EPILEPSY

Dr Sadik AL Ghazawi
Associated professor
Neurologist
MRCP,FRCP UK
‘The Sacred Disease’
‘The Sacred Disease’
Objectives

Discuss the history of the disease.

Discuss the definitions, classifications, terminology and etiology of seizures and epilepsies.

Discuss the epidemiology of seizures and epilepsies.

Talk about seizure’s presentations (semiology).

Evaluate for seizure’s mimics.

Discuss the treatment of seizures and epilepsies.

Discuss the treatment of status epilepticus.
The term “epilepsy” is derived from Greek *epilepsia*: a taking hold of or seizing.

Ancient accounts over 2500 years ago by Babylonians and Egyptians.

Detailed descriptions in *On the Sacred Disease* attributed to Hippocrates in the 5th century BC. Use of “Sacred” possibly meant to be ironic.

Late 19th century:

-Jackson: Model of focal seizures; aura evolving to psychosomatic or convulsive seizure. Use of aura for localizing seizure onset.
Historical Background

- Gowers: Detailed description of epileptic syndromes and concept of “seizures beget seizures”.

  Mid 20th century:

  • Berger, Walter, and Lennox: Ability to record human scalp ElectroEncephaloGram “EEG”.
  • Penfield and Jasper: Surgical resection of the epileptic focus.
  • Merritt and Putnam: Determination that phenytoin was an antiepileptic drug using animal seizure model.
  • Gastaut: Advances in syndromic classification and treatment.
Historical Background

Late 20\textsuperscript{th} century:

- Widespread use of simultaneous video-EEG.
- Neuroimaging
- Development of new antiepileptic drugs based on seizure mechanisms.
- Emergence of epileptology as a defined specialty within neurology and development of comprehensive epilepsy programs including epilepsy monitoring units and epilepsy surgery.
Historical Background

21st century:

- Identification of genetic basis of many syndromic epilepsies.

Neurostimulation devices: Vagus Nerve Stimulation (VNS), Responsive NeuroStimulation (RNS), Deep Brain Stimulation (DBS).

- Use of laser ablation in epilepsy surgery.
Definitions

Seizure

• is the clinical manifestation of an abnormal, excessive, and hypersynchronous electrical discharge of a population of cortical neurons.

Epilepsy:

• A brain disease characterized by recurrent seizures that are unprovoked by systemic or neurologic insults.
Epilepsy syndrome:

a particular form of epilepsy, often implying specific causes, clinical manifestations, and prognosis.

Aura:

The earliest part of a seizure and typically the only subjective experience recalled by the patient.
Definitions

Convulsion:

The motor manifestations of a seizure, usually consisting of rhythmic tonic followed by clonic movements and postures.

Semiology:

Abnormal sensations, emotions, behaviors, loss of consciousness, muscle spasms, convulsions that accompany the brain seizure activity.
Postictal period:

Time between the end of the seizure and recovery to the baseline state.

Status epilepticus:

Five or more minutes of continuous or recurrent seizures without recovery.
Definitions

Sudden Unexpected Death in Epilepsy (SUDEP):

- Sudden, unexpected, witnessed or unwitnessed, nontraumatic, and nondrowning death of patients with epilepsy with or without evidence of a seizure and in whom postmortem examination does not reveal a structural or toxicological causes.
Definitions

Automatisms:

- nonpurposeful, stereotyped, and repetitive behaviors that commonly accompany focal impaired awareness seizures (in the semiologic classification, they define automotor seizures).

  The behavior is inappropriate for the situation.

  Patients are usually amnestic to their automatism.

  Automatisms could be oral or manual.
Epilepsy is a disease of the brain defined by any of the following conditions:

1. A 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.
## Asses Risk of further seizures

<table>
<thead>
<tr>
<th>Single Seizure</th>
<th>Recurrence Risk (2 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>20-60%</td>
</tr>
<tr>
<td>No risk factors, normal EEG, normal MRI</td>
<td>20-30%</td>
</tr>
<tr>
<td>Abnormal EEG (epileptiform discharges)</td>
<td>60-70%</td>
</tr>
<tr>
<td>Focal structural lesion on imaging</td>
<td>&gt;60%</td>
</tr>
<tr>
<td>Two seizures</td>
<td>73%</td>
</tr>
</tbody>
</table>

Berg AT, Shinnar S. Neurology 1991; 41:965-972
Seizures: Classification

Generalized or Focal

Generalized abnormalities on EEG
No lesion or diffuse abnormalities on MRI
No aura
Bilaterally symmetrical onset
Often < 30 seconds

