

## Recognizing and Diagnosing Epilepsy in Primary Care

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SOWEGA-AHEC      CURE Activity      October 12, 2010

## Objectives

- Describe the diagnostic evaluation process to distinguish epileptic and non-epileptic attacks.
- Describe the use of video-EEG monitoring in achieving a diagnosis for individuals with drug-resistant seizures.
- Describe and balance the armamentarium of treatment options for the newly diagnosed and refractory patients.

## Disclosure

- **Disclosure**
  - Previous honoraria from Cyberonics
  - Institutional support by Neuropace
- **Significant Financial Involvement creating a conflict of interest**
  - None
- **Off label discussion**
  - AED use outside of FDA approved guidelines

## Seizures

- **Seizure** = a paroxysmal behavioral event caused by an excessive disordered discharge of cortical neurons (780.39) .
- **Epilepsy** = two or more unprovoked seizures on > 1 occasion (345.90 or 1).

## How Common are the Common Neurologic Disorders?

Disorder	Ann. Incid./100,000/#	Prevalence/1,000/#
■ Migraine	-/-	121/35,461,000
■ Stroke	183/ 541,000	10/2,956,000
■ Alzheimer's	1,275/468,000	67/2,459,000
■ <b>Epilepsy</b>	48/142,000	7.1/2,098,000
■ Autism	-/-	5.8/500,000
■ Parkinson's	4.2/12,000	0.5/349,000
■ MS	4.2/12,000	0.9/266,000
■ CP	-/-	2.4/207,000
■ ALS	1.6/5,000	0.04/12,000

Non-epileptic Attacks

Hirtz D et al. Neurology 2007;68:326-337.

## Epilepsy

- **Epidemiology**
  - **Epilepsy**= 2 or more spontaneous unprovoked seizures.
  - **Epilepsy Syndrome** = involves a constellation of signs.
  - Nearly 3 million people in U.S (45 million worldwide): 0.5-1.0%
- **Approximately 70% of adults with new-onset epilepsy have partial-onset (focal) seizures.**
- **The cause is unknown in 62%.**
  - In the rest, stroke in 9%, trauma 9%, alcohol 6%, neurodegenerative dz 4%, static encephalopathy 3.5%, brain tumor 3%, infection 2%
  - Age-related predisposition: even in the elderly, 25-40% unknown.
- **AEDs render 65-85% of PWE seizure free.**

French JA, Pedley TA. N Engl J Med 2008;359:166-76.

## The Diagnosis of Seizures

- A single seizure occurs in 1/10 people.
  - 30% develop epilepsy
  - Highest risk is in the young (<1 yr.) and the old (>60 yrs.)
- Seizures are only a symptom of the brain.
  - A neurological disorder
  - 2 or more high risk for recurrence\*



\*Kim LG et al. The Lancet Neurology 2006;5(4):317-322.

## Does it Sound like a Seizure?

### History v vEEG

Judged to be a clinical seizure	Seizure vEEG	No Seizure vEEG	Sensitive % 95% CI	Specific % 95% CI	Accuracy % 95% CI	PPV % 95% CI	NPV % 95% CI
Seizure	161	4	96%	50% SPS PNEA	94	98	40
No Seizure	6	4	Only 10 events were misidentified (4 IDed as ES that were NES, and 6 IDed as NES that were ES by vEEG. Agreement by blinded epileptologists= 90%.				

N=88 suspected TLE; 357 different events with 175 (49%) reproduced in EMU-matched; CPS > SPS > GTC > PNES).

k=0.7

Deacon C et al. Neurology 2003;61:1686-1689.

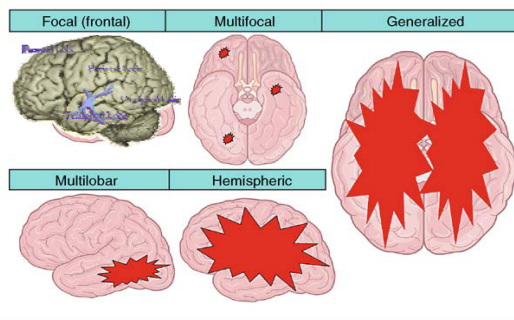
## The Diagnosis of Seizures

### History: A pitfall to diagnosis

- 1<sup>st</sup> seizure diagnosis is subject to error.<sup>1-4</sup>
  - Mainstay of diagnosis is a good eye witness<sup>4</sup>.
  - Volunteer accuracy low with wide variation.
- Overall clinical accuracy 94%<sup>3</sup>
  - Sensitivity 96%; specificity 50%
  - Misidentified seizures were simple partial & NES
- Diagnosis of epilepsy is usually straight forward (misdiagnosis rate 5-30%?).<sup>1,2</sup>
  - Population rate > hospital rate (? incidence v 20-30%)<sup>1</sup>
  - Neurologists > generalists (mistake rate 5.6 v 18.9%)<sup>2</sup>

