Epilepsy Overview for 3rd year medical students
Outline

- Classification
- New AED
- Epilepsy Surgery
- Drugs used for Status Epilepticus
- Conclusions
Seizures and Epilepsy

- **Seizure**: abnormal hypersynchronous electrical discharge form cerebral cortical neurons. Also called sub clinical seizures.

- **Clinical seizure**: the clinical manifestation of the electric seizure that depends on the site of onset and path of propagation.
Seizures

- Provoked seizures, also known as acute symptomatic seizures, occur with an identifiable proximate cause and are not expected to recur in the absence of that particular cause or trigger.
  - Most common cause is hypoglycemia, another example is drug withdrawal like benzodiazepines.

- Unprovoked seizures occur without an identifiable proximate cause, and epilepsy is defined as a condition of recurrent unprovoked seizures.

Seizures must be both unprovoked and recurrent to call it epilepsy.
Epilepsy and neurotransmitters

It is classically thought to arise from an imbalance between excitation and inhibition in a localized region, multiple brain areas or the whole brain.
• Gamma-aminobutyric acid
• The principal inhibitory neurotransmitter in the cerebral cortex
• GABA is formed within GABAergic axon terminals and released into the synapse, where it acts at one of two types of receptor:
  – GABAA, which controls chloride entry into the cell,
  – GABAB, which increases potassium conductance, decreases calcium entry, and inhibits the presynaptic release of other transmitters.

GABAergic mechanisms in epilepsy.
GABA is rapidly removed by uptake into both glia and presynaptic nerve terminals and then catabolized by GABA transaminase.

GABA agonists suppress seizures, and GABA antagonists produce seizures.

Drugs that inhibit GABA synthesis cause seizures.

Benzodiazepines and barbiturates work by enhancing GABA-mediated inhibition.

Drugs that increase synaptic GABA are potent anticonvulsants.

GABAergic mechanisms in epilepsy.
Glutamate

- Glutamate is the principal excitatory neurotransmitter in the brain and, as such, it inevitably plays a role in the initiation and spread of seizure activity.
• The release of glutamate acting on NMDA receptors can induce seizures.
• In the hippocampus (most seizures initiate from it); brain insults, traumatic brain injuries, or status epilepticus can cause an imbalance between the GABAergic and glutaminergic systems, while GABA has a hypoactivity action and glutamate exerts an excitotoxicity action
Rochester Minnesota Epilepsy Study (1935-1974)

The incidence increases in people below 10 YO and in elderly. The cumulative incidence and prevalence is sharp early and late ages.
Etiology of Newly Diagnosed Epilepsy

Cryptogenic means that we don’t know the cause of the disorder.

Most common causes are cryptogenic.
Relative risk of seizures

A 50 YO patient came to you with seizure, it’s most commonly a secondary seizure because of stroke, tumour, ... etc

No need to memorize numbers

* Not significant
• HI= head injury
Epilepsy: Diagnosis

- **History**: the most important (whether provoked or not)
  - **Description of the event** (1st time or it happened before), from the patient and his relatives since he may not remember the event details.
  - **Medications and substances** (ex. hypoglycaemic drugs)
  - **Past medical history**

- **Physical examination**: postictal, neurological deficit, cognitive dysfunction.

- **EEG** Electroencephalography

- **MRI**

- **Special testing**: genetics, metabolic
ILAE classification of seizures and epilepsy (level of diagnosis)

- **LEVEL 1:** SEIZURE TYPE
- **LEVEL 2:** EPILEPSY BASED ON SEIZURE TYPE
- **LEVEL 3:** EPILEPSY SYNDROME
- **LEVEL 4:** EPILEPSY WITH ETIOLOGY
According to seizure type:

- The classification is based on 3 key features:
  - Where seizures begin in the brain
  - Level of awareness during a seizure
  - Other features of seizures
ILAE 2017 Classification of Seizure Types Expanded Version

Focal Onset

- Aware
  - Impaired Awareness

Generalized Onset

- Motor
  - tonic-clonic
  - clonic
  - tonic
  - myoclonic
  - myoclonic-tonic-clonic
  - myoclonic-atonic
tonic
epileptic spasms
- Non-Motor (absence)
  - typical
  - atypical
  - myoclonic
  - eyelid myoclonia

Unknown Onset

- Motor
  - tonic-clonic
  - epileptic spasms
- Non-Motor
  - behavior arrest

Unclassified

Also called Secondary generalization

Focal to bilateral tonic-clonic
Focal to generalized

Definitions, other seizure types and descriptors are listed in the accompanying paper and glossary of terms.
Degree of awareness usually is not specified.
Due to inadequate information or inability to place in other categories.