Focal abnormalities on EEG
May have focal lesion on MRI
Auras sometimes present
Focal clinical features during seizure
May be longer (1-2 minutes)
**ILAE 2017 Classification of Seizure Types Expanded Version**

<table>
<thead>
<tr>
<th>Focal Onset</th>
<th>Generalized Onset</th>
<th>Unknown Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aware</strong></td>
<td><strong>Motor</strong></td>
<td><strong>Motor</strong></td>
</tr>
<tr>
<td>Impaired</td>
<td>tonic-clonic</td>
<td>tonic-clonic</td>
</tr>
<tr>
<td>Awareness</td>
<td>clonic</td>
<td>epileptic spasms</td>
</tr>
<tr>
<td><strong>Motor Onset</strong></td>
<td></td>
<td>Non-Motor</td>
</tr>
<tr>
<td></td>
<td>tonic</td>
<td>behavior arrest</td>
</tr>
<tr>
<td></td>
<td>myoclonic</td>
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<tr>
<td></td>
<td>myoclonic-tonic-clonic</td>
<td></td>
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<tr>
<td></td>
<td>myoclonic-atonic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>atonic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>epileptic spasms</td>
<td></td>
</tr>
<tr>
<td><strong>Non-Motor Onset</strong></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>typical</td>
<td></td>
</tr>
<tr>
<td></td>
<td>atypical</td>
<td></td>
</tr>
<tr>
<td></td>
<td>myoclonic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>eyelid myoclonia</td>
<td></td>
</tr>
<tr>
<td><strong>focal to bilateral tonic-clonic</strong></td>
<td><strong>Non-Motor (absence)</strong></td>
<td><strong>Unclassified</strong></td>
</tr>
<tr>
<td></td>
<td>typical</td>
<td></td>
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<tr>
<td></td>
<td>atypical</td>
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<td></td>
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</table>

1. Definitions, other seizure types and descriptors are listed in the accompanying paper and glossary of terms.
2. These could be focal or generalized, with or without alteration of awareness.
3. Due to inadequate information or inability to place in other categories.

Location of Focal Epilepsy

- Temporal
- Frontal
- Parietal
- Occipital
<table>
<thead>
<tr>
<th>Current</th>
<th>2017</th>
<th>Recent</th>
<th>Past</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal without impairment</td>
<td>Focal Aware of awareness</td>
<td>Simple Partial</td>
<td>Focal</td>
</tr>
<tr>
<td>Focal</td>
<td>Complex Partial</td>
<td>Focal with impairment</td>
<td>Psychomotor impaired of awareness</td>
</tr>
<tr>
<td>Focal of awareness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tonic-Clonic OR</td>
<td>Tonic-Clonic</td>
<td>Tonic-Clonic</td>
<td>Grand Mal</td>
</tr>
<tr>
<td>OR focal to Focal evolving to bilateral tonic-clonic seizure</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence</td>
<td>Non-Motor</td>
<td>Absence Petit Mal (Absence)</td>
<td></td>
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Etiology of Epilepsies

- Genetic (previously called idiopathic)
- Structural/Metabolic (previously called symptomatic)
- Unknown cause (previously called cryptogenic)
Epilepsy syndromes per ILAE

1- Electroclinical syndromes arranged by age of onset:

A- Neonatal: Like Otahara syndrome
B- Infancy: Like West syndrome and Dravet syndrome
C- Childhood: Like childhood absence epilepsy, benign epilepsy with centrotemporal spikes, Lennox Gastaut Syndrome
D- Adolescence to adulthood: Like juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with generalized tonic clonic seizures alone
E- Unspecific age: Like reflex epilepsy
Epilepsy syndromes per ILAE

2- Distinct constellations:
   A- Mesial temporal lobe epilepsy with hippocampal sclerosis
   B- Rasmussen’s Encephalitis
   C- Gelastic seizures with hypothalamic hamartomas

3- Epilepsies due to structural metabolic causes:
   A- Malformations of cortical development (cortical dysplasia, heterotopia, etc)
   B- Neurocutaneus syndromes (like tuberous sclerosis)
   C- Tumors
   D- Stroke
   E- etc
Epilepsy syndromes per ILAE

4- conditions associated with seizures but not a diagnosis of epilepsy

A- febrile seizures

B- benign neonatal seizures

5- Epilepsies of unknown cause.
Provoked seizures

Provoking factors include acute CNS or systemic alterations that lead to increased excitation of the brain resulting in a seizure.
Epidemiology

• 50 million people worldwide are affected by epilepsy.

