Epileptic Seizure: Definition

• An Epileptic Seizure is a transient occurrence of signs and symptoms due to abnormal excessive or synchronous neuronal activity in the brain. (Fisher 2005)

When is a Seizure Epilepsy?

• ILAE definition: Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiological, cognitive, psychological and social consequences of this condition.

• The definition of epilepsy requires the occurrence of at least one epileptic seizure.

Fisher, Epilepsia, 2005
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When is a Seizure Epilepsy?

- Proposed Operational Definition:
  - Epilepsy is a disorder of the brain associated with at least two unprovoked seizures or one unprovoked seizure in conjunction with at least a 50% probability of having another unprovoked seizure within 5 years
  - Epilepsy also is characterized by the neurobiological, cognitive, psychological, and social consequences of this condition.
  Fisher, Epilepsia, 2005

INCIDENCE

- The cumulative life time incidence of having at least one seizure is 9%. The cumulative life time incidence of having epilepsy is 3%.
- This is because 1/3 of the 9% incidence consists of children with uncomplicated febrile seizures, another 1/3 consists of patients who have only one seizure in the setting of a medical illness. The remaining 1/3 consists of patients who will be diagnosed with epilepsy.
Etiology

- Group I
  - Exacerbation of seizures in patients with epilepsy
  - Alcohol and drug abuse
  - Withdrawal of drugs
  - Miscellaneous

- Group II
  - Acute vascular event - stroke, ICH
  - Acute trauma
  - CNS neoplasm
  - Anoxic encephalopathy
  - Metabolic encephalopathy
  - Meningitis and other infections

Prognosis is good for Group I and poor for Group II patients. If they become acute repetitive seizures or status epilepticus, group II patients can have a mortality rate of ~33%.
TRAUMA

• Head trauma
• In penetrating head injuries, there is a 30-50% risk of seizures.
• 4% of all epilepsy is posttraumatic.

CNS INFECTIONS

• CNS infections- 1-5% of epilepsy cases.
• Incidence highest in childhood. Bacterial meningitis: 5 fold increased risk. Viral encephalitis: 10 fold increase. The risk lasts 2 years in bacterial meningitis and 15 years in viral encephalitis.
• Early seizures increase the risk of seizure recurrence. (10% vs 22% in viral and 2% vs 13% in bacterial meningitis.

CVA and Tumors

• CVA- Major cause in elderly patients. 55% of all epilepsies in the elderly.
• 11.6% of all epilepsies.
• Early seizures in 2.2-25% of strokes.
• Late onset seizures are a risk factor for recurrent seizures.
• Brain tumor- 3.6% of all epilepsies.
• 30% of patients with brain tumor have acute symptomatic seizures.
Presumed predisposing cause
68.7% of cases are idiopathic

Proportional incidence by age and cause for seizures

Evaluation
- There are two important things to clarify during evaluation of an acute seizure:
  1) The most difficult thing to determine is whether the episode of loss of consciousness is epileptic or non-epileptic or other event.
  2) The second important issue is whether the seizure portends development of epilepsy.
EEG

- Routine EEG is abnormal in 50-60% of the patients after a seizure. Hence abnormal EEG is helpful but normal is not.
- 2 major uses-
  - 1) to determine if epilepsy or not.
  - 2) whether Generalized or focal.

EEG

- Gen 3Hz Spike-Wave, Increase with HV – Absence
- Gen 4-6 Hz Polyspike-wave, Increase with Photic – JME
- Focal spikes in LRE
- Centro-temporal spikes – BRECT
- Hypsarrhythmia, GPFA etc.

IMAGING

- Imaging
  - Mostly in focal.
  - MRI is most useful.
  - CT scan can detect vascular lesions, tumors or SOL larger than 1 cm and injuries but low grade gliomas, malformations, heterotopias Mesial temporal sclerosis can be missed.
SPECIFIC LABS

- Serum prolactin
  - Increased after epileptic but not after non-epileptic seizures.
  - Drastic increase to 4 times normal are seen.
  - May not rise after partial seizures and levels not reliable in the presence of psychotropic drugs.
  - Should be drawn within 15-30 mins of a seizure.