No need to memorize the details.
Circled in green is what the doctor mentioned, he talked about these different types of seizures.
EPILEPSY BASED ON SEIZURE TYPE

• Generalized epilepsy
• Focal epilepsy
• Generalized and focal epilepsy
• Unknown if generalized or focal epilepsy
EPILEPSY SYNDROME

A collection of clinical signs, symptoms, imaging and genetic testing.

- An epilepsy syndrome represents a complex of clinical features, signs and symptoms that together define a distinctive, recognizable clinical seizure disorder.
EPILEPSY WITH ETIOLOGY

we know the cause
it increases with more improved tools and tests

• Diagnosis at this level requires that the primary etiology of the epilepsy has been determined.

• Advances in neuroimaging and genetics, as well as improved understanding of the role of specific autoantibodies, have allowed greater accuracy in diagnosis for many people with epilepsy
Differential diagnosis of seizures in adults:

- **Vasovagal syncope**: crowded, uncomfortable, sudden fall and wake up caused by Vasodilation and hypotension. Over stimulation of vagus nerve, can be caused by stress.

- **Cardiogenic syncope**: hypoperfusion because of arrhythmia, MI.

- **Migraine**: it can mimic different disorders

- **TIA**: focal hypoperfusion. TIA: Transient ischemic attack

- **Psychogenic pseudo-seizures**: not real

- **Panic attacks**: feel like death, sweating

- **Rage attacks**: with rage
<table>
<thead>
<tr>
<th>FEATURE</th>
<th>SYNCOPE</th>
<th>SEIZURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>POSTURE</td>
<td>UPRIGHT</td>
<td>ANY POSTURE</td>
</tr>
<tr>
<td>PALLOR AND SWEATING</td>
<td>INVARIABLE</td>
<td>UNCOMMON (cyanosis)</td>
</tr>
<tr>
<td>ONSET</td>
<td>GRADUAL</td>
<td>SUDDEN/AURA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Specific symptoms preceding another symptom.)</td>
</tr>
<tr>
<td>INJURY</td>
<td>RARE</td>
<td>NOT UNCOMMON</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hip dislocation Ex.</td>
</tr>
<tr>
<td>CONVULSIVE JERKS</td>
<td>RARE</td>
<td>COMMON</td>
</tr>
<tr>
<td>INCONTENENCE</td>
<td>RARE</td>
<td>COMMON</td>
</tr>
<tr>
<td>Urinating or defecating</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UNCONSCIOUSNESS</td>
<td>SECONDS</td>
<td>MINUTES</td>
</tr>
<tr>
<td>RECOVERY</td>
<td>RAPID</td>
<td>OFTEN SLOW</td>
</tr>
<tr>
<td>POST ICTAL CONFUSION</td>
<td>RARE</td>
<td>COMMON</td>
</tr>
<tr>
<td>FREQUENCY</td>
<td>INFREQUENT</td>
<td>MAY BE FREQUENT</td>
</tr>
<tr>
<td>PRECIPITATING FACTORS</td>
<td>CROWDED PLACES, LACK OF FOOD, UNPLEASANT CONDITIONS</td>
<td>RARE</td>
</tr>
</tbody>
</table>
DIFFERENCES BETWEEN SEIZURES AND PSEUDOSEIZURES

Expert more than one time.

