EPILEPSY AND FIRST SEIZURE EVALUATION AND TREATMENT

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OBJECTIVES

- Define Epilepsy
- Review seizure types (classification)
- Evaluation and diagnosis of epilepsy
- Evaluation of first seizure
- Treatment
SEIZURE vs EPILEPSY

SEIZURE

- physical symptom caused by excessive excitation and synchronization of a population of neurons

EPILEPSY

- recurrent seizures (two or more*) which are not provoked

*new definition of epilepsy can be made after one unprovoked seizure

http://imgbid.com/neuron
Epilepsy

“The Sacred Disease"

- Attack by demons
- Visions “sent by the Gods”.

Luke 9:42

“epilepsy is no more sacred or divine than any other disease, it has a natural cause”

“epilepsy would be considered divine only until it was understood”

- Hippocrates
400 BC

http://classics.mit.edu/Hippocrates/sacred.html
Seizures

- 8-10% of people may have a seizure in their lifetime (1/3 are febrile convulsions)

Epilepsy

- 1% of the population, 3.4 million in the US
- 150,000 new cases diagnosed in US each year
- 4th most common neurological disorder

WHAT IS EPILEPSY?

A practical clinical definition of epilepsy

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Table 2. Operational (practical) clinical definition of epilepsy

- Epilepsy is a disease of the brain defined by any of the following conditions
  1. At least two unprovoked (or reflex) seizures occurring >24 h apart
  2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years
  3. Diagnosis of an epilepsy syndrome

Epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years.
AGE OF ONSET

ETIOLOGY

1975 (Hauser & Kurland\textsuperscript{15})

2014 paradigm

- Focal epilepsy with MRI-detectable lesions
- Autoimmune
- Single-gene epilepsies: familial, de novo
- Epilepsies with complex inheritance
- Modifiers and susceptibility alleles

- Other
- Birth anoxia
- Congenital lesions
- Infectious
- Neoplasm
- Stroke
- Trauma

‘Idiopathic’
WHAT CAUSES EPILEPSY?

Newborns
- Brain malformations
- Hypoxia
- Intracranial hemorrhage

Infants and Children
- Fever
- Infection
WHAT CAUSES EPILEPSY?

Adolescence and young adult
- Traumatic brain injury
- Infection
- 30% of autistic patients
- Genetic factors

Older adult
- Stroke
- Brain tumor
- Alzheimer’s and other dementias
TYPES OF SEIZURES

**Seizures**

- **Focal**
  - Aura
  - Motor
  - Autonomic
  - Dyscognitive
  - Secondary Generalized

- **Generalized**
  - Absence
  - Myoclonic
  - Atonic
  - Tonic
  - Tonic-Clonic

ILAE – International League Against Epilepsy
FOCAL SEIZURES

- **Aware**
  - **Aura**
  - **Motor**
  - **Autonomic**

- **Loss of awareness**
  - **Dyscognitive**
  - **Secondary Generalized**

- Sensory, Psychic, Abdominal, Visual, Taste, Smell
- simple movements or more complex
- heart rate, goose bumps

ILAE – International League Against Epilepsy
GENERALIZED SEIZURES

Seizures

Generalized

Absence

Myoclonic

Atonic

Tonic

Tonic-Clonic

ILAE – International League Against Epilepsy
ILAE 2017 Classification of Seizure Types Expanded Version

Focal Onset
- Aware
- Impaired Awareness

Motor Onset
- automatisms
- atonic
- clonic
- epileptic spasms
- hyperkinetic
- myoclonic
- tonic

Nonmotor Onset
- autonomic
- behavior arrest
- cognitive
- emotional
- sensory

focal to bilateral tonic–clonic

Generalized Onset
- Motor
  - tonic-clonic
  - clonic
  - tonic
  - myoclonic
  - myoclonic–tonic–clonic
  - myoclonic–atonic
  - atonic
  - epileptic spasms
- Nonmotor (absence)
  - typical
  - atypical
  - myoclonic
  - eyelid myoclonia

Unknown Onset
- Motor
  - tonic-clonic
  - epileptic spasms
- Nonmotor
  - behavior arrest

Unclassified

1. Minor Epileptic Seizures: A Proposal from the International League Against Epilepsy (ILAE).
2. Rare Seizures: A Proposal from the International League Against Epilepsy (ILAE).
3. Unclassified Seizures: A Proposal from the International League Against Epilepsy (ILAE).
Fig. 3. Proportion of incidence cases of epilepsy (Rochester, Minnesota, 1935 through 1984), stratified by International League Against Epilepsy seizure type. TC = tonic-clonic seizures.
FOCAL SEIZURES