Conditions mimicking seizures

1) Syncope
2) Nonepileptic or psychogenic seizures
3) Breath holding spells.
4) Paroxysmal RBD
5) Panic attack

How to differentiate syncope from seizures

<table>
<thead>
<tr>
<th>Clinical findings</th>
<th>Seizure</th>
<th>Syncope</th>
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</thead>
<tbody>
<tr>
<td>Injury</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>Common</td>
<td>Rare</td>
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<tr>
<td>Postictal conf.</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Headache</td>
<td>Common</td>
<td>Rare</td>
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<tr>
<td>Focal neurological</td>
<td>Sometimes</td>
<td>Never</td>
</tr>
<tr>
<td>Postural</td>
<td>No</td>
<td>Often</td>
</tr>
<tr>
<td>Skin color</td>
<td>Cyanotic</td>
<td>Pale</td>
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</tbody>
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When to start treatment

- First thing is to assess risk of recurrence.
- Seizures with medical conditions treated by initial antiepileptics and treating the cause.
- Epileptic syndromes like BRECT may not require any treatment.
- Some structural lesions are associated with a high risk of recurrent seizures-brain tumors and AVM. So there should be no hesitation in starting treatment and considering surgical interventions if necessary.

RECURRENCE

- Risk of third seizure in a patient with 2 prior seizures is 73%.
- In one study, patients with no history of CNS insults had a recurrence risk of 8% at 1 year, 24% at 2 years and 29% at 5 years.
- Positive FMH of seizures-29% at 1 year and 46% at 5 years.
- Sibling history is more important than parent or other first degree relative.
**RECURRENCE**

- EEG – GSW- 15% at 1 year and 58% at 5 years.
- Occurrence of a previous seizure in the context of an illness or a childhood febrile seizure- 10% 1 year and 39% at 5 years.

**RECURRENCE**

- Patients with h/o previous head trauma, stroke, CNS infections, static encephalopathy have a recurrence rate of 26% at 1 year and 48% at 5 years.
- Increased risk of recurrence in patients with Todd’s paresis – 41% at 1 year and 75% at 5 years.

**RECURRENCE**

- If prior status epilepticus or multiple seizures at onset, risk is 37% at 1 year and 56% at 5 years.
- One study randomized one half of 397 patients aged 2-70 years to treatment after an acute seizure. The treated group had a 25% recurrence risk at 2 years compared to 51% in the untreated group. The steepest part of recurrence is at 2 years.
Probability of 2nd Sz

Recurrence risk for idiopathic or remote symptomatic SZ

TREATMENT

• About 80% of patients with new onset epilepsy can be successfully controlled with one drug. Carbamazepine, Phenytoin and valproate are comparable per studies. Carbamazepine is more effective than phenobarbital and Primidone in partial seizures.
• Newer drugs not usually started in acute settings
Newer antiepileptic drugs

- LAMOTRIGINE
- TOPIRAMATE
- GABAPENTIN
- TIAGABIN
- VIGABATRINE
- LEVETIRACETAM
- ZONISAMIDE
- LACOSAMIDE
- RUFINAMIDE
- PERAMPAANEL
- POTIGA

NEW AEDs

- The newer agents are all add on medications at this point.
- Can be used in both generalized and partial seizures.
- Less side effects.
- Less teratogenic.
- MORE EXPENSIVE
Important side effects

- Lamotrigine: rash – 10%. Including Steven-Johnson’s
- Topiramate: nephrolithiasis, cognitive side effects, reduces IQ points in children, heat sensitivity, glaucoma
- Levetiracetam: Depression, psychotic behavior.
- Zonisamide: nephrolithiasis, heat sensitive
- Gabapentin: weight gain, mood changes

Newer AEDs

- Lyrica: weight gain
- Banzel: depression, suicidal ideation
- Vimpat: rash, dizziness, heart rate issues
- Vigabatrin: visual field constriction
- Perampanel: Psychosis, homicidal tendency
- Potiga – urinary retention
- SIDE EFFECTS ARE LESS IF LOW DOSES ARE USED AND DOSES INCREASED SLOWLY.

SUDEP

- Sudden death in epilepsy
- Always a troublesome concept
- Incidence of .09-2.65 per 1000 patient-years.
- Exact reason is unknown
- Some patients seem to have central apneas during their seizures
SUDEP

- When patients have been on monitor, EEG seems to flatten before EKG abnormality.
- More in patients with refractory generalized tonic clonic seizures on multiple anti-seizure medications.
- More in patients with nocturnal seizures.
- Sleeping in prone position – a risk –?Is this similar to SIDS?

