Establishing Prognosis with Currently Available Data

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Establishing Prognosis

- The clinical situation – term encephalopathy or the preterm infant
- The nature and timing of the insult
  - Term infant acute insult influencing gray matter > white matter
  - Preterm infant subacute insult influencing white matter
- The tools – imaging, EEG, clinical markers including the neurological exam
- Overview of establishing prognosis in the term and preterm infant

Term Infant

Establishing prognosis
Vermont Oxford Network
- Vermont Oxford Neonatal Encephalopathy Registry established 2006
- First 400 infants studied over a 12 month period
  - Majority entered due to recognition of clinical seizures (80%)
  - Of these 80% evaluated and treated
    - 60% conventional EEG at any time
    - 20% bedside aEEG
    - 80% received anticonvulsants (up to 9 drugs used)

Encephalopathy
- Best described as “Altered mental state”
- In Vermont Oxford Network defined mod-severe encephalopathy and/or seizures
  - Stupor: no spontaneous eye opening, tactile stimulation elicits poorly sustained eye opening
  - Coma: no eye opening to vigorous tactile stimulation
- Not all encephalopathy is “hypoxic-ischemic encephalopathy”

The diagnoses in local cohort (n=99)

Shah D. et al
Pediatrics 2006; 118: 47-55
Defining ischemic injury - the high risk infant

- At delivery
  - Apgar scores less than 5 after 5 minutes
  - Need for resuscitation and intubation
    - Eker et al J Pediatr 1997;131:613-7
  - Length of IPPV and length heart rate less than 100bpm: epinephrine

- After delivery
  - Evidence of multiorgan dysfunction
  - Elevation in temperature
  - "Encephalopathy" - structured examination
    - Wyatt et al Pediatrics 2007;119:912-921

Clinical examination in encephalopathy

- Sarnat score (Arch Neurol 1976;33:696-705)
  - Stage 1 < 24 hours hyperalertness, uninhibited reflexes, normal EEG
  - Stage 2 obtundation, hypotonia, strong distal flexion and multifocal seizures
  - Stage 3 stuporous, flaccid with suppressed brainstem and autonomic function
    - with isopotential EEG
  - Infants with stage 2 <5 days or stage 1 were "normal"

- Encephalopathy score (Miller et al AJOG 2004;190:93-9)
  - Scored +1 for abnormality on feeding, alertness, tone, respiratory distress, reflexes, clinical seizure. Score day 1
    - Sens 72%, spec 94%, PPV 84%, NPV 89%

- Dubowitz scale (Mercui et al Neuropediatrics 1999;30:83-89)
  - Systematic examination after day 7 of life predictive of disability and MRI abnormalities

Hypoxic-ischemic encephalopathy

- Clinical index – prediction of 24 month outcomes
  - Base deficit >17 OR 6.1 (1.1, 32.7)
  - Seizures 10 (1.0, 69.7)
  - 5-minute Apgar 2.6 (1.0, 7.4)
  - Abnormal imaging 51.5 (5.2, 900)

- Scoring 0-2 for
  - Apgar at 5-minutes 0 > 6, 1 4-6, 2 < 4
  - Cord or initial BD 0<15, 1 15-20, 2 >20
  - Resuscitation 0 if no intubation, 1 if intubate, 2 if int + epi
  - Total score /6 score >3 75% PPV, score > 4 90%

How can we better define prognosis in the term encephalopathic infant?

- **EEG tools**
  - Conventional EEG
  - Bedside aEEG monitors

- **Neuroimaging**
  - Ultrasound
  - CT scan
  - MRI

**Conventional EEG**

- Established utility in neonatal encephalopathy with poor outcomes associated with
  - Iso-electric trace or continuous seizures
  - Prolonged burst suppression after 72 hours
    - Menache et al Pediatric Neurology 2002;27:93-100
    - Zeinstra et al Eur J Pediat Neurol 2001;5:155-60

