Seizures & Epilepsy
MHD – Neuroscience Module

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Seizures & Epilepsy

Definitions: Seizure

- “An intermittent derangement of the nervous system due to an excessive and disorderly discharge of cerebral nervous tissue”
  - J. Hughlings Jackson, 1870 (still true today)

A seizure is the clinical event

- Paroxysmal episodes of brain dysfunction manifested by stereotyped alteration in behavior
  - Clinical manifestation of a seizure is based on anatomy of the area of the brain that is seizing
  - It is the “opposite” of a stroke (“gain of function” not “loss of function”)
  - Not always associated with loss of consciousness
- A seizure alone does not equal epilepsy
  - The terms are not synonymous
**Seizures & Epilepsy**

*Epilepsy is a syndrome that includes recurrent seizures*

- "Epilepsy" implies the risk for recurrent seizures in the absence of an extra-cerebral cause
- Recurring seizures not directly provoked by infection, drug (alcohol) withdrawal, metabolic changes, or fever

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**Seizures & Epilepsy**

*What Causes A Seizure*

- Excessive or oversynchronized discharges of cortical neurons
- Ineffective recruitment of inhibitory neurons together with excessive neuronal excitation
  - GABA receptor mediates inhibition responsible for normal termination of a seizure
  - NMDA (Glutamate) receptor activation required for propagation of seizure activity

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**Seizures & Epilepsy**

*Who is At Risk: A “bad brain” is at risk to seize*

- Bimodal distribution with the highest incidence in:
  - Neonates & young children
  - Inherited
  - Congenital malformations
  - Prenatal injury
  - Increasing age
    - Trauma
    - Infection
    - Vascular disease
    - Tumors
    - Neurodegenerative disorders

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*Epilepsy incidence rates by age*

Incidence per 100,000

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*Age*
Seizures and Epilepsy

Classification: Seizures

**Partial Seizures**
- Key Feature: seizure has a focal onset in the brain
- Types:
  - Simple partial (no alteration of consciousness)
  - Complex partial (focal onset with impaired consciousness)
  - Partial seizures with secondarily generalized tonic-clonic seizures (focal onset that evolves to a bilateral convulsive seizure)

**Generalized Seizures**
- Key Feature: the entire brain seizes at once
- Types:
  - Absence
  - Myoclonic
  - Atonic
  - Tonic-clonic
  - Tonic
  - Clonic

Seizures & Epilepsy

Classification: Epilepsy

- Epilepsy syndromes
  - Relate to constellation of EEG findings + clinical presentation (seizure type plus additional features)
  - Localization-related
    - (Focal, partial)
    - Generalized
    - Idiopathic (genetically determined)
    - Symptomatic (etiology known or presumed)

Partial Seizure

Focal symptoms (hand) with no change in consciousness
Complex Partial Seizure

Focal symptoms (hand) followed by change in consciousness

Seizures & Epilepsy

How Do Patients Present? Partial Seizures

- Temporal Lobe Seizures
  - Likely the most common partial seizure
  - "Epigastric aura": epigastric rising sensation, fear, déjà vu, olfactory & gustatory sensations
  - "Buzz Word for the Boards" Seizure characterized by staring, unresponsiveness, oroalimentary & gestural automatons
  - May have contralateral limb posturing
  - MRI may show evidence of mesial temporal sclerosis: loss of hippocampal neurons

- Frontal Lobe Seizures
  - Often occur at night
  - Can involve complex movements (bicycling, fencer posturing)
  - Versive movements: the head and eyes turn to the side opposite the seizure
    - Left frontal eye fields drive the eyes to the right
    - One looks away from a seizure and into stroke
  - Focal motor seizures with Jacksonian march and post-ictal Todd’s paralysis

"Todd's paralysis" is named in honor of Robert Bentley Todd, who was a brilliant clinician-educator and also an alcoholic remembered as the intoxicated physician, rolling his carriage to visit patients equally intoxicated by the quantities of alcohol he prescribed. He also ordered 1.5 pints of brandy per day. To be fair, the “treatment of the day” was bleeding. (Proc R Soc Med)
Frontal Lobe Epilepsy

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How Do Patients Present? Partial Seizures

- Parietal Lobe Seizures
  - Uncommon seizures
  - May describe numbness or tingling, often in the lips, fingers or toes
  - Can have fixed, formed visual hallucinations

