EPILEPSY

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Disclosures

• None

Objectives

• Explain current definition and classification of epilepsy
• Identify seizure semiology and non-epileptic causes for seizure like events
• Describe the current work up and management options for epilepsy including anti-seizure medications, neurostimulation and epilepsy surgery
• Review epilepsy quality metrics, impact of epilepsy on women’s health, epilepsy in the elderly and bone health in epilepsy.

Historical Background

• Epilepsy is derived from the Greek word- Epilambanei- which means to possess, grab hold of, or to seize
• The oldest known document on epilepsy is a clay tablet written in the Sumerian language and dated at 1067-1046 B.C.
• Tablet is called antashubba which is Sumerian for "falling disease"
• Possession by demons

• Greeks believed it was a result of a curse
• Hippocrates in 400 BC had a different view

"Men think epilepsy divine, merely because they do not understand it… We will one day understand what causes it, and then cease to call it divine. And so it is with everything in the universe.”

Hippocrates

Epilepsy in the 19th/20th century

• 1857 – First anti-seizure drug, Bromide by Locock
• 1873 - John Hughlings Jackson described the electrical theory for seizures.
• 1912 – Phenobarbital is discovered
• 1934- Hans Berger invented the EEG
• 1939- First animal model for epilepsy
• 1940– Penfield develops modern epilepsy surgery
• Last two decades: Sophisticated imaging techniques, new medications, evidence-based treatment
DEFINITION

Conceptual Definitions - 2005
- Epileptic Seizure: Transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.
- Epilepsy: Disorder of the brain characterized by an enduring predisposition to generate epileptic seizures.


Practical Definition - 2014
- At least two unprovoked (or reflex) seizures occurring >24 hours apart
- 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
- Diagnosis of an epilepsy syndrome


Epidemiology
- 50 million people worldwide and ~3 million Americans
- 1 in 26 patients will have a seizure in their lifetime
- Highest incidence occurs at the extremes of life
- Nearly 70% of treated epilepsy patients enter remission
- Mortality is 2-3 times higher in epilepsy patients (SUDEP)
- Negatively affects quality of life
- Financial burden

CLASSIFICATION

INTERNATIONAL CLASSIFICATION OF SEIZURES
Epilepsia, 1981

I. Partial (Focal, Local) Seizures
   A. Simple Partial
   B. Complex Partial
   C. Partial evolving to Generalized Tonic Clonic

II. Generalized Seizures
   A. Absence
   B. Myoclonic
   C. Clonic
   D. Tonic
   E. Tonic-Clonic
   F. Atonic

III. Unclassified Epileptic Seizures
Revised classification of seizures – 2010

**Classification of seizures**

- Generalized seizures: Aiding within and rapidly engaging bilateral distributed networks
  - tonic-clonic
  - absence
  - tonic
  - absence
- Myoclonic
  - Myoclonic: Myoclonic
  - Atypical: Atypical

**ETIOLOGY**

- 1960’s
  - Lennox & Lennox, 1960. vol 1, p. 539

**ETIOLOGY**

- Genetic
  - (previously called Idiopathic)
  - Direct result of a known or presumed genetic defect
  - Genetic generalized epilepsies– Childhood absence epilepsy, Juvenile absence epilepsy, Juvenile myoclonic epilepsy
  - Cognition is normal, seizure control is favorable
  - Other genetic causes: Intellectual disability/ poor prognosis- Dravet syndrome, Ohtahara syndrome

Simple Partial = Focal seizure without impairment of awareness
Complex Partial = Focal seizure with impairment of awareness (dyssynaptic)
Secondarily generalized seizure = Evolving to a bilateral, convulsive seizure

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11/3/2016
Structural (previously called symptomatic focal)

- Congenital:
  Malformations of cortical development: cortical dysplasia, heterotopia, hemimegalencephaly

  Neurocutaneous Syndromes: Tuberous sclerosis, Neurofibromatosis, Sturge Weber syndrome

- Acquired: Stroke, tumor, trauma, infection, antenatal and perinatal insults

- Metabolic: Disturbed metabolic state – hypoglycemia, hypocalcemia, hyponatremia, high fever

Unknown causes (previously called cryptogenic)

- Epilepsies with normal imaging and no documented metabolic or immune etiology are included here

