The Pros and Cons of Treating Electrographic Seizures in the Neonate

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Roadmap of the Presentation

• Search and “Seizures”: How common are they when sought?
  – Neonates
  – Children
  – Adults
• What is their significance?
  – Association/contribution to adverse outcome
  – Potentially treatable
• How are they detected and quantified?
• How effective are anti-seizure medications and EEG monitoring?
  – Phenobarbital: efficacy and safety
  – Design of possible future efficacy trial
• Summary

Routine Outpatient EEG

Children's Hospital of Fudan University, Shanghai, PRC
How common are EEG seizures in acutely ill neonates, children and adults?

- Frequency:
  - The incidence of clinical seizures in the general neonatal population is about 2-9 per 1000 live births.
  - In HIE, >50% have seizures!
  - Common in other high risk groups: newborn heart surgery (~11%) and ECMO (20-30%)
  - A similar problem is encountered in acutely ill children (PICU) and adults (MICU).

Long-term Video-EEG
After Newborn Heart Surgery

21 of 183 (11.5%) patients monitored between September 2001 and March 2003 demonstrated one or more EEG seizure.

*(Clancy et. al. Epilepsia 2005; 46: 84-90)*

Examples of EEG Seizures after NBHS

*(Cool Cap Trial: Gluckman Lancet 2005; 365:663)*
Subclinical Seizures in the PICU

Electroencephalographic Patterns in Unresponsive Pediatric Patients
Synd A. Benaim, MD, Gail E. Schramm, MD, and Erik J. Kollymann, MD, PhD

• 178 EEGs over 3 years (mean age 7.9 years; 66 (37%) < 1yr)
• NCSE in 58 (33%): 32 generalized and 26 partial by EEG
• No NCSE in the others, but abnormal background in 120 (67%)
• Note: 36% of those < 1 year had NCSE

(Pediatric Neurol 2005; 32: 162-165)
Robert Clancy, MD: Jan. 18, 2008: Pros & Cons of Treating Subclinical

Duration of EEG Examinations Needed to Detect Subclinical Seizures in the PICU

- Occasionally detected on initial, routine 30-minute EEG examination
- Most (80%) required at least 24 hours continuous EEG monitoring
- NCSz rarely began after several days of continuous EEG examination

(Arch Neurol 2006; 63:1750-1755)

Subclinical Seizures in the PICU

Nonconvulsive Seizures in the Pediatric Intensive Care Unit: Epidemiology, EEG, and Brain Imaging Findings

- Occasional case report, June 2000 to Dec 2003
- Study criteria: JMS, no overt Sz, EEG within 24 hrs of JMS
- 16.3% of 141 (23) subjects: non-convulsive status (NCS)
- 78.3% of the 23 with NCS had abnormal neuroimaging

Retrospective case review, June 2000 to Dec 2003
- 19 patients (1 mos to 17 yrs)
- Source of patients:
  - Convulsive SE → NCSE (#5)
  - Brief convulsion(s) → NCSE (#12)
The Same Issues Exist in Adults

Emergent EEG

Indications and diagnostic yield


- Emergency EEGs (performed within 1 hour of ordering)
- 261 (12.8%) of all requested EEGs over 52 mos
- Adults (mean ages ~54-55 yrs)
- Reason for study: MS (17.6%) or R/O status (60.2%)
- Sole predictor: cardiac arrest

(Varelas et al. Neurology 2003; 61: 702-4)

The Same Issues Exist in Adults

- Associated with development of epilepsy
  - Late seizures (LS) occur in 47% of patients with status
  - AS are independent predictor (OR 2.84) for development of LS
- Often subclinical
  - Paralytic or sedative agents
  - Concurrent medical illnesses
  - Underlying neurological deficit
  - Administration of AEDs

(Henssperger et al, Ann Neurol. 1998; 44:908-12)

What is the significance of EEG seizures? Do they contribute to poor outcome?

- 68 neonates met clinical criteria (e.g., birth asphyxia, meningitis etc.) for long-term EEG monitoring: 40 (59%) had ENS and 28 did not.
  - NB: This is a paradigm to select patients for long-term EEG monitoring
- Logistic regression showed that the presence of electrographic seizures significantly correlated with death and CP.

(McBride et al. Neurology, 2000)
What is the Significance of Seizure Frequency in the Neonate?
Is it worse with more seizures?

