

# CIAN

PRIMER CURSO INTERAMERICANO DE  
ACTUALIZACIÓN EN NEUROLOGÍA



## Advances in Diagnosis, Neurobiology, and Treatment of Neurological Disorders

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CME  
Outfitters 



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## Disclosures

- Dr. Delgado-Escueta has no disclosures to report.





# Refractory Epilepsy





# Learning Objective 1

Examine key clinical concepts in the assessment of refractory epilepsy.

# ILAE Definition of “Refractory,” 2010

- “Failure to achieve sustained seizure freedom with adequate trial of at least two appropriately chosen anti-epileptic drugs (AEDs) as monotherapy or in combination.”
- AED side effects causing discontinuation doesn't count
- Efficacy counts for two AEDs
- Seizure freedom: means NO aura, no TC, no focal without LOC
- For at least 1 year or 3x the previous longest seizure free period.

ILAE = International League Against Epilepsy

Kwan P, et al. *Epilepsia*. 2010. 51:1069-1077.; Leach LP, et al. *Seizure*. 2005;14:514-520.  
Hao X, et al. *Epilepsy Behavior*. 2013;29:4-6.

# Approach To Patient with Refractory Seizures

1. Verify that seizures are epileptic in nature: **r/o PNES**
2. Define seizure type and epilepsy syndrome; **72 hrs EEG, smartphone videos of seizures, MRI epilepsy protocol and 2FDG PET scan and neuropsychological evaluation including MMPI**
3. Prove the likely cause of epileptic seizures and stop trigger factors
4. Establish an early treatment plan with appropriate antiepileptic drugs. **Monitor seizure control and adverse effects on quality of life**
5. Evaluate for possible surgery if seizures are resistant to **2 antiepileptic drugs**
6. Discuss with family: **complication, expected pathology, results of surgery**



# Part 1.

## Is the patient really drug resistant?

- Is it really epilepsy?
- Does diagnosis match AED used? Misdiagnosis: 5-30%
- Common Errors
- Drug dosing and timing
- Drug Interactions
- Predictors of drug resistance
- Consider dietary therapies earlier
- Diet, sleep and other lifestyle changes

# Psychogenic Non-Epileptic Seizures (PNES)

- Incidence in Women
  - In Iceland: 1.4/100,000 >15 yrs old; 78%
  - In Hamilton, OH: 3.03/100,000; 73
- Risk factors in Men
  - Work-related stressors
  - Low socioeconomic status
  - Increased psychosocial stressors
  - Depression and anxiety
  - Personality disorders (borderline)

# PNES: Characteristics

- Prolactin
  - Measure within 30 minutes of a seizure
    - Highly specific (95% - 96%)
    - Not sensitive (46% - 60%)
    - 300% increase from baseline:
      - ↑25 – 32 ng/ml for females;
      - >23 ng/ml for males
- Heart Rate
  - Accelerates in epileptic seizures (ES) but not PNES
- Respiration
  - Shallow and rapid with PNES; deep and heavy in ES



# Clinical Characteristics of PNES and True Epileptic Seizures

PNES		True Epileptic Seizures
59.2%	In sleep	47%
44%	Urinary Incontinence	67%
59%	Prodrome Sensory Aura Presentation	95% in TLE, <30% in FLE
55%	Postictal Confusion	✓
✓ (52% - 96%)	Forced Eye Closure	
✓ (9% - 96%)	Asynchronous Movements	
✓ (15% - 36%)	Side-to-Side Head Movements	
✓ (7% - 44%)	Pelvic Thrusts	
✓	Preserved Awareness	

# PNES: Symptoms of Underlying Stressors

- Minnesota Multiphasic Personality Inventory (MMPI) is important
- Separate:
  - Conversion reaction (somatoform)
  - Dissociative disorder (trance-like state)
  - Malingering
- Treatment
  - Cognitive behavioral therapies
    - **25% to 65% seizure freedom**
    - **>50% reduction in seizures in 70% to 80%**
  - Pharmacotherapy
    - Sertraline
      - **45% reduction of seizures**
    - Venlafaxine
      - Plus unipolar depression
      - Psychotherapy + SSRI arms