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>EPILEPTIC SZ</th>
<th>PSEUDO SZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>ONSET</td>
<td>SUDDEN</td>
<td>MAY BE GRADUAL</td>
</tr>
<tr>
<td>RETAINED CONSCIOUSNESS IN PROLONG SEIZURES.</td>
<td>VERY RARE</td>
<td>COMMON</td>
</tr>
<tr>
<td>FLAILING, THRASHING, ASYNCHRONOUS LIMB MOVEMENTS</td>
<td>RARE</td>
<td>COMMON</td>
</tr>
<tr>
<td>PELVIC THRUSTING</td>
<td>RARE</td>
<td>COMMON</td>
</tr>
<tr>
<td>ROLLING MOVEMENTS</td>
<td>RARE</td>
<td>COMMON</td>
</tr>
<tr>
<td>MOVEMENTS WAXING &amp; WAINING</td>
<td>RARE</td>
<td>COMMON</td>
</tr>
<tr>
<td>CYANOSIS</td>
<td>COMMON tone phase in respiratory muscles.</td>
<td>UNUSUAL</td>
</tr>
<tr>
<td>TONGUE BITING AND OTHER INJURY</td>
<td>COMMON</td>
<td>LESS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>COMMON</td>
</tr>
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</table>
### Differences Between Seizures and Pseudoseizures

<table>
<thead>
<tr>
<th>Feature</th>
<th>Epileptic SZ</th>
<th>Pseudo SZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stereotypical Attacks</td>
<td>Usual</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Duration</td>
<td>Seconds, minutes</td>
<td>Often, Prolonged</td>
</tr>
<tr>
<td>Resistance to Passive Limb Movement Or Eye Opening</td>
<td>Unusual</td>
<td>Common</td>
</tr>
<tr>
<td>Prevention of Hand Falling On Face</td>
<td>Unusual</td>
<td>Common</td>
</tr>
<tr>
<td>Induced by Suggestion</td>
<td>Rarely</td>
<td>Often</td>
</tr>
<tr>
<td>Postictal Drowsiness or Confusion</td>
<td>Usual</td>
<td>Often Absent</td>
</tr>
<tr>
<td>Ictal EEG Abnormality</td>
<td>Almost Always</td>
<td>Almost Never</td>
</tr>
<tr>
<td>Postictal EEG Abnormality</td>
<td>Usually</td>
<td>Rare</td>
</tr>
</tbody>
</table>

**Video EEG:** recording video with EEG electrodes.
ADVERSE PROGNOSTIC FACTORS IN EPILEPSY

- Symptomatic etiology.
- Partial onset seizures.
- Atonic seizures.
- Late onset or first year epilepsy
- Additional mental or motor handicap.
- Long duration prior to therapy. 5ys without treatment
- Poor initial response to therapy.
RIGHT ANTERIOR TEMPORAL SHARPS.
INTERICTAL GENERALIZED 3 HTZ SPIKE-WAVE DISCHARGE
GENERALIZED SEIZURE

During seizures
Intractable Epilepsy

- Impairment of quality of life due to Seizures &/ or Drugs
- 20-30% of epileptics are intractable
- Patients failing 2 drugs are likely to be intractable
- 30-40% newly diagnosed partial epilepsy will not attain a seizure remission with pharmacotherapy.
Intractable Epilepsy

• Treatment options

  New AED  AED : anti epileptic drugs

  surgery

  Vagus nerve stimulation

  special diets in children
New Anti Epileptic Drugs
Potential benefits of AED related seizure control

- Reduced social stigma نظرة اجتماعية
- Reduced negative cognitive effects from frequent seizures.
- Reduced risk of status epilepticus (if compliant)
- Reduced risk of physical injury
- Improve employment likelihood
- Helps maintain driving privileges
Risks of AED related adverse effects

- Behavioral problems
- Cognitive impairment
- Idiosyncratic reactions
- Systemic toxicity
- Teratogenicity foetal abnormalities when taken during pregnancy (we can use the least teratogenic drugs or folic acid supplements for example.
- Expense
Ideal Antiepileptic Drug

• Antiepileptogenic
• Affordable
• Compliance.
• Complete Seizure Suppression
• Minimal Side Effects
• 50% of patients fail to achieve the goal of treatment. (1985) NEJM

• 1/3 of patients treated 1984-1997 failed to become seizure free in the first year of treatment. (2000) NEJM
## History of AED