- Occipital Lobe Seizures
  - Usually darkness or sparks & flashes of light (can easily be confused with migraine)
  - Red is the most commonly described color

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How Do Patients Present? Absence Seizures

- Absence Seizures
  - Classic test question: young child who does poorly in school and noted to be frequently staring off into space
  - Presents ages 4-10: pediatric diagnosis
  - Seizures are brief (<10s) but frequent (10x/day), usually characterized by staring spells
  - EEG with 3 Hz spike-and-wave pattern
  - Treated with ethosuximide
    - One of the few very specific recommendations for treatment

3 Hz spike-and-wave pattern on EEG is considered pathognomonic for absence seizures.
Absence

Absence: Treatment

- First Aid: “Sucks to have Silent (absence) Seizures”
  - Now you just have to remember what “sucks” (ethosuximide) and what’s “silent” (absence)

- Me: “Absence seizures are treated with ethosuximide.” Period.

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How Do Patients Present? Myoclonic Seizures

- Myoclonic Seizures
  - Myoclonic: shock-like or lightening-like contraction of a group of muscles
  - Juvenile Myoclonic Epilepsy
    - Myoclonic jerks that often occur in the morning shortly after awakening in teenagers
    - Can be precipitated by alcohol use & sleep deprivation
    - Treated with valproic acid
      - Also a specific treatment recommendation
Myoclonic Seizure

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How Do Patients Present? Atonic Seizures

- Atonic Seizures
  - Sudden loss of tone
  - Can be focal (head drop) or involved all muscles
  - Very brief loss of consciousness
  - Somewhat treatment resistant

Atonic Seizures
Seizures & Epilepsy
How Do Patients Present? Generalized Seizures

• Generalized Tonic-Clonic Seizures

  – The “classic” seizure; previously referred to as “Grand Mal”
  – Tonic: contraction producing extension and arching
  – Clonic: alternating muscle contraction-relaxation
  – Often strike “out of the blue”, with flexion of the trunk, opening of the mouth & eyelids, and upward deviation of the eyes
  – Patient may scream (“ictal cry”) at the onset
  – Often loss of bladder control
  – Prolonged post-ictal confusion

  Symptoms to Ask About:
  Do you ever wake up with a bitten tongue or blood on your pillow? 
  Have you ever ended up in a room and not known how you got there?
  Any history of shoulder trauma due to unexplained falls?

Generalized Seizure

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Case Examples

• A 38 year old male with history of a left parietal cortex oligodendroglioma presents for episodic right arm tingling and occasional hand stiffening. He is aware of the symptoms when they occur and does not lose consciousness when they occur.
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Case Examples

• A 36 year old male presents for an episodic “burning smell” and epigastric rising sensation. His colleagues report that he “stares off” at his desk and has difficulty speaking for several minutes.

Seizure type: complex partial

Symptoms occur due to epileptiform discharges over the left temporal lobe, likely involving language centers (aphasia/speech arrest).

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Case Examples

• A 22 year old female is brought to the ER by her roommate. The roommate noted the patient’s eyes turn to the left side, followed by complete body shaking. On examination, she has blood on her teeth and her tongue has been lacerated.

Seizure type: complex partial with secondary generalization

Symptoms occur due to epileptiform discharges over the right frontal lobe (eyes turning), which then generalized to involved both hemispheres.

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What Else to Think About: Differential

• Cardiac
  – Syncope
  – Arrhythmias
• Movement disorders
  – Tremor
  – Dystonia
  – Asterixis
  – Myoclonus
• Stroke (TIA)
• Migraine headaches
• Infection with rigors

• Psychiatric disorders
  – Pseudoseizures-somatoform, malingering disorders
  – Panic attack/anxiety
  – Breath holding spells
• Metabolic issues
  – Hypoglycemia
  – Hyperglycemia
• Medications
  – Buproprion is commonly asked

Good rule of thumb: what’s the last thing you remember? If it’s waking up on the floor, it’s probably syncope; if it’s the ambulance or ER, it’s a seizure.
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What Else to Think About: Pseudoseizures

- “Seizures of a non-epileptic origin”
  - Considered to be psychiatric in nature
  - Can occur in patients with true epilepsy
  - Can be more complex than you think
  - A diagnosis of exclusion: assume patient’s have “real” disease until proven otherwise

Potential Clues:
- To-and-fro movements
- Pelvic thrusting
- Eye closure
- Increased respiratory rate (similar to after exercising)
- Absent post-ictal phase
However… not perfect!!!