## Definición de “refractaria” por la ILAE, 2010

- “Fallo en lograr control un sostenido de crisis mediante un manejo adecuado con al menos dos AE escogidos apropiadamente usados en monoterapia o en combinación”.
- La discontinuación de un AE por efectos secundarios no cuenta
- La eficacia cuenta para dos AE
- Libertad de crisis: significa NO aura, NO crisis TC, NO crisis focales sin pérdida de conciencia
- Por al menos 1 año o por 3 veces el período más largo que ha habido sin crisis

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# Predictors of Drug Resistance

- Age at onset
  - <1 year (Neonatal seizures)
  - >12 years
- Focal seizures
- Multiple seizure types
- High Frequency at onset/start
- Hippocampal atrophy <10% remit
- Cortical dysplasia <25% remit
- Dual pathology
- Abnormal EEG
- Failing 2 or more AEDs

Brodie MJ, et al. *Epilepsia*. 2013;54:194-198.

Wiebe S, et al. *Nat Rev Neurol*. 2012;8:669-677.

# Not Refractory → Pseudo Resistance if Misdiagnosis in 5-30%

## Examples




- Genetic generalized epilepsies (GGE) can have
  - Focal spikes or sharp waves EEG
  - Focal features in semiology, e.g., head turning to one side
- Wrong AED
- Incorrect or suboptimal: Hence “pseudo-refractory”
  - In Newly diagnosed: **56%**
  - In Chronic epilepsies: **41%**
- Pseudo-resistance are drug responsive to correct AEDs

30-45%

71%

78%

## Examples of Misdiagnosis

- |   |   |                     |
|---|---|---------------------|
| ● Focal motor                             | <br><b>versus</b> | Myoclonic           |
| ● Focal SMA                               | <br><b>versus</b> | Tonic               |
| ● Focal dyscognitive<br>or Focal with LOC | <br><b>versus</b> | Atypical<br>Absence |

SMA = supplementary motor area

Montalenti E, et al. *J Neurol Sci.* 2001;184:65-70.

Hao X, et al. *Epilepsy Behavior.* 2013;29:4-6.



# No refractaria → Pseudo resistencia si hay diagnóstico equivocado en 5 to 30%

## EJEMPLOS

- Epilepsias Genéticas Generalizadas (EGG) pueden tener en
  - Puntas focales o bien ondas agudas en EEG
  - Manifestaciones focales en semiología, por ej.: versión de la cabeza a un lado
- Antiepiléptico equivocado
- AE incorrecto o subóptimo: por tanto, “epilepsia pseudo-refractaria”
  - En diagnosticados nuevos **56%**
  - En epilepsias crónicas **41%**
- Pseudo-resistentes: responden bien al AE correcto

30-45%

71%

78%

# Making the Right AED Work

- Common Errors
- Sodium channel blockers and GABAergic drugs aggravate genetic generalized epilepsies
- Carbamazepine<sup>1</sup> for absence seizures
- Ethosuximide<sup>2</sup> for focal seizures with loss of consciousness (LOC) (previously called complex partial seizures)
- Phenytoin<sup>3</sup> for epileptic spasms
- Vigabatrin<sup>4</sup> for myoclonic seizures

<sup>1</sup>Carbamazepine is not FDA-approved for absence seizures.; <sup>2</sup>Ethosuximide is not FDA-approved for focal seizures.; <sup>3</sup>Phenytoin is not FDA-approved for epileptic spasms.; <sup>4</sup>Vigabatrin is not FDA-approved for myoclonic seizures.

Leach JP, et al. *Seizure*. 2005;14:514-520.

# Making the Right AED Work

## 50% lower than DDD

- Low dose because of side effects
- 60% seizure-free with further AED trials

## Use of 50% to 75% of DDD

- Seizures persist
- TRUE RESISTANCE

## Use of higher dose >75% of DDD

- Refer for surgical evaluation

DDD, World Health Organization defined daily dose

Wiebe S, et al. *Nat Rev Neurol*. 2012;8(12):669-677.

