifically EEG)
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**Background**

- HIE in newborns occurs in ~1.5 per 1000 live births¹
- Incurs an estimated economic burden of ~$900,000 in lifetime cost per individual²

1- Fatemi et al, Clin Perinatol 2009
2- Eunson et al, Dev Med Child Neurol 2015

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**Mechanism of injury**

Figure from Nair et al, Children 2018:
Schematic illustration of pathophysiology of HIE

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**Indications of an acute perinatal hypoxic ischemic event**

- Apgar score <5 at 5 minutes and 10 minutes
- Marker of fetal acidosis: fetal umbilical cord artery pH <7 and/or base deficit ≥ 12 mmol/L
- Evidence of multiorgan system failure consistent with HIE
- History of peripartum sentinel event:
  - Variable/sustained hear rate decelerations
  - Uterine rupture
  - Maternal hemorrhage/dehydration
  - Maternal cardiovascular collapse
- Clinical Exam

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Diagnosis: clinical exam

Adapted from Sarnat HB, Sarnat MS, Arch Neurol 1976

<table>
<thead>
<tr>
<th>Sarnat Score Categories</th>
<th>Normal</th>
<th>Stage 1 (mild)</th>
<th>Stage 2 (moderate)</th>
<th>Stage 3 (severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Level of consciousness</td>
<td>Alert, responsive to external stimuli</td>
<td>Hyperalert, responds to minimal stimuli</td>
<td>Lethargic</td>
<td>Stupor/coma</td>
</tr>
<tr>
<td>Spontaneous Activity</td>
<td>Normal change</td>
<td>Normal or decreased</td>
<td>Decreased</td>
<td>none</td>
</tr>
<tr>
<td>Posture</td>
<td>Predominantly flexed with quiet position</td>
<td>Mild flexion of distal joints</td>
<td>Distal flexion complete extension</td>
<td>Decerebrate</td>
</tr>
<tr>
<td>Tone</td>
<td>Strong flexor tone in all extremities</td>
<td>Normal or slightly up</td>
<td>Hypotonia</td>
<td>Hypertonia</td>
</tr>
<tr>
<td>Primitive Reflexes</td>
<td>Strong, easily illicit</td>
<td>Weak or incomplete</td>
<td>Weak or incomplete and/or bite</td>
<td>Absent</td>
</tr>
<tr>
<td>Moro</td>
<td>Complete</td>
<td>Intact, low threshold to illicit incomplete</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>Autonomic nervous system</td>
<td>Normal, reactive</td>
<td>Mydriasis</td>
<td>Myosis</td>
<td>Variable/nonreactive to light</td>
</tr>
<tr>
<td>HR</td>
<td>100–160</td>
<td>Tachycardia</td>
<td>Bradycardia</td>
<td>Variable HR</td>
</tr>
<tr>
<td>Respirations</td>
<td>Regular respirations</td>
<td>Hyperventilation</td>
<td>Periodic breath</td>
<td>Apnea or need ventilation</td>
</tr>
</tbody>
</table>

Total Sarnat Score /27

Adapted from Chalak et al. J Pediatr 2019:

MRI patterns of brain injury

• Barkovich score¹
  – Scoring system for T1 and T2 weighted images
  – Scores derived from extent of injury to deep nuclear gray matter structures (basal ganglia, thalamus), watershed areas (cortical, white matter) or combination of both
  – Combined basal ganglia/watershed score was most useful in predicting neurodevelopmental outcomes at 3 and 12 months, and cognitive outcomes at 12 months

• Other scoring systems: Trivedi²⁻³
  – Utilizes DWI/ADC sequences
  – Scores based on degree of injury to subcortical (basal ganglia, thalamus), posterior limb of internal capsule, white matter, cortex, cerebellum and brainstem regions
  – Higher scores, particularly in deep nuclear gray and posterior limb of internal capsule, are associated with worse neurodevelopmental outcomes

² Trivedi et al, Pediatr Radiol 2017
³ Weeke et al, J Pediatr 2018
The MRI on day 2–3 of life has a sensitivity and specificity of 100% to identify the presence and extent of brain injury (Boudes et al, Arch Dis Child Fetal Neonatal Ed 2015).

