Disclosures, relevant

- I bill for continuous EEG monitoring (about 25% of my clinical billing)
- I co-authored the Atlas of EEG in Critical Care (Hirsch and Brenner)
- I borrowed some slides from the Critical Care EEG Monitoring Consortium and Yale colleagues
  - Suzette Laroche, Nicholas Abend, Tammy Tsuchida, Sue Herman, Nicolas Gaspard, Brandon Westover, Suzette Laroche, Andres Rodriguez, Nicolas Gaspard, Emily Gilmore, Gamal Osman, Carolina Maciel, Nishi Rampal
Disclosures, unrelated

- Consultant
  - Upsher-Smith; Marinus; Monteris; Sunovion; Ceribell, Engage
- Research Support
  - Upsher-Smith; Eisai
- Honoraria for speaking
  - Neuropace
- Royalties
  - UpToDate; Medlink; Wiley
NONCONVULSIVE SEIZURES: Prevalence in critically ill adults w/ primary neuro diagnosis

% of patients with NCSz

% of patients whose seizures were exclusively nonconvulsive

Courtesy of Gaspard N and Gilmore E
Most ICU patients (~75%) have exclusively nonconvulsive seizures.
Nonconvulsive seizures: sample cases

GAMALELDIN OSMAN, MD
NISHI RAMPAL, MD
LAWRENCE J. HIRSCH, MD
Case 1

- 69-year-old man s/p heart transplant in 2010, now presenting with left-sided subdural hematoma, s/p evacuation 4 days ago (April 2016), 1 spell of shaking postoperatively that resolved after 2 mg lorazepam
- Now stuporous, trouble weaning off ventilator
Full EEG of spell during video
2 hours of Q EEG (~3 szs/hr)
4 hours of QEEG before and after increase in lacosamide (already on levetiracetam)
Case 1, after treatment

- After seizures treated, became much more alert, more oriented, extubated the next day
Case 2

46 y.o. woman w/ LMCA infarct in 2008 with residual hemiparesis and mild aphasia

Recently, husband noted episodes where she would look to the R and had shaking in her left arm. She was treated with levetiracetam and those spells stopped. Now (4/2016) presents confused and more aphasic with a GI illness.
Case 2: full EEG of nonconvulsive seizure during video
2 hours of QEEG (about 15 szs/hr)
2 hours of QEEG, before and after IV phenytoin load

1560mg IV PHT load given
Case 2, followup after treatment

- Returned to recent baseline.
- Remained on levetiracetam and phenytoin.
Case 3

- 77yo man with CNS large B cell lymphoma and pancreatic cancer, s/p right craniotomy for resection, presents with progressive L>R weakness and numbness over several days, taken to OR for evacuation of epidural, subdural empyema and debridement of craniotomy.

- Now stuporous postoperatively
Case 3: full EEG of nonconvulsive sz during video
2 hours of Q EEG
Case 3, followup

- Seizure hard to eliminate, required lacosamide, levetiracetam, phenytoin, valproate, intermittent lorazepam and eventually clobazam added.
- Seizures decreased from 16/hour to 1 every 4 hours (6/day).
- Care eventually withdrawn
83, grade I SAH and aneurysm clipping. No clinical seizures. “Because of persistent altered mental status and difficulty speaking, cEEG was started “. EEG
"25 month old F with developmental delay, intractable epilepsy, admitted for increased seizure frequency. Pt now lethargic, most likely from Ativan given in ED" -- EEG
73, astrocytoma resection, csf leak, meningitis, rare clinical seizures.

EEG 1 of 2
73, astrocytoma resection, CSF leak, meningitis, rare clinical seizures.

EEG 2 of 2
Risk factors for nonconvulsive seizures and NCSE

- Husain et al JNNP 2003
  - Severely impaired mental status
  - Oculomotor abnormalities
    - Nystagmus, sustained eye deviation, or hippus
  - Remote risk factors for epilepsy
- Schmitt SE, J Clin Nphys 2017
  - Facial/periorbital twitching (15/19 [79%] had seizures; much higher than all other clin spells/movements, n=154 patients)
- Claassen et al Neurology 2004: 570 consecutive patients undergoing continuous EEG monitoring
  - 110 (19%) with seizures
Independent predictors of CEEG-documented seizures

1. **Coma** on neuro exam at start of CEEG
   
   56% of 97 comatose patients vs. 12% of 473 other.

2. **Age < 18 years**
   
   36% of 75 patients <18 y.o. vs. 17% of 495 pts > 18.