  Access can be difficult
  Prolonged monitoring complicated with 16 channels

**Impact of neonatal seizures - outcome**

- 77 infants studied
  - 30% died
  - 21% developed epilepsy

- 43% developed cerebral palsy
  - Subtle seizures are not “subtle” with more often abnormal outcome

  - Brunquell PJ et al; J Ped 2002 140:707
Bedside aEEG tools

- Developed in the late 1960s
- Extensive experience in Europe over the last 2 decades in the recognition of severe cerebral injury and seizures

- Two key features
  - Limited channels – 1 or 2 channels ease of application and maintenance
  - aEEG tracing – asymmetric band pass filter (2-15Hz) with semi-logarithmic amplitude compression, rectification and smoothing ease of interpretation of patterns

The tools

| Brainz | Olympic | Philips | Viasys |
aEEG Patterns

- CNV Continuous normal voltage
- DNV Discontinuous normal voltage
- FT Flat Tracing
- CLV Continuous extremely low voltage.
- BS Burst-suppression

Summary of backgrounds

HIE Term Infant — aEEG Predicting outcome

<table>
<thead>
<tr>
<th>Age</th>
<th>Sensitivity(%)</th>
<th>Specificity(%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>3hrs</td>
<td>85</td>
<td>77</td>
<td>Toet, 1999</td>
</tr>
<tr>
<td>6hrs</td>
<td>91</td>
<td>86</td>
<td>Toet, 1999</td>
</tr>
<tr>
<td>6hrs</td>
<td>94</td>
<td>79</td>
<td>Eken, 1995</td>
</tr>
<tr>
<td>6hrs</td>
<td>95</td>
<td>89</td>
<td>Hellstrom-Westas, 1995</td>
</tr>
<tr>
<td>6hrs*</td>
<td>55</td>
<td>74</td>
<td>Sarkar, 2007 (abn MR/death)</td>
</tr>
</tbody>
</table>

De Vries, Arch Dis Child, 2005
Correspondence between MR and aEEG


Is aEEG better than clinical predictors?

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate model OR (CI)</th>
<th>Multivariate model OR (CI)</th>
<th>Multivariate model Combined aEEG &amp; sarnat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage aEEG &amp; Sarnat</td>
<td></td>
<td></td>
<td>1.63 (1.08-130.11)</td>
</tr>
<tr>
<td>aEEG</td>
<td>7.32 (1.84-34.1)</td>
<td>12.43 (1.04-148.44)</td>
<td></td>
</tr>
<tr>
<td>Sarnat stage 2&amp;3</td>
<td>5.00 (0.78-31.77)</td>
<td>1.68 (0.11-26.49)</td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>1.69 (0.37-7.04)</td>
<td>0.81 (0.07-6.88)</td>
<td>0.84 (0.11-6.67)</td>
</tr>
<tr>
<td>Apgar&lt;5min&lt;5</td>
<td>1.32 (0.36-5.03)</td>
<td>0.82 (0.09-8.30)</td>
<td>0.96 (0.08-8.54)</td>
</tr>
<tr>
<td>Intubation required</td>
<td>0.33 (0.06-1.82)</td>
<td>1.08 (0.07-15.98)</td>
<td>0.40 (0.04-5.04)</td>
</tr>
<tr>
<td>Intropes</td>
<td>0.05 (0.04-1.54)</td>
<td>0.34 (0.04-8.19)</td>
<td>0.23 (0.03-1.95)</td>
</tr>
</tbody>
</table>

Shalak et al Pediatrics 2003;111:351-7

Additional information from aEEG or cEEG

- Prediction of outcome based on duration of the aEEG abnormality
  - Persistence of abnormal traces more indicative of poor outcome

- Timing
  - Earlier onset of seizures may reflect earlier time of injury
    - Filan et al BJOG 2005,112:S64-7

- Presence of sleep wake cycles
Comparative imaging

Term encephalopathy

Imaging in term encephalopathy

- Vermont Oxford Neonatal Encephalopathy Registry established 2006
- First 400 infants studied over a 12 month period
  - 1/3 cranial US
    - 80% by day 3
    - Abnormalities in 5%
  - 1/3 CT scan
    - 80% by day 3
    - Abnormalities in 9%, Extra-axial blood in 22%
  - 45% MRI scan
    - median day 4, 25% after day 7
    - Abnormalities in 54%

Accurate Imaging - The most important ingredients....