- Proton MRS of thalamus and basal ganglia
- Elevated Lactate/NAA ratio predictive of poorer outcomes¹⁻²

¹ Thayyil et al, Pediatr 2010
² Shanmugalingam et al, Pediatr 2006

- Therapeutic Hypothermia
- Seizures
- Supportive care

- Neurodevelopment (Motor, Cognitive)
- Epilepsy
Therapeutic Hypothermia

**TOBY trial**¹
- Whole body cooling to 33.5°C for 72 hours
- 325 infants with HIE ≥36 weeks included: 163 cooled
- Cooled infants had lower rates of severe disability/cerebral palsy and increased rate of survival without neurological abnormality at 18 months compared to noncooled group

**Coolcap trial**²
- Selective head cooling to 34-35°C for 72 hours
- 234 infants with moderate to severe HIE ≥36 weeks included: 116 cooled
- 55% in cooled vs 66% in noncooled group had death or severe disability at 18 months
- Most benefit in those with less severe aEEG changes

¹ Azzopardi et al, NEJM 2009
² Gluckman et al, Lancet 2005

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Expanding use of cooling in HIE

- **Mild HIE**
  - Excluded from TH trials
  - Prospective studies of noncooled mild HIE:
    - 16-25% with reported neurodevelopmental disability in infancy/childhood¹⁻²
    - Higher rates of disability than normal controls, and cognitive outcomes like that of moderate encephalopathy group³
  - Preterm neonates
    - Retrospective review of preterm neonates 34-35 weeks with HIE compared to term neonates
    - White matter injury more common in preterms
  - Late cooling
    - RCT 168 term infants with HIE: 83 infants cooled for 96 hours starting 6-24 hours after birth⁵
    - Majority with moderate encephalopathy (90%)
    - Primary outcome was death or disability at 18 months
    - Bayesian analysis showed up to 2% decrease in death or disability at least 2% less in the hypothermia group

¹ Conway et al, Early Hum Dev 2018
² Chalak et al, Pediatr Res 2018
³ Murray et al, Pediatrics 2016
⁴ Rao et al, J Pediatr 2017
⁵ Laptook et al, JAMA 2017

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Emerging therapies

- Adjunctive therapy trials to standard brain cooling are under investigation as 40% of newborns continue to die or have moderate-severe disability⁴

<table>
<thead>
<tr>
<th>Endogenous</th>
<th>Exogenous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythropoetin, Darbopoietin</td>
<td>Xenon</td>
</tr>
<tr>
<td>Stem Cells</td>
<td>Allopurinol</td>
</tr>
<tr>
<td>Melatonin</td>
<td>Magnesium</td>
</tr>
<tr>
<td>Endocannabinoids</td>
<td>Sulfate</td>
</tr>
<tr>
<td>Topiramate</td>
<td></td>
</tr>
</tbody>
</table>

Emerging therapies: Targets

Figure from Nair et al, Children 2018:
Potential neuroprotective therapies in the management of HIE

Erythropoietin (EPO)

- **Phase 2** double-blinded, placebo-controlled trial
  - Newborns with moderate/severe HIE undergoing cooling receive EPO (n = 24) or placebo (n = 26) at 1, 2, 3, 5, and 7 days of age
  - Primary outcome was neurodevelopment at 12 months and MRI brain injury severity
  - No significantly increased death or serious adverse events between two groups
  - EPO treatment was associated with significantly reduced severity of brain injury on MRI, specifically in the subcortical regions
  - Improved short term markers of motor outcome

  Thus, establishing the safety and feasibility of a phase 3 study with longer follow-up

- **Phase 3 RCT** started 2017, anticipated completion 2022
  - Enrollment complete
  - Neurodevelopmental assessments through 24 months of age ongoing