AEDs in Pregnancy

- Frequency of Major Congenital Malformations (MCM) in general population 1.6-2.1% (2-3%)
- Higher risk for polyRx (5.1) than monoRx (2.6)
- Cardiac defects, oral clefts, urological defects, neural tube defects, but may involve any organ system
- Increased risk of minor malformations
- Neurodevelopmental defects common, with lifelong consequences

AEDs in Pregnancy

- Need to maintain seizure control while minimizing teratogenic effects of AEDs
- All AEDs are FDA category C or D
- Choice of AED individualized for each patient
UK Registry

- MCM monotherapy
  - Depakote (VPA) 6.2% [4.6-8.2] > CBZ 2.2% [1.4-3.4]
  - Lamictal (LTG) 3.2% [2.1-4.9]
  - Dose trend for VPA: MCM rate 9.1% for > 1000mg/d, 5.1% for less
  - Dose trend for LTG: MCM 5.4% for doses >200mg/d
- MCM polytherapy
  - VPA polytherapy higher risk than without VPA (OR 2.49)
  - Keppra (LEV) MCM rate 2.7% (n=117); polytherapy included

Cognitive effects of AED exposure in utero

- Cognition not reduced in children of women with epilepsy not on AEDs
- Cognitive outcomes reduced for polyRx compared to monoRx
- Phenobarbital vs. general population: 7 point reduction in VIQ
- Tegretol (CBZ) may not have detrimental effects
  - Depakote vs. other monoRx:
    - Special education: 30% vs. 3-6%
    - Depakote group 6-16 y/o: 10-14 point reduction in VIQ
    - Findings are dose dependent
    - Depakote worse than Tegretol, Phenytoin
- ≥5 GTCS had a negative effect on VIQ
- Disability also associated with lower parental IQ and smaller parental head circumference

Risk of Seizures

- GTC Szs
  - Maternal and fetal hypoxia and acidosis
  - Fetal bradycardia
  - Miscarriage and stillbirths
  - Fetal intracranial hemorrhage
  - Developmental delay
- Risk of complex partial or absence seizures not clear
- Status epilepticus
  - 30% maternal mortality
  - 50% infant mortality
Guidelines for Women on AEDs During Pregnancy

• Should include differential risks of AEDs
• Consistent signals of concern for Depakote
• Differential risks of other AEDs less clear
• Other than Lamotrigine, information on new AEDs is limited
• Does dose matter?
• Folate supplementation: what dose, or does it matter?
  – At least 1mg/d prior to conception if possible; in Europe, 4-5 mg/d is recommended

Guidelines for Women on AEDs During Pregnancy

• No one is guaranteed a healthy child when they become pregnant
• >90% of women with epilepsy have routine pregnancies and deliver healthy babies

AED Levels During Pregnancy

• Check levels monthly; if levels are dropping, check every 2-3 weeks
• Target range for level: prepregnancy level is best
• Have patient call you after level is drawn (1 day after for older meds, 5 days after newer meds)
• Adjusting LTG dose post-partum:
  – Decrease dose by 25-30% of the dose increase, the day of, or the day after, delivery.
  – Reduce another 25-30% after 1 week, then check level.
Epilepsy in pregnancy

• Minimum required medications.
• Avoid polypharmacy.
• Folate supplementation
• Seizures more dangerous to baby than medications.
• Frequent level checks and medication adjustments.
• U/s at least twice initially.
• Depakote most dangerous.

Recommendations – in pregnancy

If sz free for 2-5 yrs- consider stopping AED depending on the epilepsy syndrome.
If on polytherapy, consider monotherapy.
Folic acid – 2-4mg/d
Drug choice: whichever AED controls a woman’s Sz w/o side effects. To avoid Depakote especially if there is a FMH of neural tube defects.

Breast feeding

Generally safe.
All AEDs are found in breast milk in proportion to their protein binding. The more highly bound a drug is the less well it will diffuse into breast milk.
When women on phenobarbital or primidone find their breast fed children getting sedated, then need to stop breast feeding.
Proportion of serum concentration in breast milk-Tegretol- 40%, Dilantin– 20%, Primidone- 70%, Depakote <10%, phenobarbital-38%.
AEDs and contraception

• Doses of hormonal contraceptives need to be increased when women are taking AEDs that speed up metabolism of Oral contraceptive.
• Drugs involved- Phenobarb, Dilantin, Tegretol, trileptal, Topamax (>200mg/d), Lamictal (>400mg/d).
• Drugs usually not involved: Zarontin, Keppra, Gabapentin, Zonisamide.
• Levels of Lamictal drop after oral contraceptives are started. Hence dose of Lamictal will need to be increased.