<table>
<thead>
<tr>
<th>Year Introduced</th>
<th>Generic Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1857</td>
<td>Bromide</td>
<td>Bromide</td>
</tr>
<tr>
<td>1912</td>
<td>Phenobarbital</td>
<td>Luminal</td>
</tr>
<tr>
<td>1935</td>
<td>Mephobarbital</td>
<td>Meberal</td>
</tr>
<tr>
<td>1938</td>
<td>Phenytoin</td>
<td>Dilantin</td>
</tr>
<tr>
<td>1946</td>
<td>Trimethadione</td>
<td>Tridione</td>
</tr>
<tr>
<td>1947</td>
<td>Mephenytoin</td>
<td>Mesantoin</td>
</tr>
<tr>
<td>1949</td>
<td>Paramethadione</td>
<td>Paradione</td>
</tr>
<tr>
<td>1951</td>
<td>Phenacemide</td>
<td>Phenurone</td>
</tr>
<tr>
<td>1952</td>
<td>Metharbital</td>
<td>Gemonil</td>
</tr>
</tbody>
</table>

Yellow: used until now

*for memorization

No need to memorize trade names
<table>
<thead>
<tr>
<th>Year Introduced</th>
<th>Generic Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1953</td>
<td>Phensuxamide</td>
<td>Milontin</td>
</tr>
<tr>
<td><strong>1954</strong></td>
<td><strong>Primidone</strong></td>
<td><strong>Mysoline</strong></td>
</tr>
<tr>
<td>1957</td>
<td>Methsuxamide</td>
<td>Celontin</td>
</tr>
<tr>
<td>1957</td>
<td>Ethitoin</td>
<td>Peganone</td>
</tr>
<tr>
<td>1960</td>
<td>Ethuxusamide</td>
<td>Zarontin</td>
</tr>
<tr>
<td>1968</td>
<td>Diazepam</td>
<td>Valium</td>
</tr>
<tr>
<td>1974</td>
<td>Carbamezapine</td>
<td>Tegretol</td>
</tr>
<tr>
<td><strong>1975</strong></td>
<td><strong>Clonazepam</strong></td>
<td><strong>Clonopin</strong></td>
</tr>
<tr>
<td>1978</td>
<td>Valproate</td>
<td>Depakene</td>
</tr>
<tr>
<td>1981</td>
<td>Clorazapate</td>
<td>Tranxene</td>
</tr>
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</table>
## History of New AED

<table>
<thead>
<tr>
<th>Year Introduced</th>
<th>Generic Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993</td>
<td>Felbamate</td>
<td>Felbatol</td>
</tr>
<tr>
<td>1993</td>
<td>Gapabentin</td>
<td>Neurontin</td>
</tr>
<tr>
<td>1994</td>
<td>Lamotrigine</td>
<td>Lamictal</td>
</tr>
<tr>
<td>1996</td>
<td>Topiramate</td>
<td>Topamax</td>
</tr>
<tr>
<td>1997</td>
<td>Tiagabine</td>
<td>Gabatril</td>
</tr>
<tr>
<td></td>
<td>Vigabatrin</td>
<td>Sabril</td>
</tr>
<tr>
<td>1999</td>
<td>Levitracetam</td>
<td>Keppra</td>
</tr>
<tr>
<td>2000</td>
<td>Oxycarbazine</td>
<td>Trileptal</td>
</tr>
<tr>
<td>2000</td>
<td>Zonisamide</td>
<td>Zonergan</td>
</tr>
</tbody>
</table>
Possible Advantages of New AED

• More effective
• Better tolerated
• Safer
• Better for women
• Less interaction
• Broader spectrum
New AED: common concern

• High cost

• Dose related toxicity

• Pharmacodynamic interactions

• Drug levels of limited use
New AED: how they compare

- Similar in:
  Responder rate ≈ 40%
  Seizure free rate < 10%

- Differ in:
  Adverse effects
  Pharmacokinetic profile
  Efficacy for seizure type(s)
AED: Future Development

- Actions at NMDA receptors
- Actions at AMPA receptors
- GABA B receptors and absence seizures
- GABA and Glutamate transporters
- Metabotropic glutamate receptors
- Serotonin
- Neurosteroids
- Genetic studies and the nicotinic acetylcholenergic system
Epilepsy Surgery
Surgical Candidates

- Medically refractory seizures
- Physically, socially disabled
- Localization-related epilepsy we know where.
- Low risk of morbidity low side effects
- Potential for rehabilitation
Response to AED in newly diagnosed epileptics.
Kwan et al NEJM, 2000

The more AED used, the lower the response expected
Epilepsy Surgery: Types

- Medial temporal lobe epilepsy: MTS
  - Most common
  - Most successful but it affects the language areas
- Lesionectomy:
  - Tumor
  - Vascular anomaly
  - Cortical malformation
- Hemispherectomy (one hemisphere or cortex) removal: Rausmusen’s encephalitis
- Corpus callosotomy: LGS
- Vagal nerve stimulation SC (suppression of seizures): intractable, not surgical candidates
- Multiple subpial transection: eloquent areas

MTS: medial temporal sclerosis
Vagus nerve stimulation
Status Epilepticus

- Continuous or recurrent seizures without recovery of consciousness for 30 minutes or more (tendency now to use shorter time definition like 5 minutes and more.