1. Van Dorpebar CA et al. Epilepsia 2006;47(suppl 1):9-13.  
2. Leach JP et al. Seizure 2005;14:514-520.  
3. Mannan JB, Westmann UC. Seizure 2003;12:444-447.  
4. Duncan CA et al. Neurology 2002

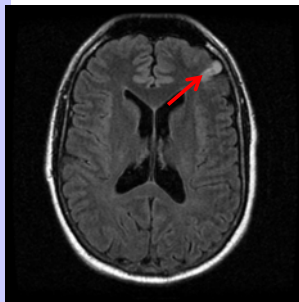
## Epilepsy Classification



Loddenkemper T et al. Epileptic Disord 2005;7:308-316.

## High Resolution MRI

- MRI is the test of choice for patients with focal seizures
- High resolution MRI is available with special protocols for epilepsy.
  - MRI-reliable indicator: visual inspection 80-90% sensitive.
  - Normal MRI are still seen in 1/3<sup>rd</sup> with focal seizures<sup>1</sup>
- High field strengths (ie 3T) may improve detection.



Bridoux BS et al. Ann Neurol 2002;51:641-644.  
Epilepsia 2004;45(suppl 5):980-991.  
Kulkarni B et al. Neurology 1998;50:1771-1782.  
Ficker D et al. Epilepsia 2005;46:1484-1490.  
Tanam WO IV et al. Science 2008;317:631-636.  
Kozak S et al. Neurology 2005;65:1026-1031.

## EEG

- IEDs may be absent with routine EEG<sup>1</sup>
  - First recording is "+" in 29-55% and in 85-90% with repeated study.
  - IEDs are rare in normal people (1.9-3.5% kids and 0.2-0.5% in adults)<sup>1</sup>
- IED recovery is related to brain location
  - Temporal vs mesial frontal<sup>2</sup>.
  - A normal EEG does not rule out epilepsy!
- Video-EEG: definitive means of diagnosis, classification, and characterization<sup>3</sup>.

1. Pilla J, Sperling MR. Epilepsia 2006;47(suppl 1):14-22.  
2. Kalishay P. In: Current clinical neurophysiology: update on EEG and evoked potentials. 1981:151-175.  
3. Tatum WO. J Clin Neurophys 2001;18(5):442-465.

## Does it Look like a Seizure?

### Inter-rater Reliability

- Historical account is the foundation for the initial diagnosis of epilepsy<sup>1</sup>.
- Semiology a useful adjunct for diagnosis<sup>2,3</sup>.
- PNEAs, PhysNEE, and ES may have overlapping features that prompts vEEG<sup>4</sup>.
  - Accuracy of inter-rater reliability for vEEG;
    - ES had good inter-rater agreement ( $k=0.69$ ; 95% CI 0.51-0.86)
    - PNEA had moderate inter-rater agreement ( $k=0.57$ ; 95% CI 0.39-0.76)
    - PhysNEE had slight inter-rater agreement ( $k=0.09$ ; 95% CI 0.02-0.27)
  - Overall agreement for "spells" was moderate ( $k=0.56$ ; 95% CI 0.41-0.73) **BUT** not real-life.

1. Van Donselaar CA et al. *Epilepsia* 2006;47(suppl 1):9.  
 2. Williamson PD et al. *Epilepsia* 1998;39(11):1182-1188.  
 3. Louis ED et al. *Movement Disorders* 2002;17(3):519-517.  
 4. Benbadis SR et al. *Neurology* 2009;73:843-846.