- About 1/3rd of the cases

Electroclinical syndrome

- Most precise diagnostic category – usually identified based on age at onset, seizure type, EEG characteristics and etiology

Aura/ Focal seizures without impairment of consciousness (simple partial)

- Aura: Subjective sensation preceding the seizure; by itself is a focal seizure

- Helpful in localization

- Temporal lobe epilepsy: 80% have auras: Déjà vu, epigastric rising sensation, distortions of time, fear, metallic taste

- Parietal lobe: contralateral arm sensation

- Occipital lobe: contralateral visual symptoms

- Simple partial seizures: Subdivided into motor (Jacksonian march), sensory, autonomic

Automatisms/ Focal seizures with impairment of consciousness (complex partial)

- Automatisms: Repetitive involuntary semipurposeful movements

- Most common: Lip smacking, chewing, fumbling, patting, picking

- Most complex partial seizures start with an aura and then lose awareness during which automatisms are seen and if this progresses, there will be generalized tonic clonic activity

- Objective signs help in lateralization and localization of seizure focus:
  Dystonic arm posture, figure of 4 posture, ictal speech arrest, early head turn, post-ictal nose wiping etc

- Frontal lobe seizures may have bizarre manifestations and often mistaken for psychogenic events
**Generalized seizures**

- Impairment of awareness
- Bilateral, often symmetric motor manifestations (exception being absence seizures)
- Myoclonic: Brief, rhythmic jerking of extremities, photic triggers
- At times, after a generalized seizure, subtle clinical signs are seen
- Fluctuating mental status after a generalized seizure is often concerning for non-convulsive status epilepticus

**Most important clinical feature for an epileptic seizure is**

**stereotypy**

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**COMMON EPILEPSIES/ ELECTROCLINICAL SYNDROMES**

**West syndrome**

- Triad of epileptic spasms + hypsarrhythmia + regression of psychomotor development
- Onset: age 3-12 months
- Sudden flexion, extension or mixed flexion-extension lasting 1-2 seconds, proximal muscles
- Clusters, after waking, lasting several times a day
- History of perinatal complications/ developmental delay
- EEG: Hypsarrhythmia, during the spasms- electrical decrement (EEG becomes attenuated)
- Treatment of choice: ACTH, Vigabatrin
- Most progress to intractable epilepsy

**Hypsarrhythmia at conventional EEG sensitivity**

**Electrodecrement seen during the spasm**
**Childhood absence epilepsy**

- Onset: age 4-10 (peak 5-6)
- Girls > boys
- Seizures:
  - Typical absence seizure: No aura, sudden onset/offset, momentary loss of awareness (staring), eyelid flutter, minor oral automatisms, 3-15 second duration
  - Generalized tonic clonic seizures and myoclonic seizures are rare at onset
- Positive family history
- EEG: 3 Hz spike-and-wave discharges
- Treatment of choice: Ethosuximide
- Outgrown 50% of the time

**EEG- 3 Hz spike-and-wave**

**Benign Epilepsy with Centro-temporal Spikes- BECTS**

(Rolandic epilepsy)

- Onset: 7-8 years
- Boys > girls
- Focal seizures- clonic/tonic activity of one side of the face, drooling, dysarthria
- Mostly occur in sleep, brief, clusters
- Neurodevelopment normal
- EEG: Spikes in the centro-temporal regions
- Treatment: May not require, case by case basis
- Prognosis: Remission in essentially all children

**Juvenile Myoclonic Epilepsy**

- Most common genetic generalized epilepsy, 5-10%
- Onset: 12-18 years
- Females > males
- Myoclonic jerks in the morning, generalized tonic-clonic seizures
- Provoked by sleep deprivation, alcohol, exposure to flashing lights, stress
- EEG: 4-6 Hz polyspike-and-wave discharges, 50% photoparoxysmal response
- Treatment: Valproic acid (now less favorable), lamotrigine, levetiracetam
- Prognosis: Lifelong therapy, remission is rare

**Status Epilepticus**

- Definition:
  Five minutes or more of continuous clinical and/or electrographic seizure activity or recurrent seizure activity without recovery between seizures.
- Subtypes: Convulsive, Non-convulsive, Refractory
- Morbidity and Mortality is high (~61%) if not treated promptly