- 40 neonates with definite electrographic neonatal seizures NS followed for outcome (CP, MR, epilepsy, etc.).
- In the whole group, “global neurologic” outcome more favorable in those with fewer seizures (<2 NS/hr) than those with more (>2 NS/hr).
- In the subgroup with HIE, more CP in those with >5 NS/hr.

(Logido & Clancy Pediatrics, 1991)

Human Data: Seizures per se Are Significantly Associated with MRS Markers for Brain Injury

(Miller et. al.: Neurology 2002; 58:542)

Human Data Demonstrate that Seizures per se Are Independently Associated with Poor Outcome

- The Boston Circulatory Arrest Study examined the neurodevelopemental effects of cardiopulmonary bypass versus deep hypothermic circulatory arrest in a homogeneous CHD population (TGA) that was completely fixed with a single operation.
- All things being equal, those with post-operative seizures detected by 48 hrs of EEG monitoring had significantly worse early and late outcomes:
  - EEG seizures appeared in 25 of 126 (19.8%) infants and were associated with an 11.2 point drop on Bayley PDI scores @ 1 year.

(Bellinger et. al. NEJM 1995; 332:549)
Association of NCSE with Outcome (Children and Adults)

- Continuous EEG seizures in children, even in the absence of clinical signs, is associated with elevated markers for brain injury (neuron specific enolase).
- 36% adult mortality when NCSE diagnosed within 30 minutes of onset.
- 75% mortality when NCSE diagnosed beyond 24 hours of onset

Adverse Effects of Limited Seizures in Experimental Models

A Single Episode of Neonatal Seizures Permanently Alters Glutamatergic Synapses


Neonatal Seizures Cause Long-Term Changes in GABA_A Receptors

Brooks-Kayal, 2001
Seizures Accelerate Anoxia-Induced Neuronal Death in the Neonatal Rat Hippocampus

Vahidnejad Dzhala, MD, Tebaalal Ben-Ari, PhD, and Edouard Mesjoev, MD, PhD

- Seizures aggravate the hypoxic state by accelerating rapid anoxic depolarization in intact rat hippocampus.
- In the presence of hypoxia, the brain usually switches to an energy saving mode ("off") by blocking synaptic activity.
- Generation of seizures "breaks the law of neuronal silence".

(Dzhala et. al Ann Neurol 2000)

Significance of Recognizing Seizures:
They are potentially treatable....

How Are Seizures Diagnosed in the ICU?
A Substantial Percentage of Neonates Have Only Subclinical Electrographic Seizures:


207 infants enrolled at Baylor or CHOP with video-EEG Confirmed seizures
- Electroclinical szs: 50% (needs only one electroclinical seizure to be classified this way)
- EEG ONLY: 33% (all EEG seizures were subclinical)
- Clinical only: 10% (no EEG correlate)
- Other: 7%

(Mizrahi & Clancy, Epilepsia 2001)

Electrographic Seizures are Very Under-Recognized by Clinical Observation Alone

NCS="no clinical signs"; CS=definite clinical signs
393 electrographic seizures in 41 neonates

(Clancy, Legido & Lewis Epilepsia 1988; 29: 256)

A Substantial Percentage of Electrographic Seizures Are Subclinical in the Neonate

<table>
<thead>
<tr>
<th>93 Infants with CNS “Insults”</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 (32%) with overt clinical seizures</td>
</tr>
<tr>
<td>11 (12%) with “subtle” seizures</td>
</tr>
<tr>
<td>52 (56%) without clinical seizures</td>
</tr>
<tr>
<td>29 with definite EEG seizures</td>
</tr>
<tr>
<td>7 with definite EEG seizures</td>
</tr>
<tr>
<td>17 with suspected EEG seizures</td>
</tr>
<tr>
<td>0 with normal EEG</td>
</tr>
<tr>
<td>1 with normal EEG</td>
</tr>
<tr>
<td>7 with normal EEG</td>
</tr>
</tbody>
</table>

(Skany et. al, Pediatric Neurology 2006; 34: 194)
Uncoupling of Electroclinical Seizures

- The AED treatment of electroclinical seizures frequently *uncouples* the two: electrographic seizures persist despite the disappearance of the clinical seizures:
  - Connell et al.’s study of continuous EEG monitoring of electroclinical seizures in 31 infants treated with phenobarbital:
    - 2 had complete cessation of electroclinical seizures
    - 6 had incomplete reduction of electroclinical seizures
    - 13 (42%) had cessation of clinical seizures but continuation of EEG seizures (ie, electroclinical dissociation)
    - 10 had no change in either clinical or EEG seizures