  In 30% of these patients, the seizures are not controlled by any available medical therapy.

Even among patients whose seizures are controlled, significant medication side effects are common.

In addition to the medical burden of epilepsy, the social and economic stress of refractory epilepsy can be devastating to the patient and family.

• 1-2% of World’s population affected ~50 Million worldwide.
Epidemiology

Seizures

- 9-10 % cumulative life incidence

Epilepsy

- 2-3 % cumulative incidence by age 75 years
- 0.5-0.8 % prevalence

There is a bimodal incidence for both seizures and epilepsy with highest rate in the first year of life and increasing again after age 60.
## Incidence and Mortality in the US

<table>
<thead>
<tr>
<th>Epilepsy</th>
<th>Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Around 180,000 people in the US are diagnosed with epilepsy each year.</td>
<td>Around 180,000 are diagnosed with breast cancer each year.</td>
</tr>
<tr>
<td>Around 50,000 people die each year</td>
<td>Around 40,000 die from breast cancer</td>
</tr>
</tbody>
</table>

* Seizures can cause car accidents, falls, burns, etc.
Case 1

1. 26 year old male with no significant past medical history presents to the emergency department because of an episode of loss of consciousness characterized by shaking of extremities.

- History, Exam? •
- Labs? •
- EEG? •
- Imaging? •
- Treatment? •
Which is the most helpful with a spell?

1. History from Patient?
2. Routine EEG
3. MRI
4. History from witness of event
Risk factors for epilepsy:

1. **Family history** (genetic predisposition to seizure disorder)
2. **Birth history and complications**, cognitive and motor development
3. **Infant or childhood seizures** (e.g. febrile seizures are associated with temporal lobe epilepsy)
4. **Past history of CNS infections**, stroke, head trauma, cancer.
History:

Detailed description of the event: Seizures are generally brief and have stereotyped patterns.

1. What was the patient doing at time of the event (e.g. occur out of sleep)?

2. Were there any warning symptoms/aura and were they focal?

3. Did he/she loose consciousness?

4. What other symptoms were present? (SOB, chest pain, etc. may suggest different diagnosis)
5. How long did the events last (most seizure last < 3 minutes)?

6. Description of the movements; falling to the ground, convulsion/myoclonus/posturing, head turn, eye movements, automatisms.

7. Did he/she loose bowel/bladder control or bite their tongue?

8. Was there postictal confusion, hemi-paresis, aphasia?
History

Generalized Tonic-Clonic seizures:

- Can arise from a partial seizure (focal to bilateral tonic clonic) or as a generalized seizure from the beginning (primarily generalized)
- Strained cry
- Generalized tonic then clonic activity
- Duration: 1-2 minutes
- Post-ictal phase
History

Absence Seizures:

Cessation of activity, staring, clonic twitches of perioral and eyelid muscles

Brief: 10-20 seconds

No post-ictal period

Multiple per day

No associated developmental delay

EEG: 3 Hz spike and wave

Can be confused with focal impaired awareness seizures.
History

Semiology of focal epilepsies:

Temporal lobe:

Déjà vu, Epigastric rising sensation, oral and manual automatisms, olfactory or auditory hallucinations, impaired consciousness, impaired language if dominant side.
Frontal lobe:
hypermotor activity, bicycling, brief, recurrent, out of sleep, quick regain of consciousness.

Occipital lobe:
elementary visual hallucinations.

Parietal lobe:
Quick propagation to other areas causes different semiologies.
History

The history can suggest other possible diagnosis for transient neurological symptoms and/or loss of consciousness.

1. **Syncope** (presyncopal symptoms, precipitating maneuvers, orthostatic BP, abnormal ECG)

2. Sleep disorders such as narcolepsy/cataplexy

3. Stroke (LOC is rare in stroke, but can occur with posterior circulation stroke)

4. Migraine
History

5. Paroxysmal Vertigo
6. Transient global amnesia
7. ETOH/drug related “blackouts”
8. Movement disorder (e.g. myoclonus, dyskinesias)

Psychiatric (nonepileptic seizures, panic attacks, hyperventilation)
Suggestive of a Seizure

- Duration: 1-2 minutes
- Clustering
- Tongue-biting
- Incontinence
- Stereotyped
- Amnesia
- Arising out of true sleep
- Eyes open
- Post-ictal dysfunction
# Seizure vs Syncope