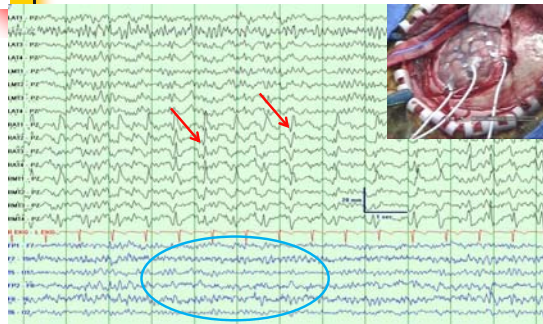
## EEG: An Important Pitfall



- Normal fluctuating rhythms confusing<sup>1</sup>.
- Normal variants (wickets) misleading<sup>2</sup>
- Artifacts may mimic abnormality<sup>3</sup>.
- Inter-observer difference exist<sup>3,4</sup>.
  - Normal if in doubt
  - Unbiased "read"

1. Benbadis SR, Tatum WO. *JCN* 2003;20:42-4.  
 2. Kirazli G et al. *Neurology* 2005;64:1879-1883.  
 3. Tatum WO et al. In: *Handbook of EEG Interpretation*. 2008;1:50.  
 4. Pillai J, Sperling MR. *Epilepsia* 2006;47(suppl 1):14-22.

## A Normal EEG Does not R/O Epilepsy!



Tatum WO et al. *Handbook of EEG Interpretation*. 2008:73.

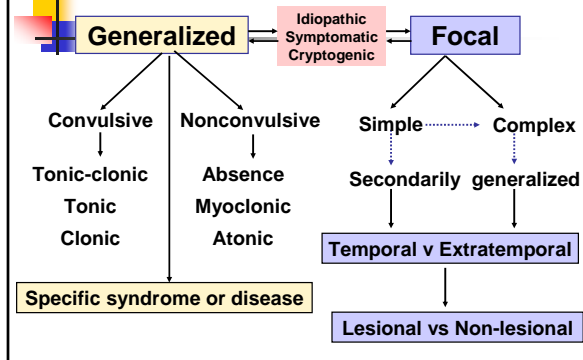
## Video-EEG monitoring

- Differential Diagnosis
- Classification
- Characterization



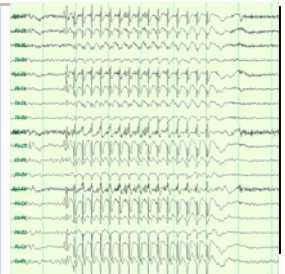
## Seizure Types

Classification: The necessary 1<sup>st</sup> step



## Idiopathic Generalized Epilepsy

- Absence, myoclonic, (clonic)-tonic-clonic
- aka IGE (presumed genetic origin)
- Syndromes
  - CAE, JAE
  - JME, GTC
- Common in children
- Normal neuroimaging
- Most respond to Tx
  - VPA, LTG, TPM, LEV, ZNS

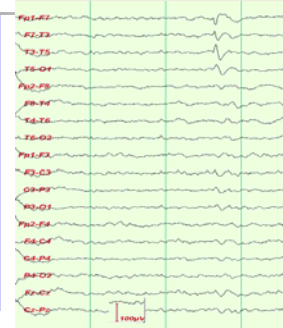


Nicolson A et al. *JNNP* 2004;75:75-79.  
 Karocski S et al. *Epilepsy & Behavior* 2005;7:51-54.  
 Wheless JW et al. *J Child Neurology* 2005;20:51-55.



## Localization-related Epilepsy

- **SPSz, CPSz, GTC Sz**
  - CPSz are most frequent
  - Cryptogenic or symptomatic
- **Most common type**
  - > 60% of epilepsies
  - More common in adults than children
- **Often due to focal CNS injury-MRI brain**
- **EEG may clarify seizures classification**
- **Treatment**
  - \*Initial: CBZ, LTG, OXC



\*Karcecki S et al. Epilepsy & Behavior 2005;7:51-564.

## "Petit Mal" Seizures

Features	Absence	CPS
History	Onset in childhood or adolescence course	Febrile sz frequent; course variable
Aura	None	Yes
Semiology	Staring Eyelid fluttering	Staring Automatisms, 2 <sup>o</sup> GTC
Duration	10-20 seconds	30-60 seconds
Post-ictal	No	Yes
EEG	Generalized spike-wave	Focal epileptiform D/C
Pathology	None	Variable

French JA et al. Ann Neurol 1993;34:774-80.  
Fakhry N et al. Neurology 1997;49:122-63.  
Villanueva Y, Sanchez JM. Epileptic Disorders 2005;7:83-90.

