The ictal interictal continuum

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Case history

• CC: 69 yo Woman p/w unresponsiveness
• PMHx: SAH s/p right MCA clipping 17 yrs prior to admission, LRE, HTN
• OSH ER: BP 210/11, HR 80, NIHSS 21, no commands, R eye did not doll, L did not cross midline, left hemiparesis
• Transferred for possible ia-tPA
• NICU: on arrival 2\textsuperscript{nd} GTC seizure, CTA normal, LP unremarkable
• Convulsions stopped with LRZ 6 mg fDPH 1.5 gm but remained comatose
Emergent cEEG

Loaded with Valproic Acid 30 mg/kg

EEG post clinically successfully treated GCSE
- 20 - 48% electrographic seizures
- 14% NCSE
- Most without any clinical signs

• Seizures stopped but cEEG showed PLEDs plus: periodic discharges with superimposed rhythmic slowing
• No change in mental status
Neuronal damage from ictal-interictal patterns?

Chong & Hirsch, 2005

PLEDs plus: periodic discharges with superimposed rhythmic slowing

The Ictal-Interictal-Injury Continuum
Are PEDs ictal?

Pro

- **Reversible confusional** state akin to NCSE during PLEDs in the elderly Terzano 1986
- **Glc metabolism:** local increase during PLEDs similar to seizure pattern on FDG-PET Handforth 1994
- **CBF:** increase during PLEDs on SPECT, reversed with successful treatment Assal 2001; Bozkurt 2002
- **EPC** (focal motor status epilepticus) may occur with PLEDs Snodgrass 1989, Baykan 2000, Kuroiwa 1980

Contra

- May have benign clinical courses with longstanding PEDs
- Chronic PLEDs Westmoreland 1986 or BIPLEDs Fushimi 2003
Ictal-interictal continuum and focal nonconvulsive seizures: Patient with encephalitis and RSE

Irregular 2 Hz generalized periodic discharges superimposed on diffuse rhythmic 2 Hz delta activity.
“GPDs-plus” = ictal-interictal continuum
Ictal-interictal continuum and focal nonconvulsive seizures: Patient with encephalitis and RSE

Irregular 2 Hz generalized periodic discharges superimposed on diffuse rhythmic 2 Hz delta activity. “GPDs-plus” = ictal-interictal continuum
What do PEDs mean?
Controversial if PEDs ictal but definitely predictors of electrographic seizures

Predictors of electrographic seizures:
• Coma on exam: 56% of comatose pts vs. 12%
• Young age: 36% of pts <18 yo vs. 17% of pts > 18.
• Epilepsy in the past medical history: 41% vs. 16%, or remote risk factors for szs
• Convulsive seizures prior to monitoring: 43% of pts with vs. 12%
• Periodic discharges (PLEDs or GPEDs) or Suppression-burst
• Oculomotor abnl’s: nystag, hippus or eye deviation
• Cardiac or respiratory arrest
• Sepsis


Incidence of seizures in the acute setting of PLEDs
58% to 100% Pohlmann-Eden et al., 1996
PEDs and seizures

<table>
<thead>
<tr>
<th>Findings</th>
<th>Seizures on cEEG monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes, n = 110</td>
</tr>
<tr>
<td><strong>Periodic epileptiform findings</strong></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>49 (45)</td>
</tr>
<tr>
<td>PLED</td>
<td>44 (40)</td>
</tr>
<tr>
<td>GPED</td>
<td>19 (17)</td>
</tr>
<tr>
<td>BiPLED</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Triphasic waves</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Frontal intermittent rhythmic delta activity</td>
<td>11 (10)</td>
</tr>
<tr>
<td>Suppression burst</td>
<td>35 (32)</td>
</tr>
</tbody>
</table>

Claassen, Neurology 2004
PLEDs plus: periodic discharges with superimposed rhythmic slowing

Technetium-99m-HMAPO SPECT: R TL increased blood flow
Ictal 99mHMPAO SPECT:
Prolonged focal SE that progressed to PLEDs

SPECT during and after PLEDs in alcoholic patient post GTC seizure

Donaire JNNP 2006

Assal 2001
• Levetiracetam 1000 mg BID
• AED serum levels: VPA 114 ug/ml, DPH 14 ug/ml, free DPH 3.1 ug/ml

EEG: isolated epileptiform discharges

Mental status improved slowly, discharged to subacute rehab 2 wks after presentation on DPH, VPA, and LEV
Done!

Successful rehabilitation: she was tapered off all AEDs for a secondary cognitive deterioration and returned to her neurological baseline

Happy ending, but …
• One month later presented to OSH with recurrent CPSE
• Restarted DPH, LEV, VPA but unresponsive

Midazolam load of 14 mg and drip up to 0.4 mg/kg/hr
PLEDs plus: with superimposed rhythmic slowing and fast activity

EEG on midazolam gtt
MRI during the ictal interictal continuum: restricted diffusion, increased CBF & CBV, decreased mean transit time (MTT)

- DWI: restricted diffusion R TL
- ADC: minimal changes

- MDZ gtt ↑ 1 mg/kg/hr
- VPA ↑
  (goal level 80-100 ug/ml)
Imaging ictal patterns

Decrease ADC/increased DWI after CPSE & seizures
- Hippocampal formation
- Cortical areas adjacent to the primary pathology
- Posterior part/pulvinar of the thalamus

**MR perfusion**: increased perfusion in region of decreased diffusion Szabo 2005

Lansberg ‘99

Initial DWI shows diffuse, gyriform cortical hyperintensities

5 months later diffuse low signal intensities

ASL

Detre 1996
Wean off MDZ without recurrent seizures. PLEDs persisted for almost 2 wks.
MRI during the ictal interictal continuum: almost complete resolution of the previously noted changes
Benzodiazepine Trial for the Diagnosis of Non-Convulsive Status Epilepticus.