3. **Past medical history of epilepsy**
   
   41% of 68 patients w/ PMH epil vs. 16% of 502 w/out.

4. **Clinical seizures** prior to monitoring
   
   43% of 134 patients with vs. 12% of 436 w/out.

5. Periodic discharges (PLEDs or GPEDs) or Suppression-burst
   
   Claassen 2004
• 3 centers, CCEMRC database (Emory, Brigham and Women, Yale): 5427 cEEG sessions over 3 years
• Used machine learning method (RiskSLIM), cross-validated
• 2HELPS2B model had AUC of 0.82
• Scale [0-7]: BIRDS (2 points); LPDs, LRDA, or BIPDs (1); prior sz (1); sporadic EDs (1); freq >2 Hz for any periodic or rhythmic pattern (1); “plus” features (1).
Table 2. Optimized Risk Score for Seizure Probability

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Probable risk of Sz, %</td>
<td>5</td>
</tr>
<tr>
<td>Actual prevalence of Sz, % (95% CI)</td>
<td>3 (2-3)</td>
</tr>
</tbody>
</table>
Time to record the first seizure comparing non-comatose and comatose patients.

Claassen 2004
How long should patients be monitored?

- 24 hours if not comatose
- 48 hours or more if comatose
  - Longer if periodic discharges, withdrawing sedation or AEDs
- Routine EEG is not adequate in critically ill patients
• 665 consecutive cEEG cases; 72 hour window
• Clinical predictors of szs:
  – Coma (31% had seizures; OR 1.8, p<0.01)
  – Prior szs at any point (34% had seizures, OR 3.0, p<0.001)
Time-dependent risk of szs on cEEG
Struck A et al, Annals of Neurol 2017

• If no epileptiform findings on EEG, risk of szs within 72h was 9% if neither clin risk factor present, vs 36% if both clin risk factors present (coma and prior sz).
• If epileptiform discharges found, risk jumped up to between 18% (if no clin risk factors) and 64% (coma and prior sz)
• If no ED’s developed, risk dropped below 5% between 0.4 hours (no clin risk factors) and 16 h (coma and prior sz)
## Time-dependent risk of szs on cEEG


<table>
<thead>
<tr>
<th></th>
<th>Risk at entry based on clin factors</th>
<th>Time without szs required til risk drops below 5%, if NO epileptiform findings*</th>
<th>Time without szs required til risk drops below 5%, if epileptiform findings* seen</th>
</tr>
</thead>
<tbody>
<tr>
<td>No coma</td>
<td>9%</td>
<td>0.4 hours</td>
<td>14.4 hours</td>
</tr>
<tr>
<td>No sz</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No coma</td>
<td>30%</td>
<td>12.7 hours</td>
<td>21.7 hours</td>
</tr>
<tr>
<td>Prior sz</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coma</td>
<td>13%</td>
<td>1.2 hours</td>
<td>16.7 hours</td>
</tr>
<tr>
<td>No prior sz</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coma AND Prior sz</td>
<td>36%</td>
<td>16.4 hours</td>
<td>44.2 hours</td>
</tr>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

*LPDs, BIRDs, LRDA, BIPDs or sporadic EDs*
Why do we care about nonconvulsice seizures?
Adverse physiologic effects of nonconvulsive seizures

- Increased CBF and ICP
- Increased lactate
- Increased glutamate (6 fold)
- Increased glycerol (membrane breakdown)
- Increased neuron specific enolase
- Increased edema/mass effect on serial scans
- Increased peri-injury depolarizations
Midline Shift after Intracranial Hemorrhage, w/ and w/out Nonconv Seizures

NSzs also assoc’d w/ worse NIHSS scores and trend towards worse outcome
“Nonconvulsive electrographic seizures after TBI result in a delayed, prolonged increase in ICP and metabolic crisis”

<table>
<thead>
<tr>
<th></th>
<th>ICP (mm Hg)</th>
<th>LPR</th>
<th>Glutamate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inter-ictal mean</td>
<td>9.6 +/-5</td>
<td>23.8</td>
<td>2.6</td>
</tr>
<tr>
<td>Ictal mean</td>
<td>22.4 +/-7</td>
<td>49.4</td>
<td>13.1</td>
</tr>
<tr>
<td>p</td>
<td>p&lt;.002</td>
<td>p&lt;.02</td>
<td>p&lt;.001</td>
</tr>
</tbody>
</table>
“Nonconvulsive seizures after traumatic brain injury are associated with hippocampal atrophy”

• 6 TBI patients with seizures had greater hippocampal atrophy as compared to 10 matched TBI patients without seizures (21 +/- 9 vs 12 +/- 6%, p = 0.017).