## "Petit Mal" Seizures



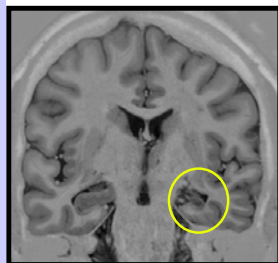
**ABSENCE**  
**Generalized**

**COMPLEX PARTIAL**  
**Focal**

## The Syndrome of TLE

### A Modern Concept

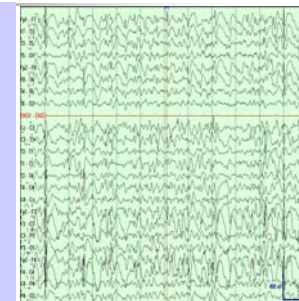
- **TLE is the most common focal epilepsy in humans<sup>1-3</sup>.**
  - Temporal lobe: 70%
    - Temporal lobe, psychomotor, limbic seizures, complex partial, focal seizures<sup>3</sup>.
    - Frontal lobe: 20%
  - Mesial structures
- **Often a focal structural lesion**
  - Early insult (2/3<sup>rd</sup> with FS)
  - Onset during childhood
- **Psychosocial disability and neuro-cognitive deterioration.**
- **Pitfalls exist in diagnosis and treatment!**



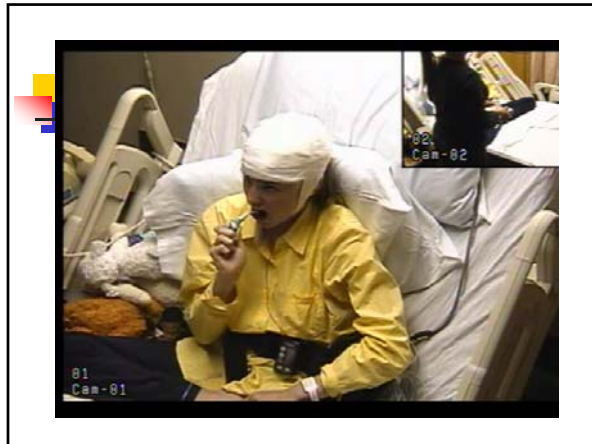
1. Blume WT. Adv Neurol 2006;97:17-25.  
2. Liu Z et al. Indian Neurol 2007;12:5-16.  
3. Revised Terminology/Concepts for organization of Epilepsies: Report of the Commission on Classification/Terminology 2010.

## Symptomatic (Encephalopathic) Generalized Epilepsy

- **Clinical features**
  - Cognitive impairment
  - Mixed seizure types
  - EEG abnormalities
- **West's Syndrome**
- **Lennox-Gastaut**
  - Infantile spasms
  - Tonic-atonc, atyp absence
- **Refractory to treatment, recurrent injury**
  - AEDs: VPA, LTG, TPM, RUF, ?LEV, ?ZNS
  - VNS & Callosotomy



Winstead P, Tatum WD. The Treatment of Epilepsy, 5<sup>th</sup> edition, Chapter 22. In: Wyllie, E, ed. Baltimore, Lippincott, 2010 (in press).



## The Reason Drugs Don't Work

- **The Diagnosis and treatment are wrong!**
  - The result is problematic on two-levels;
    - The misdiagnosis
    - The missed diagnoses
  - Present in 20-30% that undergo video-EEG.
- **The Diagnosis is right but;**
  - The AED choice is wrong
  - The AED is right, but is taken wrong
- **Drugs don't work because the epilepsy is by nature drug-resistant.**

Berabadi SR, Tatum WO, Vale FL. Neurology 2000;55(12): 1780-1784.

## Non-epileptic Attacks "Pseudoseizures": The mimics

- **Psychiatric: 90%**
  - Psychogenic (PNEA)\*
- **Physiologic: 10%**
  - Syncope
  - Sleep Disorders
  - Migraine
  - Cerebrovascular causes: TIA/stroke
  - Vestibulopathies
  - Electrolyte imbalance



## Non-epileptic Attacks

- **PhysNES:** A paroxysmal organic episode that appears to alter psychic, sensory, motor, or autonomic function with symptoms that simulate an epileptic seizure.
- **Prevalence: Unknown**
  - 20-30% at epilepsy center have NES
    - Center report of 213 seizure patients<sup>1</sup>;
      - Epileptic seizures=64%
      - Non-epileptic attacks=32%
        - Psychogenic NEA=25%
        - Physiologic NEA=7% (4% with Epilepsy had PhysNES, and 11% with PhysNES had epileptic seizures too)
      - Both ES + NEA=4%
- **Like PNEA, most patients with PhysNES have been diagnosed and treated for epilepsy.**

1. Vossler DG. J Epilepsy 1995;8:1-10.

## Syncope

Physiologic non-epileptic "seizure"



- **Clinical Features<sup>1-3</sup>**
  - Triggers are present
  - Sweating & nausea common
  - <20 seconds
  - Brief movements (<15 sec.)
  - Pallor common
  - No post-ictal
  - Myalgias are rare
- **Clonic, myoclonic, or posturing are common!**
- **vEEG may be needed**

1. Sheldon RS et al. J Am Coll Cardiol 2002;40:142-8.  
2. Zilli A et al. J Am Cardiol 2000;36:181-4.  
3. Longoni T et al. Ann Neurol 1994;36:233-7.