- Good communication between the clinical and radiological team
  - The clinical details of the infant and likely diagnoses – what the question is for the imaging? (clinician)
  - What to order? (radiology)
  - What is present in the images (radiology)
  - Prognosis and follow up (clinician)

This can be met with regular co-review of the images (daily, weekly meeting) and also quarterly-annual review of the numbers of infants imaged, diagnoses, schema for imaging etc.
Utility of Imaging in the Term Infant

- **US scan**
  - Basal ganglia injury
  - Beware the "slit"ventricle = diffuse edema as reported in 2/3 of normal population
  - Resistive index - ↑ flow, correlation with outcome when >3sd outside normal

- **CT scanning**
  - Often poor delineation early. Very variable prognosis with selective abnormalities
  - Additional concerns over radiation exposure

CT scanning – to scan or not to scan

- Cancer risk
  - Head CT in 1 year old for fatal tumor 0.07%
- Intellectual decline
  - Cranial irradiation (hemangioma, cranial tinea) resulted in reduced high school attendance (OR 0.56 >100mGy)
- Caveats
  - Dose and risk estimate cranial irradiation therapy
- Recommendation
  - Risk of radiation exposure not negligible?advise families in choices
  - Risk is inversely related to patient size

MRI scanning of the newborn brain

Recommended neuro-imaging modality for term infant with encephalopathy but limitations in translation into clinical practice due to

- Need to lie still for 30mins - sedation/anesthesia/nil
- Challenges in closely monitoring infant down the MRI tunnel – increasing monitoring and incubator
- Understanding of the right sequences for the infant’s unmyelinated brain

Magnetic Resonance Imaging in encephalopathy – Advantages

- Accurate anatomical definition at any age
- Multiple complimentary sequences:
  - Qualitative sequences –
    - coronal T1 (MPRAGE), coronal/axial T2
    - High resolution and minimize motion
  - Diffusion weighted sequences – 6 directional
  - MR Spectroscopy – PRESS or CSI
  - MR angiography and venography

Normal MRI at term

- Sagittal T1
- Coronal SPGR
- Axial T2 weighted

Diffusion weighted imaging

- Day 2
- T2
- DWI
- ADC map

Note: DWI versus ADC map for interpretation of restricted diffusion
Diffusion weighted imaging – Wallerian degeneration

Evolution of changes in MR images of newborn brain following injury

Hemiplegia and developmental delay

**Dav Changes Following Injury**

![Graph showing Dav Changes Following Injury](image)

**Hunt et al., n=28 infants ADC values in the PLIC correlated with outcome**

![Bar chart and brain scan](image)

**Pediatrics. 2004 Oct;114(4):999-1003**

**Quantification with ADC in neonatal HIE**

- Normative values for ADC in differing brain regions at differing gestational ages
  - *Rutherford M et al Pediatrics 2004;114:1004-1013*

- Indices for Following the Temporal Evolution of measures following HIE
  - *Van Pul et al AJNR 2005;26:469-481*
Diffusion and conventional MRI in timing lesions

<table>
<thead>
<tr>
<th></th>
<th>DWI</th>
<th>Conventional</th>
<th>MRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>EARLY within 48 hours</td>
<td>Restricted ADC (impact of hypothermia?)</td>
<td>No abnormality + lactate</td>
<td></td>
</tr>
<tr>
<td>SUB-ACUTE 3-10 days</td>
<td>+/- ADC changes</td>
<td>Visible changes</td>
<td></td>
</tr>
<tr>
<td>CHRONIC &gt;10 days</td>
<td>Normalized or high ADC</td>
<td>Clearly visible changes resulting in atrophy</td>
<td>NAA + lactate</td>
</tr>
</tbody>
</table>

