



College of Physicians and Surgeons

The ictal interictal continuum

Jan Claassen, MD, PhD Division of Critical Care Neurology Columbia University College of Physicians & Surgeons New York, NY 10032

<u>Disclosures</u>: <u>Research Support</u>: Columbia University Clinical Translational Science Award (CTSA), Irving Institute for Clinical and Translational Research

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 2nd 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 DeLorenzo Epil 1998, Treiman NEJM 1998

Seizures stopped but cEEG showed PLEDs plus: periodic discharges with superimposed rhythmic slowing No change in mental status

🚯 Type EEG 🕑 LFF 1 Hz 👽 HFF 70 Hz 👽 Notch Off 👽 Sensitivity 7 uV/mm 💌 Timebase 30 mm/sec 👽 🤹

 $\begin{array}{c} Fg2 - Fa - (1) +$

 Fp1 - F7
 F7 - 17

 F7 - 17
 F7 - 17

 F7 - 17
 F7

 <tr



Neuronal damage from ictal-interictal patterns?

Chong & Hirsch, 2005

PLEDs plus: periodic discharges with superimposed rhythmic slowing



Are PEDs ictal?

<u>Pro</u>

- 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

<u>Contra</u>

- 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

15 fysike (EEG 🗴 LEF 1Ha 🗴 HEF 70Ha 🗴 Match 011 🔺 Sorability /7 U/Innn 💌 Timobase 30 mm/sec 💌 🖉
a and a superior of the second and t
103-103-103-10-10-10-10-10-10-10-10-10-10-10-10-10-
ba on the many way was a set of the set of t
as i converte a for the for th
a commenter of the second of t
a a more some and a second and a second seco
al and a free to be a stand of the stand of
v. on the second s
a manual and
a man provide marker as bridged up a land added to be bridged mark with a drive the advant
a part has a contract of a con
cz. com where the second of th
con econ many which we want where the second where the second where the second where the second seco

Irregular 2 Hz generalized periodic discharges superimposed on diffuse rhythmic 2 Hz delta activity. "GPDs-plus" = ictal-interictal continuum

NCSZ from left posterior

e. e. where we have a second where the s

NCSZ from right temporal

1.0			-		- Paid						ALC: N								
Fp1-1		m	m	Mary Mary	m	m	MMX	ww	X	NW	with	m	ww	the	m	Vin	J.m.	yha	hat
C3 - P	31	man	min	when	num	man	min	Maria	mon	in Any	man	m	MM	MM	Amour	Van	- Annal	1 mm	Manin
	1~		1		and and and a second second			A	n			M	0	n.	n A	View	11	P	100000
P3 - 0 Fp2 - 1 F4 - C	N and		m	- Marina	And And	Mar	MM		~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	NM NM	my		- Av	Mm	ANN MAN		Mar Mar	And	have
	s lo	1			0.1	AWW	. 1	- N.V.			U	1	in Ver	1.1	N V N	1 1	-	· · · · ·	A
P4 - 0	2V	m	m.		www.	nnm	MMA		m	A	my	ma	v w m	my -	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	1.0A	my m	1 and	Amaly
1	TAC	1 al	- m	W	AAA	~~~~~	111100	N V	w	8	m M	V YY	* Mrs	mow 1	W.W.	VIW	Jum i	AV W	A
Ê7 - T	A.	mi	mas	man	inno	win	MILN	ANT	m	5 Ac	my	my	mind	NA	Mar	Mun	man	1 my	man
	r	W	A	- A A	A	1.V	mali			1	1.	·	V V	N-	. 1 1 . /	LAA A	01	1	Sand m
17 - P	n	1. Mr	www	a way	mar.	-vvum	1 A Mara	he crafter	1-0-1	www	Acres	- min	mon	Mar	Max	home	w w	Marmy	1 martin
P7 - 0	11	man	non	vin	mon	mm	man	man	in	no	2 mil	more	nom	(mh	mm	IAAS	man	Uma	Yam m
Fp2 - 1 F8 - 11 T8 - P P8 - 0	E A A A A A A A A A A A A A A A A A A A		N			MA				And May	WWW WWW						- PAG		hate
~~	1	100.000		ma m	A. An	AA	Do A	A A A	0.00	m	ml	A .	Λ.	AN.	. A mil	h A.A		A	and m
FZ - C	Z.	1 mm	m	where we are	Man A.	March	MMM	MWW	w	w	why A	MV	mh My	J. Kw	AS LAN	INV	mouthered	NV V	1 mil
Cz - P	214	mi	30	man	minn	Mino	min	MAA M	min	him	min	M.	MAN	MAR	MANN	Ville	marin	har	Manna
ROC -	5 625	~~~~	N	muhan	with	mm	mm.	MMM	ww	ww	mm	wh	ww	non	mm	nw	www	Mun	monthem
LOC -	AI	mon	ma	min	mm	m	mm	m	m	um	mont	in	m	m	min	ma	man	n	month
				1	1		,		1				1				1		L.