<table>
<thead>
<tr>
<th><strong>Seizure</strong></th>
<th><strong>Syncope</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>aura</td>
<td>visual, auditory fading</td>
</tr>
<tr>
<td>duration: 1-2 min</td>
<td>10-30 seconds</td>
</tr>
<tr>
<td>post-ictal phase x several minutes</td>
<td>minimal post-ictal phase</td>
</tr>
<tr>
<td>tonic-clonic activity, limb posturing</td>
<td>pallor &amp; diaphoresis</td>
</tr>
<tr>
<td>tongue-biting</td>
<td>flaccidity</td>
</tr>
<tr>
<td>Incontinence</td>
<td>Provocation by prolonged standing, hunger, heat, pain, micturition, cough</td>
</tr>
<tr>
<td>Guttural, strained cry</td>
<td></td>
</tr>
</tbody>
</table>

- **Seizure**
  - Aura
  - Duration: 1-2 min
  - Post-ictal phase x several minutes
  - Tonic-clonic activity, limb posturing
  - Tongue-biting
  - Incontinence
  - Guttural, strained cry

- **Syncope**
  - Visual, auditory fading
  - 10-30 seconds
  - Minimal post-ictal phase
  - Pallor & diaphoresis
  - Flaccidity
  - Provocation by prolonged standing, hunger, heat, pain, micturition, cough
Physical Exam

- Mental status
- Focal features
- Signs of tongue biting
- Signs of infection or trauma
Diagnostic Workup

Labs: Electrolytes, glucose, LFT, KFT, CBC, toxic screen ?, CPK ?, CSF ?

Imaging: MRI preferred to CT scan.

EEG: as soon as available.
- Sharp wave discharge
Electroencephalogram EEG
childhood absence epilepsy
– 3 Hz spike and wave
Status Epilepticus

Lowenstein in 1999

Defined status has having a seizure for 5 minutes or longer or multiple seizures without full return to baseline

This was adopted in 2010 by the European Federation of Neurological Society

In 2012 The Neurocritical Care Society used this as well
Proposed Algorithm for Convulsive Status Epilepticus
From “Treatment of Convulsive Status Epilepticus in Children and Adults,” Epilepsy Currents 16.1 - Jan/Feb 2016

**Interventions for emergency department, in-patient setting, or prehospital setting with trained paramedics**

1. Stabilize patient (airway, breathing, circulation, disability - neurologic exam)
2. Time seizure from its onset, monitor vital signs
3. Assess oxygenation, give oxygen via nasal cannula/mask, consider intubation if respiratory assistance needed
4. Initiate ECG monitoring
5. Collect finger stick blood glucose. If glucose < 60 mg/dl then
   - Adults: 100 mg thiamine IV then 50 ml D50W IV
   - Children < 2 years: 2 ml/kg D50W IV
   - Children < 2 years: 4 ml/kg D12.5W IV
6. Attempt IV access and collect electrolytes, hematology, toxicology screen, (if appropriate) anticonvulsant drug levels

**0-5 Minutes Stabilization Phase**

**Does Seizure Continue?**
- **YES**
  - A benzodiazepine is the initial therapy of choice (Level A):
    - Choose one of the following 3 equivalent first line options with dosing and frequency:
      - Intramuscular midazolam (10 mg for > 40 kg, 5 mg for 13-40 kg, single dose, Level A) OR
      - Intravenous lorazepam (0.1 mg/kg/dose, max: 4 mg/dose, may repeat dose once, Level A) OR
      - Intravenous diazepam (0.15-0.2 mg/kg/dose, max: 10 mg/dose, may repeat dose once, Level A)
  - If none of the 3 options above are available, choose one of the following:
    - Intravenous phenobarbital (15 mg/kg/dose, single dose, Level A) OR
    - Rectal diazepam (0.2-0.5 mg/kg, max: 20 mg/dose, single dose, Level B) OR
    - Intranasal midazolam (Level B), buccal midazolam (Level B)
  - **YES**
  - If patient at baseline, then symptomatic medical care

**5-20 Minutes Initial Therapy Phase**

**Does Seizure Continue?**
- **NO**
  - There is no evidence based preferred second therapy of choice (Level U):
    - Intravenous fosphenytoin (20 mg PE/kg, max: 1500 mg PE/dose, single dose, Level U) OR
    - Intravenous valproic acid (40 mg/kg, max: 3000 mg/dose, single dose, Level B) OR
    - Intravenous levetiracetam (60 mg/kg, max: 4500 mg/dose, single dose, Level U)
  - If none of the options above are available, choose one of the following (if not given already):
    - Intravenous phenobarbital (15 mg/kg, single dose, Level B)
  - **YES**
  - If patient at baseline, then symptomatic medical care