  (Connell et al Arch Dis Child 1989; 64: 459)

The standard neonatal EEG montage

| FP1-T 3 | T3- O1 |
|FP2-T 4 | T4- O2 |
|FP1-C3 | C3-O1 |
|FP2-C4 | C4-O2 |
|T3- C3 | C3-CZ |
|CZ-C4 | C4-T4 |
|C3-C4 | |

75 uV 2 sec

CEEG → “raw” C3 → C4

Filter, rectify and time compress

aEEG (CFM)
Conventional LTM vs. CFM

- CEEG is the “gold standard” for seizure detection:
  - Exact number, duration and locations
- Recorded continuously but read intermittently
- Applied by technologists and interpreted by neurophysiologists
- Difficult to trend background
- $$$$

- CFMs such as aEEG relatively insensitive to seizures (but better than no EEG)
- Recorded continuously and read at bedside PRN
- Applied and read by bedside caregivers
- Simple compressed display of background over time
- $
Robert Clancy, MD: Jan. 18, 2008: Pros & Cons of Treating Subclinical Seizure Detection by Density Spectral Array (DSA)

Sensitivity of aEEG to Detect Electrographic Seizures

C3 → C4 simulates P3 → P4 for aEEG channel

### Quantitative Characteristics of Electrographic Seizures: CEEG vs C3→4

<table>
<thead>
<tr>
<th></th>
<th>Conventional EEG</th>
<th>Single Channel EEG (C3→C4)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Seizures Detected</strong></td>
<td>N=851 (100%)</td>
<td>N=664 (78%)</td>
<td></td>
</tr>
<tr>
<td>% of records with Szs</td>
<td>125/125 (100%)</td>
<td>118/125 (94%)</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Mean Seizure Duration (Seconds)</strong></td>
<td>132</td>
<td>100</td>
<td>P ≤ 0.001</td>
</tr>
<tr>
<td><strong>Mean Number of Seizures per Hour</strong></td>
<td>7.0 (0.5-21)</td>
<td>5.2 (0.18)</td>
<td>P &gt; 0.003</td>
</tr>
<tr>
<td><strong>Mean Ictal Peak-to-Peak Amplitude (µV)</strong></td>
<td>145</td>
<td>111</td>
<td>P ≤ 0.001</td>
</tr>
</tbody>
</table>

(Shellhaas & Clancy: Clin Neurophysiology 2007: 118:2156)
Robert Clancy, MD: Jan. 18, 2008: Pros & Cons of Treating Subclinical

C₃ Seizure Easily Seen in C₃→C₄

Seizure at Fp₁ Not Seen in C₃→C₄

Sensitivity of aEEG Detection of Electrographic Seizures

6 neonatologists reviewed the aEEG tracings derived from a single channel (C₃ → C₄) of 125 conventional neonatal EEGs containing a total of 851 individual seizures:

- 22% to 57% of the 125 records were correctly identified as “positive” for at least one electrographic seizure.
- 12% to 38% of the 851 seizures correctly identified.

(Shellhaas & Clancy: Pediatrics 2007: 120:771)
The odds ratio for the neonatologists' level of expertise compared the two most experienced aEEG interpreters' results with all others combined.

The odds ratios for EEG background compared abnormal backgrounds, by category, to records with normal backgrounds.

The odds ratios for seizure locations were calculated relative to occipital onset seizures (O1/O2).

**Risk Model for aEEG Detection of ENS**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure activity in C6a, C3a</td>
<td>2.41</td>
<td>1.05-5.50</td>
<td>0.04</td>
</tr>
<tr>
<td>Neonatal age (day of life)</td>
<td>2.11</td>
<td>1.67-2.66</td>
<td>0.01</td>
</tr>
<tr>
<td>Seizure start (s)</td>
<td>1.65</td>
<td>1.05-2.61</td>
<td>0.02</td>
</tr>
<tr>
<td>Seizure duration</td>
<td>1.10</td>
<td>1.00-1.10</td>
<td>0.08</td>
</tr>
<tr>
<td>EEG background (abnormal)</td>
<td>0.54</td>
<td>0.35-0.81</td>
<td>0.00</td>
</tr>
<tr>
<td>Waveform abnormality (abnormal)</td>
<td>0.55</td>
<td>0.44-0.69</td>
<td>0.00</td>
</tr>
<tr>
<td>Standard deviation (abnormal)</td>
<td>1.21</td>
<td>0.96-1.52</td>
<td>0.04</td>
</tr>
<tr>
<td>Natmed (abnormal)</td>
<td>0.50</td>
<td>0.35-0.69</td>
<td>0.00</td>
</tr>
<tr>
<td>Hyperventilation (Sv)</td>
<td>0.97</td>
<td>0.82-1.14</td>
<td>0.82</td>
</tr>
<tr>
<td>Seizure activity (abnormal)</td>
<td>0.50</td>
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<td>1.21</td>
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*The odds ratios for seizure locations were calculated relative to occipital onset seizures (O1/O2).