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

Varelas Neurology 2003; Husain JNNP 2003, Claassen 2004; Oddo CCM 2009

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

PEDs and seizures

Table 4 Other cEEG findings in patients with seizures on cEEG, n = 110

	Seizures on cEEG monitoring							
Findings	Yes, $n = 110$	No, n = 460	р					
Periodic epileptiform findings								
Any	49 (45)	82 (20)	< 0.001					
PLED	44 (40)	46 (11)	< 0.001					
GPED	19 (17)	24 (6)	< 0.001					
BiPLED	7 (6)	13 (3)	NS					
Triphasic waves	4 (4)	25 (6)	NS					
Frontal intermittent rhythmic delta activity	11 (10)	35 (9)	NS					
Suppression burst	35 (32)	13 (3)	< 0.001					

Claassen, Neurology 2004

🕼 Type EEG 🔻 LFF 1 Hz 🔻 HFF 70 Hz 💌 Notch DII 💌 Sensitivity 7 ul//mm 💌 Timebase 30 mm/rec 💌 💈

FFI F3Viewww.pmac.semichany.enderwywany.anderwydainany.anderwydainany.anderwydainany.anderwydainany. F3E 53mmenyd a fan ar fan a F3 - 13mmenyd a fan ar fan a F3 - 13mmenyd a fan ar fan ar

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

NCSE





Midazolam load of 14 mg and drip up to 0.4 mg/kg/hr

EEG on midazolam gtt

🕼 Type (EG) 🔍 UFF TH2 🤟 HFF 70 H2 🔟 Noth OT 🔟 Sensibly 7 d//wm 🗰 Tenbase 30 mm/we 💌 🗶	C Tareface ECG v UP 1Hz v HPF 70Hz v Noteh (OT v Sensitive) 7 Julyam v Tendane 20 mm/arc v Z
B. 50 - min - Califord Chamberry Chamberry Chamberry - Anno Mark - And - minter and Mark - And Anno A Mark - An	
G. P may manufacture and a manufacture and a man which a dark a manufacture data data and a second	
P3-01-Annowing and an and a second	
re-re-hand which which have a which and have a hard a second and have a hard a second hard a second hard a second hard a second her hard a	1 F2-FALL Manuscher Martin Martin Manuscher
re con we have been a final providence marked more thank the more than being that the second the second that the second the second that the second the	really when and and here the second and the second
a ser a water and a series and a	ma a second ward with the man of the man man ward ward ward ward ward ward ward ward
a continue of ward ward and in any barrier and the former of the market of the second and the second of the second	a compression with the more than the more and the more thank the second of the second
Fpi-F7/www.united.com/www	M F8-F7
17. 17 m m. Market whether a second water and the second and the	n 17 - Trade and a start and the second and the sec
77- P7- m	W 77 - Prower and we have a second with the second with the second second with the second secon
pp-01-pp-ph//ph//ph//ph//ph//ph//ph//ph//ph//	
rez: @www.muliculi-twww.muliculi-twww.hutwww.hutwy.hutwiculi-twww.hutwy.hutw	h ester a far a
w. in the second of the second	
a - be of MM & Apple of the Month of Manual Apple of the	a some was a function of the second of the s
16-33 and March March March March March - March March March 100 and March March March March March - And March	a 16- co- An
1 800	1 sec
is control internal control of the internal control of the part of the control of the	n a anna mana Mana mana mana Mana Mana mana m
ES- BS- ARAP ARAPARA	le construction of the second s
ade or added and many provide a developed and added and a second and a developed developed developed developed de damend o	a washing a Amerika sang akto a sang Asa Mantu Asa sang Asa sang Asa sang sa sang sa sang sang sang sang s
ent country that that that that that that that the the the that the the the the the the the the the th	an an and many many that that that that that that that tha

PLEDs plus: with superimposed rhythmic slowing and fast activity

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



Imaging ictal patterns



Initial DWI shows diffuse, gyriform cortical hyperintensities

Decrease ADC/increased DWI after CPSE & seizures

Hippocampal formation
Cortical areas adjacent to the primary pathology
Posterior part/pulvinar of the thalamus
Szabo 2005, Kim 2001, Farina 2004

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

Lansberg '99

5 months later diffuse low signal intensities

ASL





Detre 1996

Chu 01

Suppression burst



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
 - \circ Respiratory depression, hypotension, or other adverse effect

 $_{\odot}$ 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:

- Repetitive generalized or focal spikes, sharp-waves, spike-and-wave or sharp-and-slow wave complexes at <u>>3/sec</u>
- 2. Repetitive generalized or focal spikes, sharp waves, spike-and-wave or sharp-and-slow wave complexes at <3/sec and secondary criterion
- Sequential rhythmic, periodic, or quasi-periodic waves at ≥ 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 previouslyabsent normal EEG patterns

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)
- 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. epil 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

Acknowledgements

Depart. of Biomedical Informatics

- Adler Perotte, MD
- Samantha Kleinberg, PhD
- David Albers, PhD
- George Hripcsak, MD, MS

Division Critical Care Neurology

- J Michael Schmidt, PhD
- Stephan A. Mayer, MD
- NICU Fellows
- NICU nurses
- Neurology residents

Department of Neurosurgery

- E Sander Connolly, MD
- Neurosurgery residents

Comprehensive Epilepsy Center

- Bin Tu, MD
- EEG Technicians
- Epilepsy attendings
- Epilepsy fellows