Pseudoseizure

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Evaluation of a Seizure

- Unprovoked first seizure in adults (AAN)
  - EEG (brain wave test) should be considered as part of the routine evaluation
  - Brain imaging (CT or MRI) should be considered routine
  - Lab tests (CBC, glucose, electrolytes), LP, tox screen may be helpful
    - Spinal tap is not required but should be considered in appropriate patients (concern for infection)
    - Elevated serum prolactin measured 10-20 min after a suspected event should be considered to help differentiate seizure vs. pseudoseizure
      - In the literature, but not commonly done in real practice
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Treatment of a Seizure

- First unprovoked seizure (in a child*)
  - Treatment with AED is not indicated for the prevention of the development of epilepsy
  - Treatment with AED may be considered where the benefits of reducing the risk of a 2nd seizure outweigh the side effects

Good Rule of Thumb: The First Seizure is For Free.

Don’t feel “obligated” to treat unless there is a good reason!!!

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Treatment of a Seizure: “Trick” Question

- Classic Test Question: A 3 year child presents for a single generalized seizure that resolved after 5 minutes. The child has a normal neurologic examination but is noted to be febrile. What treatment is indicated?

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Febrile Seizures: Most Common Seizure Disorder in Children

- Febrile Seizures
  - Typical age range 3 mo-5 yrs
  - Unusual to start at the extreme ends – most before age 3
  - Fever >38.4°C
  - Related to pace of temperature development

- Simple febrile seizure
  - <15 min
  - Generalized/non-focal
  - < 2 within 24 hours

- Most children outgrow
  - Greater risk of adult epilepsy if at least 2 factors
    - Family history of non febrile seizures
    - Abnormal neurological examination
    - Focal seizures with or without Todd’s paralysis
    - Prolonged seizures

DO NOT “NEED” TO TREAT! Can give rectal diazepam.
Seizures & Epilepsy
Status Epilepticus: One You “Have To” Treat!

• A Neurological EMERGENCY!!!!
  – Continuous seizure activity (variably defined as >5 minutes, with long-term consequences at >30 minutes)
  – Greater than 2 seizures in a row and patient does not regain consciousness in between
• Most common causes:
  • Medication non-compliance
  • New onset seizures, infection, trauma, SAH, stroke, drugs (legal and illegal), toxin, mets, non-compliance with seizure meds

Seizures & Epilepsy
Status Epilepticus: One You “Have To” Treat!

• ABC’s: Airway, Breathing, Circulation
• Check blood glucose, consider giving thiamine first
• Lorazepam 0.1 mg/kg IV up to 4x’s (usually 2-4 mg)
  – IM midazolam is an option with no IV access
• Phenytoin 10-20 mg/kg IV
  – Infuse no greater than 50 mg/min
• Consider ICU admission for propofol or IV midazolam

1. DO NOT STICK THINGS IN A PATIENT'S MOUTH!!! THEY WILL NOT “SWALLOW THEIR TONGUE.” THEY WILL CHOKE ON YOUR FINGER THAT THEY JUST BIT OFF.
2. TREAT THE SEIZURE FIRST—DON’T WAIT ON LABS/IMAGING.

Approach to the treatment of seizures
Aim for one medication at the lowest dose with the smallest side effect profile

• “Unfortunately, a clear first choice for specific treatment situations, such as initiation in the newly diagnosed patient, selection of the first add-on drug, or use in a woman anticipating pregnancy, does not exist”
Approach to the treatment of seizures

Aim for one medication at the lowest dose with the smallest side effect profile

- Monotherapy
- Second Monotherapy
- Dual Therapy
- Additional Monotherapies
- Start evaluation for epilepsy surgery
- Vagus Nerve Stimulation
- Ketogenic Diet

Epilepsy Surgery

Cautionary Tale: Patient H.M.
- Seizure disorder starting at the age of 10
- Anterior 5-6cm of the medial temporal lobe removed bilaterally
- Seizures improved, IQ increased (possibly due to lower AEDs)
- Profound anterograde amnesia for declarative memories (conscious recollection of facts or experiences) that never improved
  - Unable to add new words, remember people met after 1953, or recall events after the surgery
  - Cannot identify anything by smell
  - Cannot discriminate between warm or painfully hot
  - Hunger/thirst sensation does not change after eating
  - Able to learn new skills & procedures (implicit memory)