**20-40 Minutes Second Therapy Phase**

**Does Seizure Continue?**
- **NO**
  - There is no clear evidence to guide therapy in this phase (Level U):
    - Choices include: repeat second line therapy or anesthetic doses of either thiopental, midazolam, pentobarbital, or propofol (all with continuous EEG monitoring)
  - **YES**
  - If patient at baseline, then symptomatic medical care

Disclaimer: This clinical algorithm/guideline is designed to assist clinicians by providing an analytic framework for evaluating and treating patients with status epilepticus. It is not intended to establish a community standard of care, replace a clinician's medical judgment, or establish a protocol for all patients. The clinical conditions contemplated by this algorithm/guideline will not fit or work with all patients. Approaches not covered in this algorithm/guideline may be appropriate.

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Case 2

26 year old man with PMH significant for epilepsy presents with episode typical of his breakthrough seizure. He is on dilantin, keppra and vimpat.

- Labs?
- Imaging?
- Treatment?
Treatment of Epilepsy
Seizure First Aid

- Don't hold the person down or try to stop his movements.
- Time the seizure with your watch.
- Clear the area around the person of anything hard or sharp.
  - Loosen ties or anything around the neck.
- Put something flat and soft, like a folded jacket, under the head.
  - Turn him or her gently onto one side.
- Do not try to force the mouth open with any hard implement or with fingers.
- Be friendly and reassuring as consciousness returns.
Choosing an Anti-Epileptic Drug (AED)

- Type of seizures (generalized vs. focal)
- Can medication be loaded?
- Other comorbidities
- Medication interactions (including contraceptives)
- Short and Long Term Adverse Effects
- Teratogenicity
- Daily, BID, or TID dosing
- Cost and Insurance coverage
- Formulation (liquids, crushable, sprinkles, etc.)
Medications for seizure type

Focal

- Carbamazepine
- Oxcarbazepine
- Phenytoin
- Phenobarbital
- Gabapentin
- Lacosamide
- Pregabalin
- Tiagabine
- Vigabatrin

Generalized

- Valproate
- Lamotrigine
- Levetiracetam
- Topirimate
- Zonsiamide
- Felbamate

Absence

- Ethosuximide

Tonic

- Rufinamide
Common Antiepileptic Drugs (AEDs) side effects

Carbamazepine: Rash, neutropenia, **hyponatremia**, Stevens Johnson syndrome, osteoporosis, numerous drug interactions. **May make myoclonus worse.** Liver enzyme inducing. Will reduce efficacy of oral contraceptive pills (OCPs)

Oxcarbazepine: **Hyponatremia**, rash, Stevens Johnson syndrome. Mild induction of hepatic enzymes. Will reduce efficacy of OCPs

**Sodium valproate:** Rash, **tremor**, **weight gain**, hair loss, menstrual changes, thrombocytopenia, **hyperammononemia**, pancreatitis.
Lamotrigine: Rash, Stevens-Johnson syndrome, toxic epidermolysis. Risk of adverse events increased with valproic acid.

Topiramate: Weight loss, cognitive impairment, renal calculi, metabolic acidosis.

Levetiracetam: Drowsiness, irritability, mood swings

Pregabalin: Weight gain, peripheral edema

Phenytoin: Gum hypertrophy, acne, hirsuitism, coarse facies, osteoporosis, ataxia (cerebellar atrophy). Note: Zero-order kinetics: small dose increase may produce large changes in levels.
Safety and Epilepsy
Know the Driving laws

Epilepsy Foundation: www.efa.org
Women, Epilepsy and Pregnancy

Fetal malformations

Occur in first trimester –

Background risk 2-3% –

In Epilepsy risk ~4-7% –

Risk increases with:

- Valproic acid >> other anti-epileptic drugs (AEDs).
- Polytherapy
- High Drug levels
Epilepsy Surgery

Up to 30% of persons with epilepsy have pharomacoresistant epilepsies.

Many of them can be candidates for epilepsy surgery (resection of the epileptogenic focus) and this can be done after a comprehensive evaluation using non-invasive and invasive EEG monitoring, advanced neuroimaging (MRI with epilepsy protocol, PET, SPECT), and functional brain mapping.

Best outcome is seen in lesional temporal lobe epilepsies (up to 70-90% cure rate).
Other options

Vagus Nerve Stimulation (VNS)

Brain stimulation devices: Responsive NeuroStimulation (RNS), Deep Brain Stimulation (DBS).

Ketogenic or Low carbohydrate diet

Palliative surgeries:

- Corpus Callosotomy; Subpial transections
The END

Thanks