## Post-ictal Behavior

- The post-ictal state is distinctive for a seizure.
- Aggressive behavior rarely occurs during/after seizures<sup>1-4</sup>.
  - "Negative" aura
  - Threat with automatisms<sup>2</sup>
  - Biting, spitting, aggressive gestures.<sup>2</sup>
- Reactive "violence" is not organized, goal-directed, nor modifiable.<sup>2-4</sup>
- Psychosis may follow a lucid interval with hallucinations, delusions, paranoia, and aggression.<sup>5-7</sup>



1. Tomper P et al. Neurological Sciences 2005;26(suppl 3):S210-S214.  
2. Tomper P et al. Epilepsia 2006;47:1488-93.  
3. Freeman D. Neurologic Clinics 1999;17:249-283.  
4. Dalakas-Costantini M et al. Epilepsia 1994;35:1505-1511.  
5. Oshiro T et al. Epilepsia 2006;47:2131-2134.  
6. Langstaff M. From BK. British J Psychiatry 1988;152:246-252.  
7. Kawamoto K et al. Epilepsia 1999;40:107-109.

## REM Behavior Disorder

### Physiologic non-epileptic seizure



5-10% of seizures occur only during sleep.

Frontal lobe epilepsy is activated by sleep.

OSAS may present or worsen seizures.

During sleep seizures and sleep disorders are suspect.

Derry CP et al. Arch Neurol 2006;63:705-709.

## Sleep Disorders

- **Causes**
  - **NREM:** sleep terrors, sleep walking, confusional arousals
  - **REM:** REM behavior D/O, nightmares
  - **Other:** EDS, cataplexy, hallucinations, paralysis, hypnic jerks, enuresis
- **Semiology**
  - Overlap: Sleep D/Os and FLE
  - Non-stereotyped condition
- **Diagnosis and Treatment**
  - History, history, history!?
  - vEEG and PSG + expanded EEG montage.

Signs	NREM	REM Behavior	Epilepsy	PNEA
Recall	None	Bad dream	None except with FLE	Usually None
Stereo typic	No	No	Yes	No
PSG	SWS arousal	REM + EMG	IEDs or ictal discharges	Awake or drowsy
Time	1 <sup>st</sup> 1/3 <sup>rd</sup> of night	Last 1/2 of night	Anytime	Varies

Nobilia L. Sleep Med Rev 2007;11(4):251-4.  
 Mahowald MW. Medical Clinics of North America 2004;88:669-78.  
 Malow B. J Clin Neurophysiol 2002;19:522-534.

## Migraine

- **Comorbidity**
  - Inter-related with seizures
  - 20% of PWE have migraine/30-50% PIMLHA
- **Semiology (visual symptoms)**
  - **Epilepsy:** movement of circular out to in/opposite hemi-field v achromatic linear patterns. Spread in seconds, tonic eye movement, automatisms, GTC, or post-ictal state suggest seizures.
  - **Migraine** is longer (> 5 mins), and may impair concentration (confusional) & awareness/vision (basilar); common N/V; neurological signs the rule (in basilar migraine).
- **Diagnosis & Treatment**
  - EEG abnormalities? (DS/OIRDA and IEDs-PLEDs) though late in course.
  - Treatments overlap (VPA/TPM/GBP)



Rogawski MA. Arch Neurol 2008;65(6):1546-7.  
 Syvertsen M et al. J Headache Pain 2007;8(4):224-30.  
 Marks D, Ehrenberg B. Neurology 1992;43:2476-2483.  
 Pansyiotopoulos T. Epileptic Disord 1999;1(4):205-16.