Symptoms depend on the region of the brain that is activated.
FOCAL ONSET AWARE

(aka Simple Partial Seizures)

- Aura
  - Sensory
  - Motor
  - Psychic
  - Autonomic
- Typically last < 2 minutes
FOCAL ONSET IMPAIRED AWARENESS

(aka Complex Partial Seizures)

- Focal seizure with impaired consciousness
  - loss of awareness
  - confusion
- Typically last < 2 minutes
FOCAL TO BILATERAL TONIC-CLONIC

(aka secondary generalized)

- Focal seizure spreads to both sides of the brain.
- May appear like a generalized seizure if subtle focal seizure signs are not apparent
- Followed by confusion, fatigue, and sometimes with temporary paralysis
- Typically last 1-3 minutes
FOCAL SEIZURE

Right Frontal seizure
FOCAL SEIZURE

Continuation of the same seizure with change in amplitude and frequency
FOCAL SEIZURE

Continuation of the same seizure with spread to the other hemisphere
GENERALIZED TONIC-CLONIC

- Loss of consciousness and post-ictal confusion/lethargy
- Lasting 1-2 minutes
- Tonic phase
  - Stiffening and fall
  - Often make a crying sound
- Clonic Phase
  - Rhythmic arm/leg jerking
ABSENCE SEIZURES

- Brief staring spells ("petit mal")
  - 3-20 seconds
  - Triggered by hyperventilation
  - Onset 4 and 14 years of age
  - Often resolve by 18 years of age
- Normal development and intelligence
MYOCLONIC SEIZURE

- Brief, shock-like jerk of a muscle or group of muscles
- Lasting < 1 second
- May cluster
TONIC AND ATONIC SEIZURE

Tonic seizures
- tonic contraction of muscles

Atonic seizures
- Sudden loss of muscle tone
- Falls, head nods or jaw drops.
- Consciousness usually impaired
- Duration - usually seconds, rarely more than 1 minute
EVALUATION OF SEIZURE

- HISTORY
  - Neurologic Exam
  - Brain imaging: CT or MRI
  - Electroencephalogram (EEG)
  - Blood tests (including drug screen)
  - Lumbar puncture (if meningitis is suspect)
EVALUATION OF SEIZURE

- Seizure or not?
- Provoked or Unprovoked
- Seizure type? (focal vs. generalized)
- What tests should be ordered?
- Start treatment?
- Which drug?
- What about driving?
WAS IT A SEIZURE?

- Syncope
  - Cardiac (arrhythmia)
  - Non-Cardiac (hypotension)
- TIA/Stroke
- Metabolic (hypoglycemia, hyponatremia)
- Migraine
- Sleep Disorders (Narcolepsy)
- Movement Disorders (Paroxysmal Dyskinesia)
WAS IT A SEIZURE?

- Psychogenic Non-Epileptic Spells (PNES)
- Malingering
- Panic Attacks
- Intermittent Explosive Disorder
- Breath-holding Spells

*Misdiagnosis is usually worse than delayed diagnosis*

**First Seizure**

- **25-30%** of first seizures are “provoked”
- “first” was really the “first”?

<table>
<thead>
<tr>
<th>Type</th>
<th>Recurrence Risk (2 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provoked, no brain injury</td>
<td>3%</td>
</tr>
<tr>
<td>Provoked, brain injury</td>
<td>10%</td>
</tr>
<tr>
<td>Single, Unprovoked</td>
<td>42%</td>
</tr>
<tr>
<td>Recurrent, Unprovoked</td>
<td>70-80%</td>
</tr>
</tbody>
</table>

Evidence-based guideline: Management of an unprovoked first seizure in adults


ABSTRACT

Objective: To provide evidence-based recommendations for treatment of adults with an unprovoked first seizure.

Methods: We defined relevant questions and systematically reviewed published studies according to the American Academy of Neurology's classification of evidence criteria; we based recommendations on evidence level.