# Making the Right AED Work – Drug Interactions

## First Generation AEDs

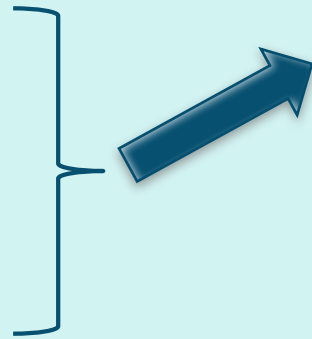
Even

Lamotrigine

Topiramate

Zonisamide

Felbamate



Induce cytochrome P450 isozymes



Reduce AED plasma levels



Reduce loss of seizure control

## Other Examples:

Carbapenem



↓ VPA levels 49-70%

Methotrexate



Pb, PHT, CARB

Oral Contraceptives

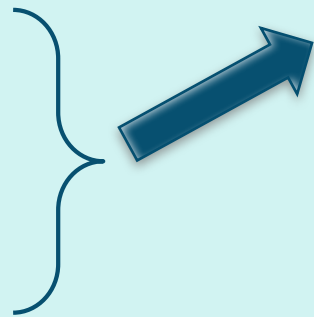


Decrease lamotrigine action

# Uso apropiado de los antiepilépticos - Interacciones

**Antiepilépticos de primera generación**

Lamotrigina  
Topiramate  
Zonisamida  
Felbamato



**Induce isoenzimas del citocromo P450**



**Reduce niveles séricos de AE**



**Reduce o pierde el control de crisis**

## **Other Examples:**

**Carbapenem**



**↓ niveles de AVP en 49-70%**

**Methotrexate**



**Pb, PHT, Carb**

**Oral Contraceptives**



**Disminuye acción de lamotrigina**



# Making the Right AED Work

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# Changing Landscape

## EMU and Epilepsy Surgery

- Actual literature does not reflect contemporary surgical practice and **results**
- **Know** who are highly experienced epilepsy specialists and epilepsy surgeons in well established centers
- Patient selection criteria and operative approaches – intraoperative/extraoperative mapping, Functional BOLD MRI – have changed our approaches for the better
- **Bottom Line:** Experienced clinical specialist and epilepsy surgeon e.g. “things happen”

# EMU y Cirugía de Epilepsia

- La literatura actual no refleja las prácticas quirúrgicas contemporáneas
- Especialistas en epilepsia y cirujanos de epilepsia altamente experimentados en centros establecidos
- Criterios de selección de pacientes y enfoques operatorios
- Mapeo intraoperatorio y extraoperatorio, BOLD MRI funcional -- han cambiado nuestro enfoque para mejor

## Part 2.

- Routine EEG vs 72 hour ambulatory EEG

- Smart phone video to validate patient description

### Imaging Targets

- Hippocampal Sclerosis (HS)
- Cortical Dysplasias
- MRI negative Cortical Dysplasias

### Epilepsy Monitoring Unit

- IV portal, EKG monitoring, Continuous pulse oximetry
- Interictal
- Ictal semiology/EEG (video EEG)
- SPECT during ictus
- Are intracranial electrodes needed? If yes, stereo EEG, IC strip/grids

### Neurologist: Discuss results

Order functional MRI for language and recent memory mapping  
Neuropsychological psychometrics; Need MEG? MagnetoEEG? Need Wada?

# Changing Landscape

## EMU and Epilepsy Surgery

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## Answer

- Temporal lobe: amygdalo-hippocampal is engaged during oroalimentary automatisms
- EEG - did not show focal onset until she started masticating when 5 Hz sharp waves appeared at T3 F7 SP1 with phase reversal at T3 & SP1.

# First 10 Seconds of Extra-Temporal: Focal with Loss of Awareness

**Bilateral Motor Automatism**

**10 sec**

**Reactive Automatism**

**20 sec**

- Motor automatisms of both upper and lower extremities described as frenetic, bizarre, bimanual, bipedal bicycling movements.
- Almost always mean engagement of frontal lobe.

Delgado-Escueta AV, et al. *Neurology*. 1977;27:144-155; Delgado-Escueta AV, et al. *Annals of Neurology*. 1982;11: 292-300; Walsh GO, et al. *Neurology*. 1984;34(1):1-13; Delgado-Escueta AV, et al. *Neurology*.1985;35(2):143-154; Maldonado H, et al. *Epilepsia*.1988;29(4):420-433; Swartz BE, et al. *Epilepsy Research*.1990;5:61-73.