**Use of EEG Electrodes Across the Forehead**

Fp3 → Fp4 simulates “forehead” placement for single-channel EEG

**“Forehead Channel” Simulated by Fp3 → Fp4**

(Wusthoff: AES Presentation, Dec 2007)
Robert Clancy, MD: Jan. 18, 2008: Pros & Cons of Treating Subclinical CEEG

<table>
<thead>
<tr>
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<th>CEEG</th>
<th>C3ÆC4</th>
<th>Fp3ÆFp4</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (and %) EEG records with at least one seizure</td>
<td>126 (100%)</td>
<td>111 (96%)</td>
<td>92 (79%)</td>
<td>p=0.0001  p=0.0001  p=0.0001</td>
</tr>
<tr>
<td>Number of seizures detected</td>
<td>100 (80%)</td>
<td>92 (77%)</td>
<td>60 (54%)</td>
<td>p=0.0001  p=0.0001  p=0.0001</td>
</tr>
<tr>
<td>Mean seizure duration (seconds)</td>
<td>147 ± 228</td>
<td>121 ± 206</td>
<td>64 ± 192</td>
<td>p=0.001</td>
</tr>
<tr>
<td>Mean maximal p-p ictal amplitude (μV)</td>
<td>81.6 ± 74</td>
<td>90.0 ± 78</td>
<td>54.0 ± 44</td>
<td>p=0.14</td>
</tr>
</tbody>
</table>

(Wusthoff: AES Presentation, Dec 2007)

Does PB work? What is the value of EEG monitoring in the sick neonate? Do monitoring and successful treatment of EEG seizures improve outcome?

- Current data inadequate to decide if PB is truly efficacious
- Essentially NO data addresses the results of treatment versus no treatment (ethics)
- Is there an alternative way to show PB efficacy other than conventional RCT?
- How to integrate treatment trial in current era of hypothermia
How Do We Judge the Effectiveness of Anti-Seizure Medications Such as Phenobarbital?

<table>
<thead>
<tr>
<th>Desired Pharmacologic Properties Of Anti-Seizure Medications</th>
<th>Full EEG Monitoring Parameters to Measure the Pharmacologic Effects of Meds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevent seizure initiation</td>
<td>Reduced seizure counts (target = 0 seizure count)</td>
</tr>
<tr>
<td>Reduce “temporal” duration of seizures</td>
<td>Briefer seizure durations (target = 0 seizure duration)</td>
</tr>
<tr>
<td>Reduce “spatial” spread of seizures</td>
<td>Fewer brain regions involved with seizures (target = 0 regions affected)</td>
</tr>
</tbody>
</table>

Correlation Between Seizure Frequency and Seizure Burden
(#Szs/hr vs. % of time with seizures in any brain region)

Spearman correlation = 0.58

(Shellhaas & Clancy: Clin Neurophysiology 2007; 118:2156)

Parameters to Measure the “Spatial” Spread of Electrographic Seizures

(Clancy: Clin Perinatology 2006; 33:649)
Hypothetical Depiction of Distributions of EEG Seizures and PB Administration after NBHS in 3 Neonates:
Disease Progression Model

Disease Progression Modeling Example

Disease Progression Modeling Example
Summary

- Subclinical seizures and subclinical status are common in all ICU populations (neonates, children & adults) and likely contribute to ultimate outcome.
- The youngest are especially “at risk”.
- They may or may not be preceded by a known or witnessed history of seizures.
- Routine 30 minute EEGs are often inadequate to detect their presence.
- Efficacy and safety of PB has still not been demonstrated.
- Impact of EEG monitoring on mortality and long-term morbidity remains to be determined.

Special Thanks to my CHOP Colleagues!

Bill Gaynor
Gil Wernovsky
Susan Nicolson
Tom Spray
Rick Ittenbach
Bob Zimmerman
Dan Licht
Becky Ichord
Dennis Dlugos
Renee Shellhaas
Nick Abend
Courtney Wusthoff