1- Wu et al, Pediatr 2016

Biomarkers of HIE

- Serum:
  - Cell specific
  - S100B, Neuron specific enolase, GFAP¹⁻²
  - Inflammatory
  - IL6/8/16, VEGF³⁻⁴

  - Currently none in clinical use: studies showing correlation with neurodevelopmental outcomes and degree of injury limited⁵

- NIRS: near infrared spectroscopy
  - Monitors continuous regional cerebral tissue oxygenation
  - Independently not reliable in first 24 hours, after 24 hours sensitivity increases but specificity still low
  - Increased sensitivity and specificity when combined with other neuromonitoring tools such as amplitude EEG⁶

1- Massaro et al, J Pediatr 2018  
2- Celtik et al, Brain Dev 2004  
3- Chalak et al, J Pediatr 2014  
4- Walsh et al, Pedatr Crit Care Med 2013  
5- Bennet et al, Sem Fetal Neonat Med, 2010  
6- Lemmers et al, Pediatr Research 2013
Risk factors for seizures
• ~48% neonates with HIE present with acute symptomatic seizures¹⁻²
  – High rates of EEG only seizures
  – w/ clinical seizures
Risk factors of acute EEG seizures in neonates with HIE²
  – Evaluated clinical (birth related) factors, initial exam, initial EEG background:
    • Normal
    • Excessively discontinuous
    • Severe: depressed and undifferentiated, burst suppression, or extremely low voltage
  – Abnormal EEG background was most closely associated with risk of EEG seizures
    • Positive predictive value (PPV) 66%, Negative predictive value (NPV) 88%

¹- Srinivasakumar et al, Pediatr 2015
²- Glass et al, Neurol 2014

Acute symptomatic seizures and outcome in HIE
• Multiple animal and human studies have revealed that prolonged seizures in neonates induce or worsen already-existing brain injury via increase in metabolic demands and formation of reactive O2 species¹
• Neonatal electrographic seizure burden correlated with poor neurodevelopmental outcome²
• Treatment of EEG seizures vs clinical only seizures in neonates with HIE³
  – EEG treated seizures: shorter time to treatment from seizure onset, a significant decrease in the cumulative electrographic seizure burden, decrease in the number of overall seizures, and lower MRI injury scores

²- McBride et al, Neurology 2000
³- Srinivasakumar et al, Pediatr 2015

Timing of seizures in HIE
• Mean onset 9.5-19.9 hours in different studies²

<table>
<thead>
<tr>
<th>Time to &lt; 1% risk (hrs)</th>
<th>Epileptiform DC</th>
<th>No Epileptiform DC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute neonatal encephalopathy</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td>Stereotyped clinical event</td>
<td>6</td>
<td>27</td>
</tr>
<tr>
<td>Other high risk condition</td>
<td>8</td>
<td>23</td>
</tr>
</tbody>
</table>

Adapted from Worden et al, Epilepsia 2019

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EEG: An important tool for prognostication in HIE

EEG Background patterns:
- Normal
- Excessively discontinuous
- Depressed/undifferentiated
- Burst suppression
- Extremely low voltage

Adapted from Murray et al, Pediatrics 2009:
Classification of EEG background activity

- Grade 0: Normal
  - Continuous with normal physiologic features
- Grade 1: Normal/Mild
  - Continuous with slightly abnormal activity (e.g. mild asymmetry, mild voltage depression, poorly defined SWC)
- Grade 2: Moderate
  - Discontinuous with IBI <10s, no clear SWC, or clear asymmetry or asynchrony
- Grade 3: Major
  - Discontinuous with IBI 10-60s, severe attenuation, or no SWC
- Grade 4: Inactive/Severe
  - Amplitudes <10uV or severe discontinuity with IBI >60s

EEG Background patterns:
- Normal
- Excessively discontinuous
- Depressed/undifferentiated
- Burst suppression
- Extremely low voltage