**Status Epilepticus**

- Emergency treatment (IV): Benzodiazepines, immediately followed by a maintenance anti-seizure medication EVEN after clinical seizures stop
- Fosphenytoin, Valproate, Levetiracetam, Lacosamide commonly used
- Refractory status: Coma with Pentobarbital, Midazolam, Propofol
- Prognosis depends upon the cause

Brophy et al, Neurocrit Care 2012 Aug;17(1):3-21
EPILEPSY IMITATORS

Non-epileptic Events
- Physiologic
  - Syncope
  - Complex migraine
  - TIA
  - Paroxysms
  - Movement disorders
- Psychogenic
  - Psychogenic Non-Epileptic Seizures (PNES)
  - Children
    - Temper tantrums
    - Behavioral staring
    - Behavioral outbursts
    - Breath holding spells

Psychogenic Non-Epileptic Seizures (PNES)
- Female > Males; all age groups
- Mean time to diagnosis: 7-9 years
- Comorbid psychiatric diagnoses
- Prior sexual abuse in 20-50%, especially females
- Gold standard test for diagnosis is Video-EEG monitoring
- ~40% of Epilepsy Monitoring Unit (EMU) admissions

Syncope
- Closest imitator of epilepsy
- Sudden, unpredictable, may have a prodrome
- Recurrent brief LOC
- Can be stereotypic
- “Convulsive myoclonus”
- Serious injury
- Prompt recovery
- No confusion/disorientation afterwards

Differences between epileptic seizures and PNES

<table>
<thead>
<tr>
<th>Signs</th>
<th>Examination Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychogenic non-epileptic seizures</td>
<td>Seizure eyelid opening, grunting of hand dropping over face, evidence of visual fixation?</td>
</tr>
<tr>
<td>Epileptic seizures</td>
<td>Vague severity, impaired normal reflex, extensor plantar response</td>
</tr>
<tr>
<td>Occurrence from EEG-confirmed sleep, postictal obturation/confusion, stereotypic breath holding postictally</td>
<td></td>
</tr>
</tbody>
</table>
Diagnoses in PNES

- Only 5.3% of PNES patients have epilepsy
- Avoid being judgmental
- Refer to a neurologist
- Provide support during follow-up
- Encourage psychotherapy follow-up

Martin et al, Neurology 2003;61:1791-2

WORK-UP

- Best Diagnostic Tool for Epilepsy: Your Ear (History)
- Second Best: Electroencephalogram (EEG)

EEG

- Routine EEG:
  Sensitivity of a single EEG: 50%
  Three or more serial EEG's, Specificity increases to 80-90%
- Ambulatory EEG:
  Better than routine EEG
  Disadvantages: Mostly no video, too much artifact, cannot fix electrodes
- Video-EEG monitoring: "Gold Standard"

Neuroimaging

Structural:
- CT Head
- MRI brain Epilepsy Protocol – most valuable for localizing the lesion

Functional (Pre-surgical work up):
- Positron Emission Tomography (PET)
- Single Photon Emission Computed Tomography (SPECT)
- Magnetoencephalography (MEG) – spikes

MRI- Mesial Temporal Sclerosis

MRI- Focal Cortical Dysplasia
FIRST SEIZURE: TREAT or NOT

Decision making

- **Treat**
  1. Acute or remote symptomatic seizure (cerebral insult)
  2. Clinically Unstable Patient
  3. Seizure related complications (fracture or aspiration)

- **Recommend Treatment**
  1. When the risk of recurrence is high
  2. When a second seizure may be dangerous
  3. When it benefits patient’s work and function

- **Not Treat**
  1. Low risk of recurrence
  2. Patient’s choice with good understanding of risks

Treatment Options

- Anti-Epileptic Drugs (AEDs)
- Surgery
- Neurostimulation
- Diet

AED’s

First generation AED’s - Important adverse effects

<table>
<thead>
<tr>
<th>AED</th>
<th>Adverse effects</th>
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<tbody>
<tr>
<td>Phenytoin</td>
<td>Dose related: Dizziness, Diplopia, Ataxia, Nystagmus</td>
</tr>
<tr>
<td></td>
<td>Chronic: Hirsutism, Gingival hypertrophy, Neuropathy, Vitamin D Deficiency, Osteoporosis</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Dose related: Tremor, Diplopia, Ataxia, Nystagmus</td>
</tr>
<tr>
<td></td>
<td>Chronic: Hyponatremia, Osteoporosis</td>
</tr>
<tr>
<td>Valproic Acid</td>
<td>Weight gain, tremor, hepatotoxicity, alopecia, pancreatitis, PCOS</td>
</tr>
</tbody>
</table>
Second/ Third generation AED’s

