ASSESSMENT & TREATMENT OF SEIZURES

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I have no relevant financial relationships or affiliations with commercial interests to disclose.

Learning Objectives

1. List the different types of seizures
2. Correlate partial seizure symptoms & neuro-anatomic localization
3. Describe the differential diagnosis for seizures
4. Describe the principles of selection & implementation of antiepileptic drug therapy
US EPILEPSY STATISTICS

PREVALENCE:
- 2.2 million people in the United States with epilepsy
- 10,000 people in Oklahoma alone

INCIDENCE:
- 4-7/1000 people/year (.5-1%)
- 150,000 new cases/year
- Single seizure: 9%

> 65 million people worldwide

Statistics from Institute of Medicine Report 3/2012

THE LIFE OF AN EPILEPTIC

- I've had seizures all of my life, so it's been an adventure, to balance the living of today, and fear of the future.
- It effects every aspect of living; your career, fun, and even raising children; from holding a baby to driving a car, you learn that nothing is for certain.
- Working is often difficult, your life is like a yo-yo, no matter how good of a worker you are, a few seizures and they let you go.

THE LIFE OF AN EPILEPTIC (Cont.)

- My friends have helped a lot, by learning about me, the person; they accept the individual, without any reservation.
- If we could educate the world, give them the chance to know, epileptics are ordinary people; good friends and happy lives are our goals.
OVERVIEW

- Definitions
- Diagnosis
- Classification
- Treatment

DEFINITIONS

- A seizure is a sign or symptom of cerebral paroxysmal discharge.
- Epilepsy is a tendency to have recurrent seizures.
- The Epilepsies are syndromes or diseases characterized by a tendency to have recurrent seizures along with other clinical characteristics.
Old Definition of Epilepsy

- A disorder of the brain characterized by an enduring tendency to have epileptic seizures and by the neurobiologic, cognitive, psychologic, and social consequences
- Diagnosis based on at least 2 unprovoked seizures more than 24 hours apart

ILAE 2005

ILAE (International League Against Epilepsy) Definition

Epilepsy is defined as one or more seizures with a high likelihood of recurrence, not due to another immediately triggering cause, such as low blood sugar.

WHAT HAPPENED?

Credit to John DeToledo, MD
Clinical question #1: Was it a seizure?

- Careful history is the most important
  - The patient may be the least helpful in some cases
  - Eye-witness if at all possible
  - Prior spells?

- Conditions That Can Mimic Epileptic Seizures
  - Hyperventilation, syncope
  - Migraine, TIA (transient ischemic attack)
  - Panic attack, psychogenic seizures

DISORDERS THAT MAY MIMIC EPILEPSY

- Gastroesophageal Reflux
- Breath-holding
- Migraine
  - Confusional
  - Basilar
  - With recurrent abdominal pain and cyclic vomiting
- Sleep disorders (especially parasomnias)
- Cerebrovascular events
  - Pallid infantile syncope
  - Vasovagal attacks
  - Vasomotor syncope
  - Cardiac arrhythmias
- Movement disorders
  - Stuttering attacks
  - Paroxysmal choreoathetosis
  - Nonepileptic myoclonus
  - Tics and habit spasms
- Psychological disorders
  - Panic disorder
  - Hyperventilation
  - Rage
  - Pseudoseizures
- Psychological disorders

Clinical question #2: Does the patient have epilepsy?

- Precipitated seizures
  - Metabolic: Uremia, hypoglycemia, hyperglycemia, hepatic failure
  - Toxic: Drug overdose or withdrawal
  - Infectious: Meningitis/encephalitis
Seizure vs Epilepsy

Seizures

- Nonepilepsy (precipitated)
  - Cardiovascular
  - Drug related
  - Syncopal
  - Metabolic
  - Toxic
  - Poison
  - Infectious
  - Febrile
  - Pseudosz

- Epilepsy (recurrent sz)
  - Idiopathic (primary)
  - Symptomatic (secondary)

SEIZURE DIAGNOSIS

- Physical/Neurological Exam
- EEG
  - Photic stimulation
  - Hyperventilation
  - Sleep deprivation
- Anatomic studies
  - CT
  - MRI
- Special studies
  - SPECT
  - PET
- Special studies
  - Intensive CCTV/EEG monitoring

Laboratory Evaluation of Patients with Seizures

- Glucose, oxygen
- Electrolytes, BUN
- Calcium, magnesium
- Drug screen
- Lumbar puncture
- Screen for inborn errors (<5 years)
- EKG
Electroencephalography (EEG)

- Epileptiform EEG patterns (such as spikes and sharp waves) can substantiate the diagnosis and classify focal or generalized.
- Neither a normal EEG nor interictal abnormalities alone refute or confirm the diagnosis.
- If EEG is normal, repeat with sleep-deprivation.
- Video EEG monitoring if there is a concern about nonepileptic events or seizures do not respond to medication.