# Reconstructing Focal with Loss of Awareness (Psychomotor Seizures)

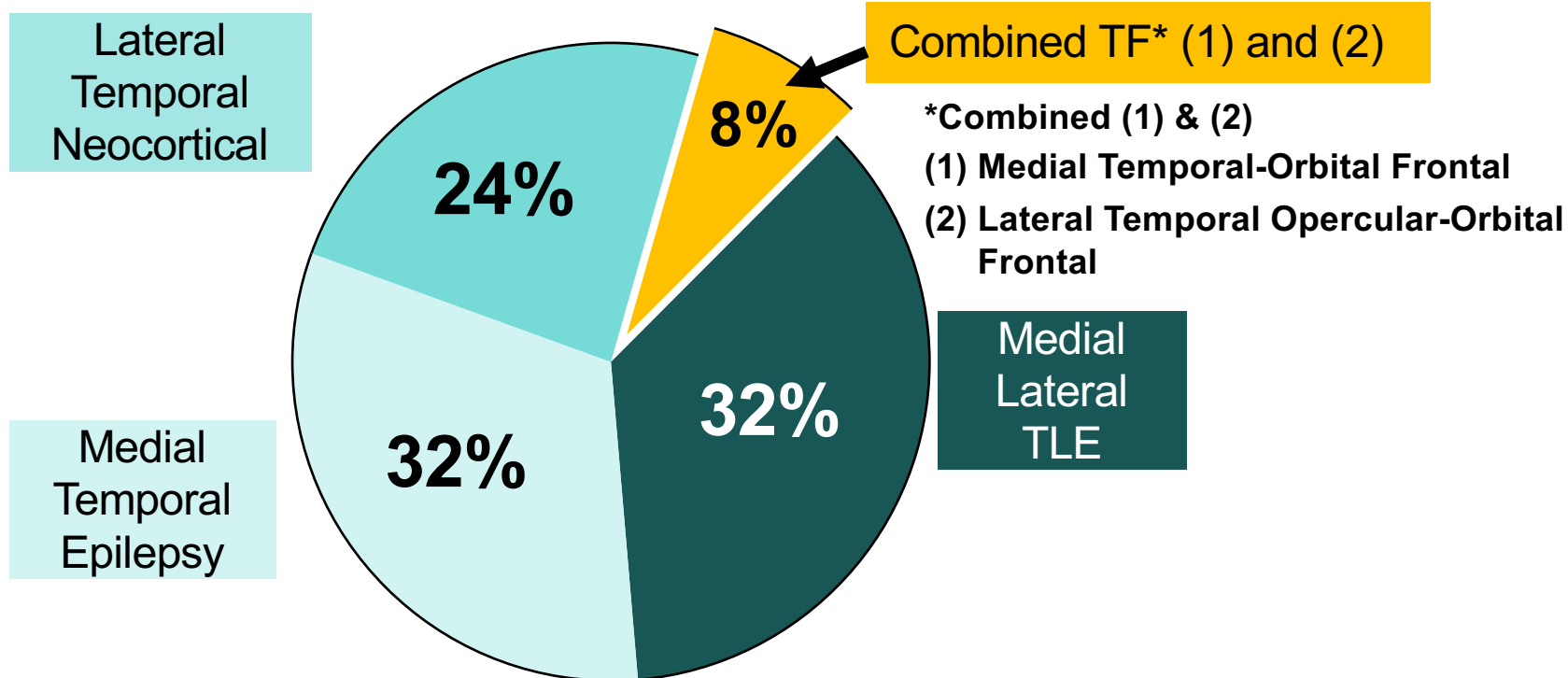


Of all temporal lobe epileptic seizures, slightly over half (60%) will start with arrest, motionless staring, mastication, lip-smacking.

Delgado-Escueta AV, et al. *Neurology*. 1977;27:144-155; Delgado-Escueta AV, et al. *Annals of Neurology*. 1982;11:292-300; Walsh GO, et al. *Neurology*. 1984;34(1):1-13; Delgado-Escueta AV, et al. *Neurology*. 1985;35(2):143-154; Maldonado H, et al. *Epilepsia*. 1988;29(4):420-433; Swartz BE, et al. *Epilepsy Research*. 1990;5:61-73.