• Hippocampi ipsilateral to the electrographic seizure focus demonstrated a greater degree of volumetric atrophy as compared with nonseizure hippocampi (28 +/- 5 vs 13 +/- 9%, p = 0.007)

Vespa PM et al, Neurology 2010
Metabolic crisis occurs with seizures and periodic discharges after brain trauma
Vespa P et al, Ann Neurol 2016 (UCLA, Columbia)

• Prospective, 2 center study of 34 TBI patients undergoing invasive monitoring including intracortical depth EEG
  – 20 had simultaneous depth EEG and mdialysis
• Seizures or periodic discharges (PDs) were seen in 62% of patients
  – Seizures seen in 8/34 (24%)
  – PDs w/out seizures seen in 13/34 (38%)
• 43% of the seizures or PDs were noted on intracortical depth EEG only (not on scalp)
Metabolic crisis occurs with seizures and periodic discharges after brain trauma, CONT’D
Vespa P et al, Ann Neurol 2016 (UCLA, Columbia)

• Patients were on prophylactic phenytoin or levetiracetam, plus midazolam for sedation (2-6 mg/hr)
• Metabolic crisis defined as elevated lactate:pyruvate ratio (LPR) and decreased extracellular glucose
• Single mini-depth w/ 6 contacts
  – Pericontusional in 13 patients
• Hourly microdialysis samples
Metabolic crisis occurs with seizures and periodic discharges after brain trauma, CONT’D
Vespa P et al, Ann Neurol 2016 (UCLA, Columbia)

- Microdialysis results:
  - During szs or PDs (within patient analysis):
    - Microdialysis glucose was lower (0.8 vs 1.7, p<0.001)
    - Lactate/pyruvate ratio was higher (38 vs 29, p<0.001)
  - Noted in normal-appearing tissue
  - Findings just as pronounced with PDs as with seizures

- Safety:
  - No signif hemorrhages or CNS infections
  - No evidence of injury on later MRI (6 months, done in 20/34 subjects)
• 90 comatose SAH patients
• Invasive multimodality monitoring including depth electrode in most
• 36% had PDs on depth and scalp EEG, 23% on depth only
• 31% had seizures, but 2/3 of these were only visible on depth, not scalp
• RESULTS:
• Increasing frequency (from 0.5 Hz to 3.0 Hz) was assoc’d with increasing CBF, but dropping tissue oxygen, reaching hypoxic levels when PDs >2.0 Hz.
• Drop in tissue oxygen correlated with time of PDs
Electroencephalographic Periodic Discharges and Frequency-Dependent Brain Tissue Hypoxia in Acute Brain Injury

Seizures Not Excluded

A Partial pressure of oxygen in interstitial brain tissue

![Box plot with frequency vs. partial pressure of oxygen in interstitial brain tissue](image)
Figure 3. Partial Pressure of Oxygen in Interstitial Brain Tissue (Pbto$_2$) at the Onset of High-Frequency Periodic Discharges (PDs)

Includes 27 episodes in 8 patients. Relative Pbto$_2$ is normalized to maximum. Line indicates median; whiskers, SDs.

$^a$ Indicates significant differences of respective time points compared with Pbto$_2$ at 5 to 10 minutes before high-frequency (>1.5 Hz) PD onset revealed by bootstrapping (500 repetitions).
• CONCLUSIONS

• On average, in comatose SAH patients, the brain can compensate for increased metab demand via increasing CBF up to about 2 Hz, but not faster than that.
Electrographic SE and long-term outcome in critically ill children
Wagenman KL, ..., Abend N. Neurology 2014

- Long term follow-up of 137 children who were developmentally normal prior to admission to the PICU
- 23% had NCSE
- On multivariate analysis, electrographic SE was assoc’d with:
  - Worse functional outcome (on pediatric extended GOS; odds ratio 6.4)
  - Lower QOL (23 points lower; p = 0.001)
  - New-onset epilepsy (47% vs 11%; O.R. 13.3, p = 0.002)
Seizure burden is independently associated with short-term outcome in critically ill children
Payne ET, … Hahn C. Brain 2014

- N=259 PICU patients undergoing CEEG
- Outcome: neurological decline (on Peds Cerebral performance Category score, PCPC)
- Seizures in 36%
- Neurological decline in 67%
- If seizure burden was >20%, marked rise of chance and severity of neurological decline (but not mortality)
Seizure burden > 12 min per hour (20% seizure burden) associated with increased probability and magnitude of neurological decline across all diagnostic categories.