Results and recommendations: Adults with an unprovoked first seizure should be informed that their seizure recurrence risk is greatest early within the first 2 years (21%-45%) (Level A), and clinical variables associated with increased risk may include a prior brain insult (Level A), an EEG with epileptiform abnormalities (Level A), a significant brain-imaging abnormality (Level B), and a nocturnal seizure (Level B). Immediate antiepileptic drug (AED) therapy, as compared with delay of treatment pending a second seizure, is likely to reduce recurrence risk within the first 2 years (Level B) but may not improve quality of life (Level C). Over a longer term (>3 years), immediate
• After 2 unprovoked seizures, risk of 3rd by 5 yrs: 73%
(59-87%, 95% CI
SEIZURE EVALUATION

- Assess structure
  - MRI brain

- Assess function
  - EEG

- Medication indicated?
NEUROIMAGING
  - MRI brain
(3T Epilepsy Protocol)
EEG within 24hrs has up to 51% yield
Sleep deprived EEG up to 34% yield

TREATMENT

FACTORS:

- Provoked vs. Unprovoked seizure
- Single seizure vs. Recurrent seizures
- Testing results (CT/MRI, EEG)
- Type: Focal (partial) vs. Generalized epilepsy
TREATMENT

- Maximize Quality of Life

- The Treatment has to be right for the seizure type
  - Focal vs Generalized

- The Treatment has to be right for the individual
  - Comorbid medical conditions, gender

- Ultimate goal is no seizures, no side effects
TREATMENT

- Anticonvulsant medication
- Diets: ketogenic, MAD, LGIT
- Devices: VNS, RNS
- Surgery: resection, transection, laser, radiosurgery
AEDs in US

- 1857 - bromides (Br)
- 1912 - phenobarbital (PB)
- 1937 - phenytoin (PHT)
- 1944 - trimethadione (TMD)
- 1954 - primidone (PMD)
- 1960 - ethosuximide (ESM)
- 1974 - carbamazepine (CBZ)
- 1975 - clonazepam (CZP)
- 1978 - valproate (VPA)
- 1993 - felbamate (FBM)
- 1993 - gabapentin (GBP)
- 1995 - lamotrigine (LTG)
- 1997 - topiramate (TPM)
- 1997 - tiagabine (TGB)
- 1999 - levetiracetam (LEV)
- 2000 - oxcarbazepine (OXC)
- 2000 - zonisamide (ZNS)
- 2005 - pregabalin (PGB)
- 2008 - rufinamide (RUF)
- 2009 - Vigabatrin (VGB)
- 2009 - lacosamide (LCM)
- 2010 - ezogabine (EZB)
- 2014 - clobazam (CLB)
- 2014 - eslicarbazepine (ESL)
- 2014 - perampanel (PER)
- 2017 - brivaracetam (BRV)
Fig. 1. Chronology of antiepileptic drug introduction over the past 150 years.
<table>
<thead>
<tr>
<th>AED’s target</th>
<th>Mechanism of Action</th>
<th>Players</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na channel blockers</td>
<td>Inactivate Na ch</td>
<td>CBZ, PHT , FosPHT, OXC, LTG, ZSM</td>
</tr>
<tr>
<td>Ca channel blockers</td>
<td>Inhibit T-type Ca ch</td>
<td>ESM, GBP, PGB</td>
</tr>
<tr>
<td>GABA enhancers</td>
<td>Inhibit L-type Ca ch</td>
<td>BZDs, Barbituates, Primidone</td>
</tr>
<tr>
<td>Agonists</td>
<td>GABA-A receptor: ↑ Cl</td>
<td>Tiagbine</td>
</tr>
<tr>
<td>Reuptake inh</td>
<td>hyperpolarizing cell</td>
<td>Vigabatrin</td>
</tr>
<tr>
<td>Transaminase inh</td>
<td></td>
<td>Flebamate, Topiramate</td>
</tr>
<tr>
<td>Glutamate blockers</td>
<td>Antagonize GLU recept</td>
<td>TPM, ZSM, AZM</td>
</tr>
<tr>
<td>Carbonic anhydrase inh</td>
<td>Cause intracellular K</td>
<td>Progesterone, Allopregnanolone</td>
</tr>
<tr>
<td>Hormones</td>
<td>GABA-A receptor: ↑ Cl</td>
<td>Valproate</td>
</tr>
<tr>
<td>Unknown</td>
<td>SV2a receptor</td>
<td>Levetiracetam</td>
</tr>
</tbody>
</table>
Inhibitory Synapse
# Overview of Medical Therapy

(Partial List)