# First 10 Seconds of CPS

**Arrest, motionless staring, mastication, and lip-smacking  
almost always signify Temporal Lobe Epilepsy**



## 53 seconds after onset of TLE: CPS



Contralateral dystonic posturing of an arm was first noted by Kotagal et al., 1989, in 15% of temporal lobe complex partial seizures, **53 seconds after onset.**

# Auras

## Parietal Lobe Origin

Parietal opercular and temporal-insular cortex	Gustatory auras
Postcentral cortex	Somatosensory auras

## Temporal Lobe Origin

Cortex of transverse superior temporal gyrus (Heschl's gyrus)	Simple auditory hallucinations Psychical seizures
Cortex of superior temporal gyrus	Psychical seizures and Complex auditory hallucinations
Cortex of temporoparietal-occipital junctions	Complex auditory and visual hallucinations

## Combined

Temporal neocortex and medial temporolimbic structures	Dreamy state: experiential hallucinations, dysmnestic phenomena, illusions of comparison
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# Focal with Loss of Awareness (ILAE, 2017)

## Temporal

3 consecutive phases:

1. Motionless stare
2. Oroalimentary automatisms
3. Reactive quasi-purposeful movements

## Extratemporal

No motionless stare and/or oroalimentary automatisms at onset.

### Motor Signs:

1. Suprasylvian signs such as contraversive head/eye movements, postures, or partial motor jerks
2. Early complex bimanual/bipedia automatisms, pelvic thrusts, sexual gestures
3. Ambulatory Automatisms / Running, Walking

# Epilepsy Surgery Change in Landscape, 2017

## Focal

### RESECTION / ABLATION

#### **TLE**

Tailored  
**vs.** Classic ATL  
**vs.** Thermal  
laser ablation  
**vs.** Ultrasound  
laser ablation

#### **Extra-TLE**

Corticectomy  
Lobectomy  
Hemispherotomy  
Hemispherectomy  
Corpus Callosotomy  
Multiple Subpial  
Transection

## Multi-Focal

### STIMULATION / MODULATION

Vagal Nerve Stimulation (VNS)  
Trigeminal Nerve Stimulation (TNS)  
Ant. Thalamus Stimulation  
Responsive Neurostimulation (RNS)

# Part 3.

- Follow-up by Neurologist

## Brain Stimulation/ Neuromodulation

- VNS
- Anterior Nucleus Thalamus
- Responsive Neurostimulation (RNS)
- Thermal or ultrasound laser ablation

## Surgery Results

- Tailored Resection vs ATL in TLE vs HS
- TLE + Cortical Dysplasia
- Hemispherectomy / Hemiperectomy
- Corpus Callosotomy / Multiple Subpial transection

Return to Neurologist  
for follow-up care

# Epilepsy Surgery Change in Landscape, 2017

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# Temporal Lobe Epilepsy

- 40-50% adult epilepsies
- 25-30% childhood epilepsies
- History of febrile seizures
- Usually symptomatic with structural lesion (rarely genetic)

Tellez-Zenteno JF, et al. *Epilepsy Res Treat.* 2012;630853.

Fontana E, et al. 2006. *Epilepsia.* 2006;47:26-30.

# Temporal Lobe Epilepsy (TLE)

- Mesial Amygdala-Hippocampectomy TLE
  - Temporal basal limbic (Weiser)
- Anterior Temporal Polar
- Combined Mesial-Orbitofrontal
- Temporal Opercular
  - Heschl gyrus epilepsy
- Temporal Plus
  - 27% of suspected TLE
  - Inferior frontal cortex; suprasylvian opercular; temporo-parieto-occipital (TPO) junction

# Brain Imaging and Outcome after Anterior Temporal Lobectomy (ATL) Surgery

- Unilateral hippocampal sclerosis
  - 78% seizure free at 2 years
  - 54% seizure free at 10 years
- MRI Normal
  - 18% seizure free at 10 years
  - 41-48% seizure free at 8 years
- Bilateral MRI lesions
  - 58% seizure free at 2 years

Fong JS, et al. *Epilepsia*. 2011;52:1393-1401.