Reflex Epilepsy

- In 1997 at least 618 children suffered convulsions in Tokyo while watching an episode of “Pokemon” that included 5-seconds of flashing red lights in the eyes of “Pikachu”
## Supplemental Slides

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Level</th>
<th>Side effects</th>
<th>Black Box</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Valproic Acid (Depakote)</strong></td>
<td>Start: 250 TID Maint: 250-500 TID Max: 3000mg/d</td>
<td>5-10</td>
<td>Weight gain, Somnolence, Nausea/vomiting, tremor, Thrombocytopenia, Pancreatitis</td>
<td>Depatoxicity, Tanning, Hypoglycemia, Dose, Liver, Harris, Diabetes, Thrombocytopenia</td>
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<tr>
<td><strong>Carbamazepine (Tegretol)</strong></td>
<td>Start: 200 BID Maint: 200-400 TID Max: 2400mg/d</td>
<td>4-12</td>
<td>Rash, Dizziness, Hypotension</td>
<td>Aplastic anemia, Angioedema, MDS, Agranulocytosis, Pancreatitis</td>
</tr>
<tr>
<td><strong>Phenytoin (Dilantin)</strong></td>
<td>Start: 100 TID Max: 200-500mg/d (QD) TID Max: Based on level Total: 10-20mg (1-2DPP has non-linear kinetics)</td>
<td>15-40</td>
<td>Ataxia/nystagmus, Gingival hyperplasia, Hirsutism, Coarse facial features, LAD, Osteomalacia, Peripher neuropathy, No black box warning</td>
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<td><strong>Phenobarbital (Keppra)</strong></td>
<td>Start: 90-250mg/d (QD-BID) Maint: Same Max: ?</td>
<td>15-40</td>
<td>Sedation</td>
<td>None</td>
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<td><strong>Lamotrigine (Lamictal)</strong></td>
<td>Start: 25 QOD for 2 wks, then 25 QOD for 2 weeks, then increase by 25-50 BID for 1-2 wks Maint: 100-200 mg/d (BID) Max: 200 mg/d (BID)</td>
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<td>Suicidal ideation (1-5%), Chest pain, Change in reflexes</td>
<td>Rash (Stevens-Johnson), Contraindication</td>
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<td>Start: 300-600 mg/d (BID) increase by 150 mg (QOD) or 600mg Qoq Maint: 1200 (BID) Max: 2400mg/d (BID)</td>
<td>12-16(10-monohydrol metabolite)</td>
<td>Dizziness, Abdominal pain, Tremor, Nausea</td>
<td>No black box warning, Contraindication</td>
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<td>Start: 25-50 mg/d (QD-BID) increase by 25-50mg/wk Maint: 200-400 mg/d (BID) Max: 800 mg/d (BID)</td>
<td>4-10</td>
<td>Cognitive slowing (&quot;Dopamine&quot;); Weight gain, Depression, Decreased Sensation</td>
<td>No black box warning, Contraindication</td>
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<td><strong>Levetiracetam (Keppra)</strong></td>
<td>Start: 500 BID Maint: 2000 mg/d (BID)</td>
<td>5-40</td>
<td>Hypersomnia, Dizziness, Abdominal pain, Tremor, Alaxia</td>
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<td><strong>Pregabalin (Lyrica)</strong></td>
<td>Start: 150 mg/d (TID) Max: Varias w/ reason for use</td>
<td>5-10</td>
<td>Peripheral edema, Dizziness, Somnolence, Weight gain, Tremor</td>
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Seizures & Epilepsy

Definitions: Epilepsy

- The Hebrews & Greeks agreed that an epileptic seizure occurred because a spirit took possession of the person
  - Greeks: a god
  - Hebrews: the devil
- Epileptics were feared; all contact was dangerous because the spirit might leave the epileptic and enter the mouth of the observer
  - Spitting was recommended as a precautionary measure, generally at the epileptic

Epilepsy (Greek): To seize upon or to take hold of; this isn't that "old" of an issue—the term has been changed to "cerebroelectric disorder" in some nations to reduce the stigma of epilepsy.