Guideline: Management of an unprovoked first seizure in adults

- Clarifies when a person’s risk for another seizure warrants medication.
- Nearly 50 studies reviewed
- After a first seizure, risk for another is greatest within the first 2 years
- Risk varies from 21-45%

Greatest risk of another seizure

- Strong evidence in those with
  - Previous brain injury: stroke, brain tumor, head trauma
  - Epileptiform discharges on EEG
- Moderate evidence in those with
  - A significant abnormality on brain imaging
  - Nocturnal seizures
Early Treatment
- About half of patients who have a first seizure will never have another seizure.
- Early treatment lowers the risk of another seizure by 35% within the first 2 years.
- Early treatment rather than waiting for another seizure is unlikely to increase or decrease the likelihood of remaining seizure free.
- 31% will experience a drug side effect (usually mild and reversible).

Conclusions
- There is no black-and-white recommendation about early treatment.
- Individual circumstances, balance of risks and benefits, and personal preferences should be taken into account and the patient should participate in the decision-making process.
Seizure Classification

The International Classification of Epileptic Seizures

Clinical Observation

EEG Findings

Partial Sz

- Focal or localization related

Generalized Sz

- Bilateral initially
- Widespread cerebral involvement

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CLASSIFICATION

Partial seizures

- Simple
- Complex (dyscognitive)

Generalized seizures

- Absence
- Myoclonic
- Tonic-clonic
- Atonic

Continual seizures: Status epilepticus

Partial Seizure

Simple

- Consciousness preserved

Complex

- Consciousness impaired
- Secondarily generalized
- Bilateral cerebral involvement

Consciousness impaired + automatisms

Secondarily generalized

- Consciousness impaired
- Bilateral cerebral involvement

- Automatics

Continual seizures: Status epilepticus
Simple Partial Seizure Features

“Focal Motor Sz”/“Focal Sensory Sz”
- Consciousness intact
- Signs/symptoms variable
  - Motor
  - Somatosensory
  - Autonomic
  - Psychic
- May have focal EEG abnormality

Simple Partial Seizures

Complex Partial Seizure Features

“Temporal Lobe Sz”/“Psychomotor Sz”
- Impaired consciousness
- Ictus duration, 1 min.
- Blank stare
- Automatisms
- Amnesia for ictal event
- Focal EEG abnormality
Left-sided Focal Spike

Complex Partial Seizures

MRI-detected hippocampal atrophy; the most common surgically remediable epilepsy
Types of Generalized Seizures

- Tonic-clonic
- Clonic-tonic-clonic
- Clonic
- Tonic
- Absence (typical, atypical)
- Myoclonic
- Atonic

Generalized Tonic-Clonic Seizure

- Occurs in all age groups
- Involves complete loss of consciousness
- Previously referred to as a “grand mal” seizure

Absence Seizure

- Most common in children
- Involves a brief disruption of consciousness
- Previously referred to as a “petit mal” seizure

Between Seizures:
- Normal appearance

During Seizure:
- Vacant stare
- Eyes roll upward
- Lack of response
Absence Seizure Features
- Childhood onset
- Brief loss of consciousness (10-20 sec)
- Staring spell
- No post-ictal period
- Subtle myoclonic movement
- Simple automatisms
- EEG 3 cps spike and wave

Generalized Spike & Wave

Myoclonic Seizure (minor motor)
- Brief, shock-like muscle contractions (jerks)
  - Head
  - Upper extremities
- Usually bilaterally symmetrical
- Consciousness preserved
- Precipitated by awakening or falling asleep
- May progress into clonic or clonic-tonic seizures
Atonic Seizure (drop attacks)

- Impaired consciousness
- Loss of muscle tone
- Head drop
- Fall
- Brief duration
- Injury common

Treatment

REMEDIES FOR EPILEPSY
from Owsai Temkin, The Falling Sickness

- Blood of the tortoise.
- Testicles of the hippopotamus.
- Feces of the land crocodile.
- Root of strychnos gathered at the time of the waning of the moon, put into a piece of linen, and hung around the neck.
- Scrapings from the selenite stone found by night at the waxing of the moon.
- Filings of iron sharpened on whetstone from Naxos.
### Antiepileptic Drugs (Oldest)

- 1857: Bromides
- 1912: Phenobarbital (Luminal)
- 1935: Mephobarbital (Mebaral)
- 1938: Phenytoin (Dilantin)
- 1946: Trimethadione (Tridione)
- 1947: Mephenytoin (Mesantoin)
- 1949: Paramethadione (Paradione)
- 1951: Phenytoin (Dilantin)
- 1952: Metharbital (Gemonil)
- 1953: Phenacemide (Phenurone)
- 1954: Primidone (Mysoline)

### 1st Generation Antiepileptic Drugs (Old)

- 1957: Methsuximide (Celontin)
- 1957: Ethotoin (Peganone)
- 1960: Ethosuximide (Zarontin)
- 1968: Diazepam (Valium)
- 1974: Carbamazepine (Tegretol)
- 1975: Clonazepam (Klonopin)
- 1978: Valproic Acid (Depakene)
- 1981: Clorazepate (Tranxene)
- 1982: Divalproex (Depakote)