If it lasts more than 5 mins, we have to start treatment:
Assessment
Gluco check: the first and most important thing to do for the patient.
APCs
Benzodiazepine and antiepileptics (Fast working drugs)
Induced comma if this doesn’t work. (Midazolam, propofol, etc.)
**Initial assessment**
- Neurologic examination
- General evaluation with attention to respiratory and circulatory status
- O2 ± mechanical ventilation PRN
- IV catheters inserted (at least two)
- Blood work:
  - Electrolytes, Ca, Mg, Phos, glucose, LFTs, CBC, toxicology, AED level(s)
  - Fingerstick glucose
  - Cardiac monitoring with pulse oximetry
  - Frequent vital signs
  - Consider glucose + thiamine IV

**Initial therapy**

- **In first IV:**
  - Lorazepam 0.1 mg/kg IV or 4 mg IV (max 2 mg/minute)
  - Alternative:
    - Diazepam 0.15 mg/kg IV up to 10 mg per dose (max 5 mg/minute)
  - Wait 1 minute for response then additional lorazepam PRN

- **If no IV access:**
  - Midazolam 10 mg IM if weight >40 kg

- **In second IV:**
  - Fosphenytoin 20 mg/kg PE at 100 to 150 mg PE/minute OR
  - Phenytoin 20 mg/kg at 25 to 50 mg/minute OR
  - Valproic acid 30 mg/kg at 10 mg/kg/minute OR
  - Levetiracetam 40 to 60 mg/kg (maximum 4500 mg) over 15 minutes

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**Correct metabolic abnormalities if present**

**Second-line therapy**

- Repeat fosphenytoin if given previously (5 mg/kg PE) or choose among first-line drugs not already given
- Intubation, mechanical ventilation
- Continuous blood pressure, cardiac monitoring
- Prepare for continuous midazolam or propofol infusion

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**Refractory status epilepticus**

**Begin continuous EEG monitoring**

- **Midazolam**
  - Initial dose: 0.2 mg/kg IV bolus, given at 2 mg/minute
  - Continue infusion beginning at 0.1 mg/kg/hour; titrate upward to seizure freedom
  - May use infusion of up to 3 mg/kg/hour
  - If seizures stop, continue for 24 hours before tapering
  - If seizures persist after 45 to 60 minutes, change to propofol or pentobarbital
  - Use vasopressor support if necessary
  - Maintain therapeutic levels of phenytoin, phenobarbital, or both

- **Propofol**
  - Infusion, 1 to 2 mg/kg loading dose, over 5 minutes
  - Continue infusion, titrated upward to seizure freedom
  - Rates may be as high as 10 to 12 mg/kg/hour but preferably for <48 hours
  - After seizure control, maintain for 24 hours
  - If seizures persist after 45 to 60 minutes, change to pentobarbital
  - Use vasopressor support as necessary
  - Maintain therapeutic levels of phenytoin, phenobarbital, or both

- **Pentobarbital**
  - Initial dose: 5 mg/kg over 10 minutes
  - Repeat as necessary until seizures stop
  - Then, pentobarbital 1 to 5 mg/kg/hour for 24 hours of seizure freedom
  - Use vasopressor support if necessary
  - Maintain therapeutic levels of phenytoin, phenobarbital, or both
CONCLUSIONS:

• Epilepsy is still a challenge
• New AED improved our treatment
• Need for more understanding of basic mechanism of epilepsy and its genesis
• Need to develop specific and target specific treatment
• Surgery is quite effective in properly selected patients but quite underused
• Intravenous benzodiazepines, phenytoin, phenobarb and valproic acid are available, effective and safe Rx for status epilepticus
THANK YOU