## Psychogenic nonepileptic Attacks

### Pseudoseizures

- **Incidence: 4/100,000 in the population<sup>1,2</sup>**
  - 300,000-400,000 in the US; Women vs men
  - Delay of 7 years or more until diagnosis.
- **Video-EEG= gold standard for diagnosis<sup>3</sup>**
- **Consequences of misdiagnosis;**
  - Misdiagnosis: Driving, employment, AEDs
  - Missed diagnosis: ? death and injury
- **Presentation:**
  - 2/3<sup>rd</sup> motor activity & 1/3<sup>rd</sup> limp collapse<sup>4</sup>
  - 1/3<sup>rd</sup> with pseudostatus<sup>5</sup>

1. Davis EJ. Europ Neurol 1994;51:153-156.  
 2. Chang SS et al. Neurology 2006;66:1720-1731.  
 3. Martin RC et al. Neurology 2003;61:1791-1792.  
 4. Martin RC et al. Seizure 1998;7:385-390.  
 5. Rudolph M et al. Neurology 2004;63:834-5.

## Types of PNEA



Convulsive



Non-convulsive

## PNEA Historical Clues

- **History**
  - Abuse/trauma
  - Not out of sleep
  - Not amnestic
  - Not stereotypic
  - Florid ROS
  - Seizure in the clinic
  - Co-morbid dx: psychiatric/pain
  - Incontinence & injury rare



Holtkamp M et al. Neurology 2006;66:1730-1733.  
 Krumholz A. Neurology 1999;53(suppl 2):S76-S83.  
 Benbadis SR. In Wyllie E, ed. The Treatment of Epilepsy: Principles and Practice, 4<sup>th</sup> edition, 2006.

## Characteristics of PNES

### Semiology

- Eyes closed
- Side-to-side head shaking
- Intact awareness with B/L motor activity
  - Asynchronous
  - Out-of-phase activity
- Discontinuous movement (on-off)
- Back arching
- Ictal weeping/ stuttering
- Long duration



## Panic Attack v Partial Seizure?



## "Pseudo-Pseudoseizures" The Frontal Lobe

- 2<sup>nd</sup> most common site of focal seizure onset in adults<sup>1</sup>.
  - Frontal convexity: clonic jerking
  - Orbitofrontal: may look temporal (propagation)
  - Mesial (SSMA): usually tonic (not site-specific)
- Seizures often brief and stereotyped<sup>1-3</sup>.
  - Hypermotor, violent, bizarre automatisms, loud vocalizations, and screaming.
  - Paroxysmal activity though bizarre is stereotyped.
- Post-ictal state & EEG often negligible<sup>1-3</sup>.
- Non-compartmentalizing but sleep activated.

1. Jobst BC et al. Epilepsia 2000;41(9):1139-1152.  
 2. Kanner AM et al. Neurology 1990;40:1404-7.  
 3. Ryvlin P et al. Epilepsia 2006;47(suppl 2):83-86.



## Seizures & Site of Origin

Behavioral feature	Frontal origin	Temporal origin
Aura	General feeling	Epigastric
Duration	Brief	Longer
Stare	Less common	Common
Complex gestures	Common; bizarre	Less common
Post-ictal confusion	Minimal-absent	More common
Frequency	High-daily	Less-variable
Sleep activation	Classic	sporadic

Jobst BC et al. Epilepsia 2000;41(9):1139-1152.  
 Ryvlin P et al. Epilepsia 2006;47(suppl 2):83-86.  
 Kotagal P et al. Seizure 2003;12:269-281.

## Pitfalls in Epilepsy Recognizing and Diagnosing

### Pitfalls in the Approach to Epilepsy Care

- It's not epilepsy
- It's epilepsy but...
  - Not the correct type treated.
  - Instead is recognized as something else.
  - Is just really bad epilepsy that is drug-resistant.

### Reasons for Pitfalls to Diagnosis

- The diagnosis of epilepsy is a clinical judgment based upon behavior and the history of that (? observed) behavior.
- No routine biomarker exists for epileptogenicity<sup>1</sup>.
  - EEG: IEDs may support the diagnosis (???) but can not accurately reflect the severity or location of the epileptogenic lesion<sup>1</sup>.
  - Structural brain MRI, fast ripples (MEG non-invasively), TMS -EEG coupled cortical excitability metrics, PET ligands (a-methyl TRP in TS).

1.Engel J.J. Current Opinion in Neurology 2008;21:150-154.

## Summary Statements

- Epilepsy diagnosis may be challenging.
- Definitive diagnosis is achieved with video-EEG monitoring.
- Proper diagnosis and seizure classification are imperative to proper AED treatment.
- Many PWE remain drug-resistant despite best practice and other treatments exist.

WO Tatum



## QUESTIONS?



## Evaluation

- Attended Archived Activity 10.13.10 or later  
<http://www.surveymonkey.com/s/CURE9Archived>