<table>
<thead>
<tr>
<th>Focal Seizures</th>
<th>Generalized Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Generation</strong></td>
<td><strong>First Generation</strong></td>
</tr>
<tr>
<td>Phenytoin (Dilantin)</td>
<td>Valproate (Depakote)</td>
</tr>
<tr>
<td>Carbamazepine (Tegretol)</td>
<td>Zarontin (Ethosuximide)</td>
</tr>
<tr>
<td>Phenobarbital/Mysoline</td>
<td></td>
</tr>
<tr>
<td><strong>Second Generation</strong></td>
<td><strong>Second Generation</strong></td>
</tr>
<tr>
<td>Levetiracetam (Keppra)</td>
<td>Lamotrigine (Lamictal)</td>
</tr>
<tr>
<td>Topiramate (Topamax)</td>
<td>Topiramate (Topamax)</td>
</tr>
<tr>
<td>Lamotrigine (Lamictal)</td>
<td>Zonisamide (Zonegran)</td>
</tr>
<tr>
<td>Lacosamide (Vimpat)</td>
<td>Rufinamide (Banzel)</td>
</tr>
</tbody>
</table>
## 1st Generation AEDs

<table>
<thead>
<tr>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known Efficacy</td>
<td>Side effects</td>
</tr>
<tr>
<td>Familiarity/Experience</td>
<td>Hepatic inducers</td>
</tr>
<tr>
<td>Cost</td>
<td>Drug-Drug interactions</td>
</tr>
<tr>
<td>Coverage</td>
<td>Hormonal changes</td>
</tr>
<tr>
<td></td>
<td>Teratogenicity</td>
</tr>
</tbody>
</table>
Overview of Medical Therapy (Partial List)

- Broad spectrum anticonvulsants
  -(If you don’t know if it’s partial or generalized)
    - Levetiracetam
    - Lamotrigine
    - Topiramate
    - Zonisamide
    - Valproate
HELP

- Referral for Neurology Consult
# 1st Seizure Clinic Study

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Time between FS event and EEG (average days)</td>
<td>Reduce Number of Days</td>
<td>27.03 days</td>
<td>2.688 days</td>
</tr>
<tr>
<td>2 Time between FS event and Neurology appointment (average days)</td>
<td>Reduce Number of Days</td>
<td>31.53 days</td>
<td>6.460 days</td>
</tr>
<tr>
<td>3 Percent of Cts vs. MRIs ordered for that event (% of all images captured)</td>
<td>Reduce % of CTs ordered</td>
<td>CT: 85.57%, MRI: 26.80%</td>
<td>CT: 78%, MRI: 48%</td>
</tr>
<tr>
<td>4 Average number of ER encounters related to the FS event</td>
<td>Reduce number of subsequent ER encounters</td>
<td>0.6186 encounters</td>
<td>0.1224 encounters</td>
</tr>
<tr>
<td>5 Percent of 1st generation AEDs prescribed following FS event</td>
<td>Reduce % of 1st generation AEDs prescribed</td>
<td>2.10%</td>
<td>0%</td>
</tr>
<tr>
<td>Querying and Counseling about Anti-Epileptic Drug (AED) Side Effects during ED or Clinic Visit</td>
<td>Increase % of patients counseled</td>
<td>24.74%</td>
<td>85.70%</td>
</tr>
<tr>
<td>Counseling About Epilepsy Specific Safety Issues during clinic</td>
<td>Increase % of women counseled</td>
<td>51.00%</td>
<td>90.00%</td>
</tr>
<tr>
<td>6 Percent of women counseled on epilepsy and pregnancy</td>
<td>Increase % of women counseled</td>
<td>2.04%</td>
<td>100.00%</td>
</tr>
</tbody>
</table>
Is this Epilepsy?

3 CASES

- 48 M: first time convulsion
- 32 F: uncontrolled convulsions x 2 years
- 20 F: New onset convulsion
48 M

First time convulsion

- History: no medical issues
- Neuro exam: subtle left arm weakness
- Blood work: normal
- CT: right frontal tumor
- EEG: right frontal slowing

DIAGNOSIS: provoked seizure, not necessarily epilepsy

TREATMENT: tumor removal, +/- AED (most would start Tx)
32 F

Uncontrolled convulsions x 2

- History: migraine and “spells”
- Neuro exam: normal
- Blood work: normal
- MRI: normal
- Labs: normal
- Video-EEG: “seizures” of body thrusting and flailing arms

**DIAGNOSIS:** PNES (psychogenic non-epileptic spells)

**TREATMENT:** psychological evaluation
New onset convulsion

- History: febrile seizures as infant
- Neuro exam: normal
- Blood work: normal
- MRI: left mesial temporal sclerosis
- EEG: left temporal epileptiform activity

DIAGNOSIS: left temporal lobe epilepsy

TREATMENT: anticonvulsants
(if refractory refer for epilepsy surgery)
SUMMARY

- Define Epilepsy
- Review seizure types (classification)
- Evaluation and diagnosis of epilepsy
- Evaluation of first seizure
- Treatment