LoPinto-Khoury C, et al. *Epilepsia*. 2012;53:342-348



# Surgery Outcome: TLE with Hippocampal Sclerosis – Best Outcome

- Seizure free between 60% to 80%;
- 84% with Temporal Lobectomy + Ahippocampectomy risks:
  - Infection
  - Hemorrhage
  - Deep venous thrombosis
  - Anesthesia complications
  - Visual field defects
  - Language/naming
  - CN paresis
  - Paresis/plegia

# Complications of Temporal Lobe Epilepsy Surgery

- |  |      |
|--|------|
| ● Mortality (hemorrhage, infarct, PE, SUDEP)     | <1%  |
| ● Persistent Dysphasia                           | 1-3% |
| ● Severe Visual Field Defects                    | 2-4% |
| ● Hemiparesis (transient or permanent)           | 2-4% |
| ● Transient Anomia (language dominant resection) | 20%  |
| ● Minimal Visual Field Defects                   | >50% |

# Follow-up after Surgery for Refractory TLE +/- HS: Seizure Free Classification

Engel 1	1 yr	2 yrs	5 yrs	5-10 yrs	Average
Wieser et al. 1975-1999 368 cases (mean 7.2 yrs) SAH : Engel1	71%	70%	65%	62%	66.95%
McIntosh et al 1978-1998 325 cases (mean 9.6 yrs) ATL : Engel1	68%	62%	54%	47%	
Spencer et al 1996-2001 339 cases Modified ATL : Engel1		46%	69%		

# Surgical Rates in Epilepsy

- Surgical success rates for temporal lobe epilepsy at the California Comprehensive Epilepsy Program, UCLA & VA Med Centers

Status	Lateral (%)	Medial (%)	Mediolateral (%)	Total (%)
No seizures	4	→ 70	43	48
Rare auras	14	10	7	11
Rare CPS	23	10	21	20
90-95% reduction	5	10	0	4
50% reduction	18	0	14	14

# Surgery Outcome: TLE with Focal Cortical Dysplasia

Cortical Dysplasia		Seizure Free
<b>Type I</b>	Dyslaminar on Histology MRI ↓ volume white matter ↑ signal FLAIR and T2	43%
<b>Type II</b>	Dyslaminar and dysmorphology of neurons including:	75%
<b>Type IIA</b>	↓ FLAIR at GM-WM junction	
<b>Type IIB</b>	Balloon cells (tumor like, ↑ dense FLAIR MRI ↑ thickness, sulcal depth ↑ FLAIR across cerebral cortex and subcortical ↑ T1 weighted only in subcortical ↑ T1 weighted and FLAIR at GM-WM junction	88%
<b>Type III</b>	Plus other lesions HS Tumor vascular malformations	

# Resultado quirúrgico: epilepsia del lóbulo temporal con displasia cortical focal

Displasia cortical		Libre de crisis
<b>Tipo I</b>	Dislaminación en histología IRM ↓ volumen de sustancia blanca ↑ señal FLAIR y T2	43%
<b>Tipo II</b>	Dislaminación y dismorfología de neuronas incluyendo:	75%
<b>Tipo IIA</b>	↓ <b>FLAIR en unión sustancia gris-blanca</b>	
<b>Tipo IIB</b>	Células en balón (simulando tumor ↑ densidad y grosor en MRI FLAIR, profundidad de surcos ↑ FLAIR en corteza cerebral y región subcortical ↑ T1 pesado solo en subcortical subcortical ↑ <b>T1 FLAIR en unión sustancia gris-blanca</b>	88%
<b>Tipo III</b>	Más otras lesiones, esclerosis hipocampal Malformaciones tumorales vasculares	

Hong SJ, et al. *Neurology*. 2017;88:734-742.