<table>
<thead>
<tr>
<th>Increase in maximum hourly seizure burden</th>
<th>Odds Ratio for PCPC Worsening</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>1.13</td>
<td>1.05-1.21</td>
</tr>
<tr>
<td>5%</td>
<td>1.82</td>
<td>1.25-2.63</td>
</tr>
<tr>
<td>10%</td>
<td>3.29</td>
<td>1.57-6.89</td>
</tr>
<tr>
<td>20%</td>
<td>10.8</td>
<td>2.48-47.5</td>
</tr>
<tr>
<td>30%</td>
<td>35.7</td>
<td>3.90-327.6</td>
</tr>
<tr>
<td>50%</td>
<td>387.4</td>
<td>9.64-&gt;999.9</td>
</tr>
</tbody>
</table>
Seizure burden in SAH associated with functional and cognitive outcome
De Marchis GM et al, Neurology 2016 (Columbia U.)

- 402 consecutive adult patients with SAH undergoing continuous EEG from 1996-2013
  - Median duration of CEEG: 96 hours
- Seizures in 50 patients (12%)
  - 46/50 were in NCSE
  - All seizures were nonconvulsive
  - Median seizure burden was 6 hours
Seizure burden in SAH associated with functional and cognitive outcome, cont’d
De Marchis GM et al, Neurology 2016 (Columbia U.)

• At 3 months, on multivariate analysis, seizure burden was assoc’d with 3 months disability, mortality, and cognition (as measured by TICS)

• Functional outcome:
  – Detection of any seizure was assoc’d with a 3-fold increase of unfavorable outcome (O.R. 3.67, p=0.01)
  – If NCSE, even higher (O.R. 4.84, p=0.007)
  – Every hour of nonconvulsive seizure was assoc’d with a 10% higher odds of disability or death at 3 months
Cognitive outcome at 3 months:
  – On multivariate analysis (correcting for age, Hunt-Hess, year of inclusion, etc), seizure burden (but not presence of any sz) was assoc’d with TICS score (telephone interview for cognitive status)
  – For every hour of seizure, there was a small but significant decline in TICS score (p=0.01)
Seizure burden in SAH associated with functional and cognitive outcome, cont’d

De Marchis GM et al, Neurology 2016 (Columbia U.)
“Hold still, Carl! ... Don’t ... move ... an ... inch!”
American Clinical Neurophysiology Society’s Standardized Critical Care EEG Terminology

J Clin Nphys, 2013

Most slides from the official CCEMRC Training Module (acns.org)

Lawrence Hirsch, Nicolas Gaspard, Brandon Westover, Suzette Laroche
Main Terms for Rhythmic and Periodic patterns

- Describe with main term # 1 followed by #2, with modifiers added as appropriate.

<table>
<thead>
<tr>
<th>Main term #1</th>
<th>Main term #2</th>
</tr>
</thead>
<tbody>
<tr>
<td>(G) Generalized</td>
<td>(PDs) Periodic Discharges</td>
</tr>
<tr>
<td>(L) Lateralized</td>
<td>(RDA) Rhythmic Delta Activity</td>
</tr>
<tr>
<td>(BI) Bilateral Independent</td>
<td>(SW) (Poly)Spike-&amp;-Wave/Sharp-</td>
</tr>
<tr>
<td>(Mf) Multifocal</td>
<td>and-Wave</td>
</tr>
</tbody>
</table>
“Similarity of Lateralized Rhythmic Delta to PLEDs in Critically Ill Patients”
Gaspard N et al, JAMA Neurol 2013

- LRDA seen in 5% of patients and independently predicted seizures:
  - 63% had seizures during the acute illness
    - vs 57% with PLEDs and 20% in controls
    - >80% of seizures were nonconvulsive
Risk of acute seizures with LRDA vs LPDs
Gaspard N et al, JAMA Neurology 2013

EEG Findings During Entire Recording

- All seizures
- Seizures during CEEG

Incidence of Acute Seizures, %

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of subjects</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>241</td>
<td>19%</td>
</tr>
<tr>
<td>Focal Slowing Only</td>
<td>105</td>
<td>63%</td>
</tr>
<tr>
<td>LRDA</td>
<td>27</td>
<td>63%</td>
</tr>
<tr>
<td>LPDs</td>
<td>49</td>
<td>57%</td>
</tr>
</tbody>
</table>
Risk of acute seizures with LRDA vs LPDs

Gaspard N et al, JAMA Neurology 2013