**Monitoring:** EEG, pulse ox, BP, ECG, respiratory rate, with dedicated nurse.

**Antiepileptic Drug Trial:**
- Sequential small doses of rapidly-acting short-duration benzodiazepine such as midazolam at 1mg/dose.
- Between doses, repeated clinical and EEG assessment.
- Trial is stopped after any of the following:
  - Persistent resolution of the EEG pattern (and exam repeated)
  - Definite clinical improvement
  - Respiratory depression, hypotension, or other adverse effect
  - A maximum dose is reached (such as 0.2 mg/kg midazolam, though higher may be needed if on chronic benzodiazepines)

- Test is considered positive if there is resolution of the potentially ictal EEG pattern AND either an improvement in the clinical state or the appearance of previously-absent normal EEG patterns (eg. posterior dominant “alpha” rhythm). If EEG improves but patient does not, the result is equivocal.
• Due to thrombocytopenia VPA stopped
• Recurrence of NCSE -> Phenobarbital started
• Neuro: encephalopathic
• While weaning phenobarbital started on LTG

• Left > right facial twitching developed with PLEDs proper
• Benzodiazepine trial: 1 mg midazolam repeated doses of (total of 4 mg) -> facial twitching resolved and PLEDs gone but otherwise no neuro improvement = Equivocal

• Serial NSE levels throughout hospital course did not correlate with EEG activity
FDG-PET: decreased metabolism in the right temporal lobe

Phenobarbital discontinued.
Discharged to NH 1 month after admission on TPM, DPH, and LEV
Outcome: 2 months after discharge

• continuing to improve in an active rehabilitation program
• Interactive
• able to recognize family members
• moves all four extremities
• mobilized to a chair
• undergoing ventilator weaning
Criteria for Nonconvulsive Seizure

Any pattern lasting $\geq 10$ secs satisfying any one of these 3 primary criteria:

**Primary Criteria:**
1. Repetitive generalized or focal spikes, sharp-waves, spike-and-wave or sharp-and-slow wave complexes at $\geq 3/$sec
2. Repetitive generalized or focal spikes, sharp waves, spike-and-wave or sharp-and-slow wave complexes at $<3/$sec and secondary criterion
3. Sequential rhythmic, periodic, or quasi-periodic waves at $\geq 1/$sec and unequivocal **evolution in frequency** (gradually increasing or decreasing by at least 1/sec, e.g. from 2 to 3/sec), **morphology, or location** (gradual spread into or out of a region involving at least 2 electrodes).
   - Evolution in amplitude alone not sufficient
   - Change in sharpness without other change in morphology not adequate

**Secondary criterion:** After administration of a rapidly-acting AED:
- Significant **improvement in clinical state** or
- appearance of previously-absent **normal EEG patterns** (such as a posterior dominant rhythm)
- Not satisfactory: resolution of the “epileptiform” discharges leaving diffuse slowing without clinical improvement and without appearance of previously-absent normal EEG patterns

Chong et al, 2005 modification of Young et al 1996
Strategies to support treatment decisions for patients in the ictal-interictal continuum: determine similarities to seizures

1. EEG signature:
   - Classify into PLEDs plus (low amplitude rhythmic discharge) and PLEDs proper (Reiher 91)

2. Physiologic measurements
   - Benzodiazepine trial
   - CBF and CBV (SPECT, CT perfusion, MR perfusion imaging, arterial spin labeling)
   - Cerebral metabolism (PET scanning)
   - Multimodality monitoring (PbtO2, hemodex for CBF, microdialysis for glutamate and GABA)

3. Quantify neuronal injury
   - Imaging studies (ADC, MR spectroscopy)
   - Serum markers (neuron specific enolase)
   - Microdialysis endpoints (LPR, glycerol)
Practical approach to patients with PEDs:

1. **Investigate the cause**: this may be guided by specific PED pattern (history, MRI, CSF, angio, brain biopsy)

2. Conventional **AED prophylaxis** for seizures:
   Levetiracetam (alternatives: oxcarbazepine, CBZ, DPH, VPA, TPM, GBP); at this point should not use cIV AEDs for PEDs without seizures

3. May do **benzo trial** to determine ictal nature

4. **Continue cEEG monitoring** for potential nonconvulsive seizures or status epilepticus.

5. **Long-term treatment**: individualize based on other EEG findings (e.g. epileptiform discharges) and underlying brain injury
   - Acute PLEDs that resolved without seizures -> taper AEDs/one month after acute illness.
   - Acute PLEDs with seizures: AED treatment for 3-12 months
   - Consider DPH, phenobarbital, and benzos may adversely affect motor recovery after stroke (Camilo and Goldstein, 2004).
SIRPIDs: Stimulus-Induced Rhythmic, Periodic or Ictal Discharges

Prevalence: 22% (33/150) consecutive cEEG patients

Hirsch Epilepsia 2004 and 2007
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