# Epilepsy Surgery Change in Landscape, 2017

## Focal

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6. Discuss with family: **complication, expected pathology, results of surgery**



# Discussion

# Answer

- Description
  - While sitting/reading, she pressed the call button and closed her eyes. She took deep breaths for a few seconds then started masticating, swallowing, smacking her lips - not responding to questions. She put the magazine away, placed her left hand behind her head while masticating/swallowing/lip-smacking. She was unable to name a pencil. She looked at the nurse but did not speak.
- Focal seizures with loss of consciousness (LOC) with initial oroalimentary automatisms and gradual recomposure

# Brief Clinical History

24-year-old R-handed Female

- 6 months of age:
  - She was lying on a bed which fell from a balcony 10 stairs high. The bed fell apart on impact and she hit the left side of her head on the marble floor. She was not stiff but her eyes rolled up and she was unresponsive.
  - She regained consciousness within 30 minutes.
  - Several hours later, she had repeated episodes of eye blinking with the eyes rolling upwards which stopped in the hospital.
- No seizure recurrence until 11 years of age.

# Brief Clinical History

24-year-old R-handed Female

- 11-24 years of age, she had > 500 seizures:
  - Warnings: stomach pain +/- discomfort in breast/chest
    - No nausea or vomiting. Occasional pain in left hand.
  - Seizure: Her eyes look different. She is pale/yellow. The hair on her arms stand. She salivates excessively and loses speech. Her eyes roll up and blink repeatedly. She masticated and smacked her lips - like eating.
  - She starts to speak in Farsi/English, but with no sense. Many times she has difficulty speaking on recovery.
  - She may have had 2 GTC without incontinence.

# Examination

- General examination - unremarkable
- Neurologic examination - unremarkable except
  - Recent memory - 4/7 pictures, 2/5 words
  - Concrete interpretation of proverbs, similarities and differences

## Based on the Aura, Name Possible Sites of Seizure Engagement

- Warnings: stomach pain +/- discomfort in breast/chest
  - No nausea or vomiting
  - Occasional pain in left hand
  - The hair on her arms stand

## Answer

- Medial or amygdalo-hippocampal or temporal-opercular or orbitofrontal or mesial frontal
  - Aura of epigastric discomfort
  - Pallor, deep breathing, piloerection



# Classification of Temporal Lobe Epilepsy

## 1. Medial TLE (temporal lobe epilepsy)

- a) Hippocampal-Parahippocampal epilepsy
- b) Amygdalar epilepsy
- c) Hippocampal Parahippocampal-Amygdalar epilepsy

## 2. Lateral TLE

- a) Superotemporal neocortical epilepsy
- b) Inferotemporal neocortical epilepsy

# Classification of Temporal Lobe Epilepsy

## 3. Combined medial and lateral TLE

## 4. Syndromes of Combined Temporal and Extra TLE

### a) Perisylvian TLE

- Anterior perisylvian or temporofrontal opercular epilepsy
- Posterior perisylvian or temporo-central-parietal opercular epilepsy

### b) Combined temporal opercular and posterior orbital frontal epilepsy

### c) Combined mesial temporal and posterior orbital frontal epilepsy

# Seizure Location and Clinical Symptoms

	<b>Aura</b>	<b>Ictus</b>
<b>Hippocampal-Parahippocampal</b>	Olfactory or gustatory sensations; Epigastric or abdominal symptoms	Confusion, Apnea, Masticatory/ Gesticulatory/ Verbal automatisms
<b>Amygdalar</b>	Viscerovegetative symptoms ie. changes in respiration/ heart rate, pupillodilation	Early masticatory automatisms
<b>Lateral Superotemporal neocortical</b>	Vestibular/Auditory hallucinations	Initial staring and arrest of motion followed by verbalization, vocalization, swallowing, orobuccal dyskinetic movements, hypersalivation, coughing and hiccups during confusion & amnesia
<b>Lateral Inferotemporal neocortical</b>	Prosopagnosia or no aura	Arrest of motion, verbalization, vocalization, hypersalivation and orobuccal dyskinesias

# Description

- **First seizure**

- She stopped reading, she quickly rolled her eyeballs upwards, blinked three times, moved her head upwards and slightly, blinked two more times as she stared for 8 seconds unresponsive.

- What is the seizure type?

# Description

- **Second seizure:**
  - She stopped hyperventilating and stared as she blinked once, paused, eyeballs rolled quickly upwards as she blinked three times and continued staring unresponsive for 13 sec.
- What is the seizure type?

# Answer

- ABSENCE with 3 per second spike and wave complexes, typical for pyknoleptic (2 to 200 attacks per day) Childhood Absence Epilepsy (CAE).



# Questions & Answers





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