MR imaging in hypoxic-ischemic injury

- Timing
  - False negatives on DWI (30%) in first 12 hours
  - False negatives on day 3-4
  - DWI Sequence utilized – recommend b-value of 700-1000msec. Note effect of T2 shine through with edema
    - Status epilepticus
    - Encephalitis
  - Recommend generation of ADC map and quantification of ADC in set regions.
- Hypothermia
  - Diffusion imaging is related to temperature
  - Hypothermia may delay evolution of changes


- Term infant with HIE:
  - CT for neurosurgical need
  - MRI at day 7

Term infant with HIE:
- Moderate - Severe HIE MR with DWI day 2
- Mild - Moderate HIE MR day 7-10 reliant on conventional MR

MR protocol includes diffusion imaging with ADC measurements in 5 regions, axial T2 and T1; MRS over left basal ganglia
Magnetic Resonance Imaging and Term Asphyxia

- 73 Term infants with HIE between 1-17 days and all infants with abnormal PLIC developed neurodevelopmental abnormality (n=41)
- Normal PLIC = normal in 28/32
- Correctly predicted outcome in 93% of infants with grade II HIE (Sarnat score)
- Second series showed that moderate or greater basal ganglia injury highly predictive of spastic quadriparetic CP or death

Neurological and perceptual-motor outcome at 5 - 6 years of age in children with neonatal encephalopathy: relationship with neonatal brain MRI.

- 68 infants with one minute Apgar <5 and neurological abnormalities during the first 48 hours
  - 22 % died in the neonatal period
  - 19 survivors (36 %) had cerebral palsy.
  - The remaining 34 were considered normal at 2 years of age but at 8 years
  - 15 % had minor neurological dysfunction and/or perceptual-motor difficulties
  - 1 (2 %) had only cognitive impairment
  - 25 (47 %) were normal.
  - 80 % of those with minor neurological dysfunction and/or perceptual-motor difficulties had mild/moderate basal ganglia or more marked white matter lesions.

Cortical highlighting in infants at day 7 following stage II HIE
Clinico-pathological correlate

**Parasagittal injury**

neonatal period – proximal axial weakness

later – mild cerebral palsy
- intellectual impairment
- visuospatial & language

Isolated Basal Ganglia Injury

Putamen & lat. thalamus
perirolandic areas

Fullterm infant (day 17) after perinatal asphyxia due to uterine rupture

Clinico-pathological correlate

Isolated basal ganglia injury

neonatal period – hypotonia

later – spastic quadriplegia, movement disorders
- relatively spared intellect and language
Encephaloclastic brain on MRI – T1 and T2 weighted images

Clinico-pathological correlate

Diffuse neuronal injury including basal ganglia
Neonatal period – seizures, hypotonia, hypertonia/dystonia
Later – mental retardation, spastic quadriparesis, seizures, Pseudobulbar palsy, blindness, sensorineural hearing loss

Establishing prognosis in the term infant

- Nature of the insult
- Timing of the insult
- What prognosis are we predicting?
  - %Long term outcomes evaluated at 2 years
- Why have we never combined tools in a systematic manner?
  - Early evaluation
    - Clinical risk factors – Apgar score, acidemia, systemic neurological examination, future – prenatal genetic and epigenetic markers
    - EEG features – background (aEEG or EEG) for moderate-severe injury; increase sensitivity with absence of sleep-wake cycling
  - Neuroimaging
    - Most accurate prognostic marker – accurately obtained and interpreted.
    - Concern over sensitivity for mild deep nuclear gray matter
    - Concern over the impact of hypothermia on the “visibility” of the injury on MRI
Establishing prognosis

Premature infant

Clinical Factors in Predicting Outcome in the Premature Infant

- Clinical risk factors
  - Gender, immaturity, prolonged ventilation, sepsis, necrotizing enterocolitis, surgical therapy for PDA,
- Neurobehavioral examinations
  - Hammersmith neonatal examination at term
  - NNNS
  - Preemie neuro
  - APIB
  - Amiel-Tison neurological examination
- Generalized movements

Normal neurological exam in newborn period reassuring – normal = normal
Preterm infants with abnormal neonatal exam may show recovery.
US + exam best predictor.

