Prediction of outcome in HIE neonates receiving therapeutic hypothermia

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Why do we care?

Prediction of neurodevelopmental outcome remains a major challenge for clinicians treating newborns with neonatal encephalopathy, and for parents this is a key question.
Why prior methods to predict outcome may no longer be valid

- Therapeutic hypothermia (TH) is being widely used and current cooled cohorts may differ from those involved in studies assessing outcome.

- When neonates are cooled, less injury may occur, so early markers of injury and outcome are likely to be different.

- TH will change metabolism affecting biochemical markers. The development of injury may be delayed and the optimal timing for measurement of outcome markers may change.
Candidate Methods to Predict Outcome

- **Clinical assessment**
  Apgar score, Sarnat exam, Thompson score

- **Neurodiagnostic assessment**
  aEEG, EEG or NIRS

- **Serum biomarkers**
  pH, base deficit, lactate, S100B, GFAP, IL-8, vascular endothelial growth factor, neuron-specific enolase (NSE)

- **Neuroimaging**
  head ultrasound, MRI and MRS
Classification of aEEG patterns by pattern recognition and voltage methods

Normal Trace
- Normal
- lower margin >5μV
- upper margin >10μV

Moderately abnormal
- lower margin ≤5μV
- upper margin >10μV

Severely abnormal
- lower margin <5μV
- upper margin <10μV

Normal Voltage
- CNV
- Continuous Normal Voltage

Discontinuous Normal Voltage
- DNV

Burst Suppression
- BS

Low Voltage
- LV

Flat Trace (isoelectric)
- FT

Sleep wake cycling

6cm
Abnormal trace did not reliably predict outcome prior to 36 hours in HT treated infants

Prior to cooling era:
Abnormal outcome is seen when aEEG background does not return to normal by 24 hours

In cooling era:
Abnormal outcome is seen when aEEG background does not normalize by 48 hours
Time to develop SWC and outcome

Median time to SWC was 36 hours in HT group with normal outcome.

Never developing SWC was a strong predictor of death or disability. PPV=64%, NPV=90%

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# Clinical staging of HIE: Modified Sarnat

<table>
<thead>
<tr>
<th></th>
<th>Stage 1 Mild</th>
<th>Stage 2 Moderate</th>
<th>Stage 3 Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level of consciousness</strong></td>
<td>Hyperalert</td>
<td>Lethargic</td>
<td>Stuporous</td>
</tr>
<tr>
<td><strong>Tone</strong></td>
<td>Normal</td>
<td>Mild hypotonia</td>
<td>Flaccid</td>
</tr>
<tr>
<td><strong>Posture</strong></td>
<td>Mild distal flexion</td>
<td>Strong distal flexion</td>
<td>Decerebrate</td>
</tr>
<tr>
<td><strong>Activity</strong></td>
<td>Normal</td>
<td>Decreased</td>
<td>None</td>
</tr>
<tr>
<td><strong>Primitive reflexes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suck</td>
<td>Weak</td>
<td>Weak or absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Moro</td>
<td>Strong</td>
<td>Incomplete</td>
<td>Absent</td>
</tr>
<tr>
<td><strong>Autonomic function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pupils</td>
<td>Dilated</td>
<td>Constricted</td>
<td>Variable</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Tachycardia</td>
<td>Bradycardia</td>
<td>Variable</td>
</tr>
<tr>
<td>Respiration</td>
<td>Normal</td>
<td>Periodic</td>
<td>Apnea</td>
</tr>
</tbody>
</table>

Modified from Sarnat and Sarnat, *Arch Neurol* (1976)
The stage of encephalopathy at <6 hours of age and at 24, 48, and 72 hours of study intervention and at discharge.

Stage of encephalopathy was examined in 101 cooled infants at <6 hours, during cooling, at end of cooling, and at discharge.

- Severe encephalopathy at <6 hours was significant predictor of death/disability
- Persistence of severe or moderate encephalopathy throughout the 72-hour cooling period was associated with a higher risk of death/disability.
- At discharge, hypertonia, fisted hands, abnormal movements, absent gag, asymmetric tonic neck reflex, or need for NG/GT feeds increased the risk of death/disability