<table>
<thead>
<tr>
<th>AED</th>
<th>Important adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamotrigine</td>
<td>Dizziness, Diplopia, Ataxia, Nystagmus, Skin rash, Insomnia, Aseptic meningitis</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Neuropsychiatric manifestations: depression, irritability</td>
</tr>
<tr>
<td>Oxcarbazepine/</td>
<td>Dose-related: Tremor, Diplopia, Ataxia, Nystagmus, Hyponatremia (highest with OXC)</td>
</tr>
<tr>
<td>Eslicarbazepine</td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Weight gain, edema, myoclonus</td>
</tr>
<tr>
<td>Topiramate/</td>
<td>Headaches, word finding difficulty, cognitive changes, parathoxia’s, closed angle</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>glaucoma, metabolic acidosis, anhidrosis</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>Dizziness, nausea, vomiting</td>
</tr>
<tr>
<td>Perampanel</td>
<td>Psychosis, Homicidal ideation</td>
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Newest AED

- Brivaracetam – February 2016
- Similar mechanism of action like levetiracetam, but 20 fold higher affinity
- Adverse effects: Headache, somnolence (higher than 600 mg/day), fatigue, dizziness, GI disturbance
- No significant drug interactions

Success of AED’s in newly diagnosed epilepsy

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<th>Patients who had many seizures prior to starting AED therapy were less likely to be seizure free</th>
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Drug resistant epilepsy – ILAE Definition

Failure of adequate trials of two (or more) tolerated, appropriately chosen and appropriately used antiepileptic drugs regimens to achieve freedom from seizures

Who is a candidate for pre-surgical evaluation

- Any patient with intractable focal epilepsy
  - Seizures difficult to control
  - Unacceptable side effects to AED's
• United States - >100,000 epilepsy surgery appropriate candidates
• About 10,000 candidates added annually
• Only ~2,000 surgeries are performed every year

Why few surgeries?
• Lack of information among referring providers about benefits and recent advances
• Patient hesitation (~5%)
• Lack of funding despite cost effectiveness

Why do surgeries?
• Seizure freedom
• Prevent complications of long term epilepsy (cognitive)
• Prevent sudden unexpected death in epilepsy (SUDEP)
• Big improvement in Quality of Life (mainly employment and driving)
• Very few surgery related complications

Surgical vs Medical therapy – time for referral
80 patients with temporal lobe epilepsy, randomized to best medical treatment while surgery is delayed one year (40 patients) vs immediate evaluation then surgery (40 patients – 36 operated)

Seizure freedom rates

<table>
<thead>
<tr>
<th>Seizure type</th>
<th>Medical group</th>
<th>Surgical group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex partial</td>
<td>8%</td>
<td>58%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All seizures including auras</td>
<td>3%</td>
<td>58%</td>
<td>&lt;0.001</td>
</tr>
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Wiebe et al., NEJM 2001;345:311-8

Intracranial monitoring

Types of surgeries
• Lobectomy
• Lesionectomy
• Hemispherectomy
• Stereotactic Laser Thermal Therapy
• Multiple subpial transections
• Corpus callosotomy

Neurostimulation – VNS and RNS

Vagal Nerve Stimulator (VNS)
Responsive Neurostimulation (RNS)
**DBS for epilepsy: Pending FDA approval**

Deep Brain Stimulation (DBS)
Anterior nucleus of Thalamus

- Electrical stimulation delivered to targeted areas of the brain.
- Select brain signals detected and recorded by the system.
- Recorded data collected by physicians during clinical studies.