EEG/aEEG in the Premature Infant

- EEG
  - Maturational patterns are well described
  - Few systematic studies with follow up
- aEEG in the preterm infant
  - Increasing studies
  - Relationship of abnormalities to acute pathology – high grade IVH
  - Relationship of delay in maturation to disability
MRI will compliment Cranial Ultrasound

- Intraventricular hemorrhage
  - Post-hemorrhagic ventricular dilatation
    - Standardize measurements in the preterm infant with PHVD
      - Davies MW et al Arch Dis Child Fetal Neonatal Ed 2000;82(3):F218-23
  - Periventricular leukomalacia
    - Cystic versus Diffuse – superiority of MRI over CUS in diffuse PVL is clear in 4 independent studies

- Outcome
  - Mixed data related to outcomes – motor better than cognitive
  - CUS weekly to term: 62% of children at 2yrs with CP had abnormalities but in 29% of infants first detected after 28 days of life specificity of 95%, sensitivity of 76%
    - deVries LS et al Pediatr 2004;114(5):815-20
    - Wheater et al Dev Med Child Neurol 2000;42(8):364-7

Image interpretation

- Interpreting MRI’s of neonates, particularly of prematurely-born neonates, requires some degree of specialized knowledge.

- White matter injury and abnormalities of volume are more common than in other age groups.

Qualitative MR Imaging

- Defining the cerebral lesion
  - White matter lesions have been defined in upto 75% of preterm infants
    - T1 weighted scoring
    - T2 weighted scoring
    - Combined scoring of signal and structure
  - May differ in relation to the pathology and timing of the lesion
White matter abnormalities


Diffuse Excessive High Signal Intensity (DEHSI)


Scoring for MRI

MRI was scored for white matter disturbance with a score between 1-3 for each:
1. the presence of cysts,
2. white matter volume reduction,
3. periventricular WM signal abnormality,
4. ventricular size,
5. corpus callosal thinning.
What does the MR WM signal mean?

Deep White Matter Histopathology and Signal Abnormality Correlation

MRI Cerebral Abnormalities at Term Predict Neurodevelopmental in the Premature Infant
MRI WMI at Term Predicts Neurodevelopmental in the Premature Infant

<table>
<thead>
<tr>
<th>Extent of White Matter Abnormality</th>
<th>None (N=49)</th>
<th>Mild (N=78)</th>
<th>Mod. (N=26)</th>
<th>Severe (N=7)</th>
<th>F(X²)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>M (SD) MDI score</td>
<td>92.5 (15.7)</td>
<td>85.3 (14.2)</td>
<td>77.6 (17.2)</td>
<td>69.7 (25.2)</td>
<td>124.8</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>M (SD) PDI score</td>
<td>94.6 (13.6)</td>
<td>90.9 (11.0)</td>
<td>88.1 (17.5)</td>
<td>56.2 (25.4)</td>
<td>36.8</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>% Cognitive delay (&gt;2SD)</td>
<td>6.5</td>
<td>15.3</td>
<td>29.6</td>
<td>50.0</td>
<td>10.80</td>
<td>.008</td>
</tr>
<tr>
<td>% Motor delay (&gt;2SD)</td>
<td>4.3</td>
<td>4.7</td>
<td>25.9</td>
<td>66.7</td>
<td>32.3</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>% Cerebral palsy</td>
<td>2.0</td>
<td>6.0</td>
<td>24.1</td>
<td>66.7</td>
<td>25.7</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>


Summary on Preterm Infant

- Prognosis is best understood in terms of the timing and nature of the insult
- Combination of clinical, EEG and neuro-imaging is likely to yield best insight

Conclusion – Establishing Prognosis

- Nature and timing of the cerebral lesion
  - Term infant
  - Preterm infant
  - Complimentary information
  - Currently under studied in combining clinical and technological evaluations of the newborn brain
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