### 2nd Generation AEDs

- 1993: Felbamate (Felbatol)
- 1993: Gabapentin (Neurontin)
- 1994: Lamotrigine (Lamictal)
- 1996: Topiramate (Topamax)
- 1997: Tiagabine (Gabitril)
- 1999: Levetiracetam (Keppra)
- 2000: Oxcarbazepine (Trileptal)
- 2000: Zonisamide (Zonegran)
- 2005: Pregabalin (Lyrica)
**Newer AEDs**

- 2008: lacosamide (Vimpat)
- 2009: rufinamide (Banzel)
- 2009: vigabatrin (Sabril)
- 2010: clobazam (Onfi)
- 2011: ezogabine (retigabine) (Potiga)
- 2012: perampanel (Fycompa)
- 2013: eslicarbazepine (Aptiom)
- 2016: brivaracetam (Briviact)

**POTENTIAL ADVANTAGES OF NEW AEDS**

- Different mechanisms of action
- Improved pharmacokinetics with less need for therapeutic drug monitoring
- Fewer drug interactions
- Improved therapeutic ratios
- Fewer adverse events
- Improved tolerability in special populations
- Long-acting formulations available


**Considerations in the Selection of AED Therapy**

- Efficacy for seizure type
- Epilepsy syndrome
- Etiology
- Side effect profile
- Safety
- Mechanism of action
- Drug interactions
- Route of elimination
- Pharmacokinetics
- Need for laboratory monitoring
- Dosing requirements/drug formulations
- Speed, ease of initiation
- Co-morbidities
- Cost
**Female patients**

- Consider effects on
  - OCP (oral contraceptive pills)
  - teratogenicity
- Prescribe folic acid 1-4 mg (milligrams)

**Initiating Treatment**

- Broad-spectrum AEDs (antiepileptic drugs) are appropriate for all seizure types
  - levetiracetam (Keppra), valproate (Depakote, Lamictal, Lamotrigine), topiramate (Topamax)
- Focal onset seizures: any AED except ethosuximide (Zarontin) may be effective
- Choice may depend on comorbidities, adverse events and cost (GoodRX.com)

**BROAD SPECTRUM AEDS**

- VPA (valproate, Depakote)
- FBM (felbamate, Felbatol)
- LTG (lamictal, Lamotrigine)
- TPM (topiramate, Topamax)
- LVT (levetiracetam, Keppra)
- ZNS (zonisamide, Zonegran)
- RFD (rufinamide, Banzel)
- VGB (vigabatrin, Sabril)
- CLB (clobazam, Onfi)
- BRV (brivaracetam, Briviact)
LIMITED SPECTRUM AEDS

- PB (phenobarbital)
- PHT (phenytoin, Dilantin)
- CBZ (carbamazepine, Tegretol)
- GBP (gabapentin, Neurontin)
- TGB (tiagabine, Gabitril)
- OXC (oxcarbazepine, Trileptal)
- PGB (pregabalin, Lyrica)
- LCS (lacosamide, Vimpat)
- PER (perampanel, Fycompa)
- ESL (eslicarbazepine, Aptiom)

INDIVIDUALIZING THERAPY

- Use drug most appropriate for patient’s seizure disorder
- Titrate to effective level
- In case of treatment failure or toxicity, substitute an alternative agent
- If necessary, combine two non-sedating agents (avoid phenobarbital and BZD)

Guidelines for Combination Therapy

- Avoid combining AEDs with similar or additive side effects
- AED blood levels are available even for the new drugs
Counseling

- Until seizure free (in most states for > 6 months):
  - No driving car (or operating high risk power equipment)
  - No swimming alone or bathing in a closed-drain tub
  - No climbing on ladders (or other high places)
- Avoid sleep deprivation & alcohol
- Avoid alcohol
- Mood
  - High rates of depression & suicidal thoughts
  - AEDs sometimes can contribute
- Urge compliance with AED
  - Daily schedule, pill box
  - Expected side effects

EMERGING AEDS (NONAPPROVED)

- stiripentol
- talampanel
- losigamone
- remacemide
- SGB-017 (ADCI)
- PNU-151774E (or NW-1015)
- fluorofelbamate
- JZP-4
- propyl-isopropylacetamide (PID)
- M-TMCD
- VX-765
- valproemide
- ganaxolone (CCD 1042)
- carisbamate
- YP3089
- 2-deoxyglucose (2DG)
- NAX-5055
- huperzine
- T-2000
- tonabersat
- sulthiame
- ICA-105665
- seletracetam
- *everolimus

NON-MEDICATION OPTIONS

- Surgery
- Vagus Nerve Stimulation
- Deep Brain Stimulation
  - Neuropace
Referral to neurologist

- When the diagnosis is in question
- When the patient has failed to respond to two seizure medications (drug resistant)
- If you are uncomfortable for any reason