WHEN TO STOP TREATMENT

• In children, it is reasonable to try stopping treatment after 2 years of seizure freedom.
• Acute symptomatic seizures do not recur once the cause is treated.
• Usually Juvenile myoclonic epilepsy needs life long treatment.
• Seizures associated with MTS, tumors, CVA, AVM etc. need to be treated lifelong.

REFRACTORY EPILEPSY

• Epilepsy is medically refractory in 30% of the cases.
• These patients fail multiple AEDs and combinations either due to inefficacy or side effects.
• If 2 AEDs have failed, the third will work only 20% of the time.
Surgical Treatment
Epilepsy surgery aimed at removing the
seizurogenic zone.

• 2 important criteria are-
  – Seizure should be localizable to a small brain region.
  – Removal of the zone should not cause deficits.

TEMPORAL LOBE EPILEPSY

• Patients with temporal lobe epilepsy with Mesial temporal sclerosis are eminently treatable with surgery.
• The cure rate is 80-90% without medications.
• Seizures need to be localized to the mesial temporal region.
Neocortical epilepsy

• To determine that the patients do not have the more common Mesial temporal epilepsy.
• **Lesional**-If there is a reasonable relationship between seizure characteristics and the lesion and the lesion is surgically accessible, surgery can proceed.
• If there is discordance, then intracranial monitoring is required.
Neocortical -lesional

- Surgery involves resection of the lesion including limited surrounding tissue. Sometimes resection of the surrounding tissue needs to be guided by intracranial monitoring.
- Surgical success is best when entire lesion can be resected.
Neocortical – nonlesional and migrational disorders

- Precise seizure onset localization is often difficult.
- Excellent surgical results can be obtained in the majority of the patients but with considerable expense in terms of time and money.

Surgical outcome

- Patient selection- continuum- From single focus- seizure free with focal resection to Lennox-Gastaut syndrome – no benefit from surgery.
- Location of epileptic zone-results more favorable after temporal rather than extratemporal resection – due to larger epileptogenic zone or proximity of eloquent cortex.

Surgical outcome

- Duration of epilepsy.
  - Matter of debate.
  - Plays a role in Temporal lobe epilepsy by way of kindling and secondary epileptogenesis.
  - Duration has an impact on neuropsychological and psychosocial outcome.
Investigations

- Video EEG: Patient continuously monitored with VEEG. Medications stopped and seizures are recorded with time-locked EEG. Seizures can be localized in 60% of the cases.
- MRI: to pick up MTS
- Neuropsychological evaluation: to pick up presurgical deficits and predict post-surgical deficits.
- All 3 need to be concordant for success.

Intracranial electrodes

- These are electrodes placed on the brain surface after craniotomy or by stereotaxy.
- They can localize seizures not-localizable by scalp EEG.
- The electrodes are stimulated to test brain function at various points to predict deficits after surgery. This can be done in the OR or outside.
Vagus Nerve Stimulation

- In patients who are medically refractory but are not surgical candidates.
- The left Vagus nerve is stimulated at regular intervals with a pacemaker like device which is implanted in the chest under the skin.
- This reduces seizure frequency by 60-70%.
- Useful in patients who have frequent seizures but are not surgical candidates.
- Improves cognition and useful in depression also.

VNS Components

Deep Brain Stimulation

- Stimulation of the Anterior Nucleus of Thalamus.
- SANTE – 68% seizure reduction in 3 years.
  - No stimulation related deaths
  - No symptomatic hemorrhages.

Fisher et al.
Responsive Neuro-Stimulation (RNS)

- 191 patients with medically refractory epilepsy.
- Implanted with responsive neurostimulator connected to depth or subdural electrodes placed at 1-2 seizure foci.
- 12 week blinded period and 84 week open label period when responsive stimulation performed – randomized 1:1 responsive stimulation performed in treatment group and no stimulation in sham.
- Seizure reduction 37.9% in treatment group and 17.3% in sham group. Seizures reduced in sham group when stimulation started. QOL improved.

* Morell et al., RNS study group Neurology 2011

CONCLUSION-Out of the Shadows

- Epilepsy is one of the most disabling diseases afflicting humans since it affects the productive section of the population.
- There has been a lot of recent progress in the management of epilepsy.
- At this point, the treatment goal for every epileptic patient should be to make them seizure free.
When is a Seizure Epilepsy?

• BUT:
  – All epidemiological studies based on old definition
  – Diagnosis may be given inappropriately; eg, after a single seizure and MRI findings of uncertain significance, or diagnosis given before other causes are excluded.
  – Diagnosis has social stigma and effect on employment, insurance, etc.
  – Patients may be overtreated if diagnosis made after only one seizure.