**Diets for seizure control**

- **Ketogenic diet:** Oldest anti-epileptic treatment by fasting (starvation ketosis)
- Most appropriate in children, adults least compliant
- Modified Atkins Diet: Less beneficial than ketogenic diet

**GOAL OF TREATMENT**

ZERO SEIZURES

**Resolution of Epilepsy**

- Individuals with an age-dependent epilepsy syndrome but are now past the applicable age
- or
- Individuals who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years

Fisher et al, Epilepsia 2014, 55(4):475-482

**WOMEN WITH EPILEPSY (WWE)**

- **Hormones:** Estrogen-proconvulsant, Progesterone-anticonvulsant
- **Fertility:** Previously lower fertility, new study (WEPOD) April 2016-prospective, multi-center observational study – WWE had a comparable likelihood of achieving pregnancy, time to be pregnant and pregnancy outcomes compared to healthy peers.
- **Catamenial Epilepsy:** Cyclic exacerbation of seizures in relation to the menstrual cycle (~1/3 of women with focal epilepsy)
- **Menopause:** Erratic fluctuations in gonadal steroids may worsen seizures, Estrogen replacement can exacerbate seizures in some WWE
Epilepsy and Pregnancy

- 3-5 births/thousand will be to WWE
- 50-83% have no significant change in seizure frequency during pregnancy
- Seizure freedom for at least 9 months prior to pregnancy is associated with a high likelihood (84-92%) of remaining seizure free during pregnancy
- In established pregnancy AED not be changed

- AED exposure in utero causes congenital malformations 2-3% higher than general population
- Folic acid (0.4 – 4 mg) reduces neural tube defects

Prevalence of major congenital malformations

Class D for pregnancy

- Valproate
- Carbamazepine
- Phenobarbital
- Phenyltoin
- Primidone
- Topiramate (new to the list)

Epilepsy in the elderly

- Fastest growing segment of epilepsy population
- Incidence is 2-3x higher than general population
- Recurrence rate >90% if untreated
- Most common cause: Stroke
- Other medications may induce seizures
- Intermittent confusion may be the presenting symptom
- 80% of treated population achieve seizure control with monotherapy

Epilepsy in the elderly

- Physiologic changes may affect AED absorption and metabolism
- Start low and go slow, check AED levels
- Choose appropriate AED being mindful of other medications, tolerability and safety issues
- Phenytoin is the most frequently prescribed problematic due to many reasons
- Medications causing dizziness, imbalance, visual disturbances can lead to falls
- Concurrent diuretics with CBZ/OXC can lead to hyponatremia
Bone Health

- More than 50% of adults on AEDs have decreased bone density of either the hip or the spine
- Certain AED’s increase the risk of Osteopenia and Osteoporosis: Phenytoin, Phenobarbital, Primidone, Carbamazepine and Valproate
- Yearly DEXA scans
- Adequate nutrition, exercise, avoidance of smoking/alcohol
- Calcium and Vitamin D supplementation

Comorbidities with epilepsy and Quality of Life

Psychiatric:
- Depression (35%) and anxiety (19%)
- Suicide risk 25 times more than in general population
- Psychosis (7%)
- 2008 meta-analysis found a 1.8 fold increased risk of suicidality associated with AEDs

Cognitive

Functional status: Working and driving

Mortality: Increased risk of Sudden Unexpected Death in Epilepsy (SUDEP)

Epilepsy Quality Metrics

Mesure 8.1: Seizure Type(s) and Current Seizure Frequency(s)
Mesure 8.2: Documentation of Etiology of Epilepsy or Epilepsy Syndrome
Mesure 8.3: Electroencephalogram (EEG) Results Reviewed, Requested, or Test Ordered
Mesure 8.4: Magnetic Resonance Imaging/Computed Tomography Scan (MRI/CT Scan) Results Reviewed, Requested, or Scan Ordered
Mesure 8.5: Queruing and Counseling about Anti-Epileptic Drug (AED) Side Effects
Mesure 8.6: Surgical Therapy Referral Consideration for Intractable Epilepsy
Mesure 8.7: Counseling About Epilepsy Specific Safety Issues
Mesure 8.8: Counseling for Women of Childbearing Potential with Epilepsy

Take home points

- Obtain a good history for a proper seizure classification
- Adequate work up with EEG and MRI
- Appropriately chosen AED
- Being mindful of AED side effects, AED levels, DEXA scan
- Counseling pregnant women with epilepsy
- Assess psychiatric comorbidities in patients with epilepsy
- Consider surgical options early and referral of patients with focal epilepsy to nearest comprehensive epilepsy center for possible surgery