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EEG background correlates with outcome

- Amplitude EEG recordings have been shown to have good predictive ability soon after birth, with abnormal aEEG results in the first 6 hours having a PPV of 86% and NPV of 91%¹
- EEG background pattern correlates with MRI injury severity²
  - A normal EEG was associated with no or mild MRI brain injury at all time points (most predictive at the beginning of cooling, specificity 99%)
  - The prognostic value of burst suppression or extremely low voltage pattern for moderate to severe injury increased from the beginning of cooling (81% specific) to midcooling and thereafter (100% specific)

<table>
<thead>
<tr>
<th>EEG 36h</th>
<th>EEG 48h</th>
<th>Seizure burden</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>67</td>
<td>50</td>
<td>64</td>
</tr>
<tr>
<td>Specificity</td>
<td>100</td>
<td>100</td>
<td>82</td>
</tr>
<tr>
<td>PPV</td>
<td>100</td>
<td>100</td>
<td>78</td>
</tr>
<tr>
<td>NPV</td>
<td>75</td>
<td>69</td>
<td>69</td>
</tr>
</tbody>
</table>

Adapted from Weeke Eur J Pediatr Neurol, 2011

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Individual EEG features¹

EEG background features associated with abnormal outcomes:
- Sleep-wake cycling:
  - At 6h, SWC seen is associated with good prognosis. Those without SWC in first 6h, only 47% had abnormal outcome
  - At 48 hours, absence of SWC had PPV of 92% for an abnormal outcome
- Amplitude:
  - Normal amplitude in first 6h associated with good outcome while low amplitude at any time associated with poor outcome
  - IBI>30s or continuous discontinuous recording associated with worse outcomes
- Asymmetry:
  - 70% of those with asymmetry had an abnormal outcome
- Electrographic seizures

1. Toet et al, Arch Dis Child Fetal Neo Ed. 1999
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Quantitative EEG features

• EEG spectral power analysis:
  – Evaluates the power of each EEG frequency component
  – Neonates with brain injury/death have lower absolute spectral powers than normal/mild HIE¹
  – Similarly, total EEG power (TEP) significantly lower in infants with moderate/severe HIE compared to normal/mild HIE
  – TEP appears to provide higher prediction values for neonatal/mature MRI injury when compared to subjective EEG assessments¹

• Heart rate variability:
  – HRV was significantly lower within the first 24 h from birth in neonates with moderate-severe abnormalities on EEG recordings compared with those with mildly abnormal/normal EEG³
  – HRV was mostly affected at two main time points: 24 h of life and after 80 h of life (i.e. after rewarming completion⁴

¹ Govindan et al, Clin Neurophysiol 2017
² Jain et al, J Perinat 2017
³ Vergales et al, Am J Perinatol 2013
⁴ Massaro et al, J Perinatol 2014

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Post neonatal epilepsy (PNE) in HIE

• Incidence of PNE 10-15%¹⁻⁴
• Lower rates of PNE reported in cooled vs noncooled neonates:
  – Coolcap: 15% vs 16%
  – TOBY: 10% vs 14%
• Risk factors for PNE:
  – Newborn seizures (25% developed epilepsy), severe encephalopathy, EEG status epilepticus, MRI severe injury³
  – Higher number of ASMs to control neonatal seizures, aEEG severity, MRI severity⁴

¹ Azzopardi et al, NEJM 2009
² Gluckman et al, Lancet 2005
³ Glass et al, Pediatr Res 2011
⁴ Lui et al, Epilepsia 2017

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Take home points

• Further RCT studies needed to establish efficacy of therapeutic hypothermia in other neonatal HIE populations as well as other proposed treatment targets
• Continuous EEG monitoring recommended throughout the cooling and rewarming phase in HIE
• Prognostic power of an abnormal EEG improves with time (typically >24 hours)
• Quantitative EEG may be a helpful tool in the future for early delineation of injury severity groups