Learning Objectives

1. Identify the classification of seizure disorders.
2. Identify the appropriate diagnostic evaluation for a patient suspected of having a seizure disorder.
3. List the medications used to treat an acute convulsion.
4. Select the common medications for epilepsy and appropriately monitor them.
5. Describe the unique features of managing seizures in the pregnant patient.
6. Diagnose and treat migraine headaches.
7. Recognize the indications for neuroimaging in the evaluation of headaches.

Classification of Seizures

- Focal Seizures (partial)
  - Local
  - Ipsilateral propagation
  - Contralateral propagation
  - Secondarily generalized
    - Consciousness may or may not be impaired (simple vs complex)

Definition

- A seizure is a transient occurrence of signs or symptoms due to abnormal excessive or synchronous neuronal activity in the brain, and can be either focal (partial) or generalized

1. A 65-year-old male patient of yours presents to the ED having had a seizure in his bedroom witnessed by his wife. She heard a cry and the fall, and then saw him stiffen, shake all over, and become incontinent of urine. He was not arousable until he had been in the ED for several minutes. His seizure would be classified as:

   A. Complex Partial
   B. Generalized Tonic Clonic
   C. Grand Mal
   D. Myoclonic

   - A. Complex Partial: 4%
   - B. Generalized Tonic Clonic: 60%
   - C. Grand Mal: 39%
   - D. Myoclonic: 0%
Classification of Seizures

- **Generalized Seizures**
  - Non-convulsive (absence)
  - Convulsive
    - Myoclonic
    - Clonic
    - Tonic
    - Tonic-clonic
    - Atonic ("drop attacks")

2. The most likely cause of your patient’s seizure would be:

A. Cerebrovascular disease/stroke
B. Idiopathic
C. Metabolic derangement
D. Brain tumor

Etiology of Seizures

- Idiopathic – 62% overall ages
- Stroke – 15% overall, 49% >age 60
- Brain Tumor – 6% overall, 11% >age 60
- Head trauma
- Intracranial infection
- Cerebral degeneration
- Congenital brain malformations
- Inborn errors of metabolism

“Provoked” Seizures

- Seizures that occur within a medical setting and would not occur if the medical setting were removed
- Metabolic derangements
  - Hypo- and hyperglycemia
  - Hyponatremia
  - Hypocalcemia (usually neonates)
  - Renal failure and uremia

“Provoked” Seizures

- More rare metabolic causes
  - Hyperthyroidism
  - Acute Intermittent Porphyria
- Cerebral anoxia
  - Arrest, anesthesia, drowning, CO
  - Syncope with brief hypoventilation
- Drug toxicities/withdrawal
  - Alcohol
  - Benzodiazepines
Epilepsy

- Epilepsy is a chronic condition characterized by at least two unprovoked seizures at least 24 hours apart.

Seizure Imitators

- Syncope
- Psychiatric disorders
- Sleep disorders
- Movement disorders
- Migraines
- TIAs
- Transient global amnesia

3. Your patient’s complete history and physical is unremarkable for any provoked causes, signs of infection, drug toxicity, or neurological disease. The next step in the work-up for your patient would include:

A. Lumbar puncture
B. Toxicology screen
C. Neuroimaging (CT/MRI)
D. Prolactin level

4. Your work-up for this patient is completely negative. You diagnose an unprovoked seizure. Your first step in treatment would be:

A. Start IV phenytoin
B. Start oral phenytoin
C. Start oral valproic acid
D. Start no medications at this time
4. Your work-up for this patient is completely negative. You diagnose an unprovoked seizure. Your first step in treatment would be:

- A. Start IV phenytoin
- B. Start oral phenytoin
- C. Start oral valproic acid
- D. Start no medications at this time

Starting Antiepileptic Drugs (AEDs)

- Not necessary in individuals with a single new onset seizure or infrequent seizures
- Treat if high risk of recurrence
  - Status epilepticus
  - Hx of brain injury
  - Brain lesion on neuroimaging
  - Focal neurological abnormalities
  - Mental retardation
  - Abnormal EEG with epileptiform discharges

Starting Antiepileptic Drugs (AEDs)

- High risk seizure types
  - Any partial seizure
  - Absence seizure
  - Myoclonic seizure
  - Atonic seizure

Overview of AEDs

- Broad Spectrum (all seizure types)
  - Carbamazepine (Tegretol)
  - Phenytoin (Dilantin)
  - Lamotrigine (Lamictal)
  - Valproic Acid (Depakene)
  - Levetiracetam (Keppra)
  - Oxcarbazepine (Trileptal)
  - Phenobarbital
  - Topiramate (Topamax) - adjunctive
  - Zonisamide (Zonegran) - adjunctive

Antiepileptic Drugs

- Start with AED monotherapy
- Selection is individualized based on:
  - Seizure type
  - Other medications (enzyme induction)
  - Comorbid conditions
  - Potential adverse effects
  - Patient preferences and cost
- Do not consider combination therapy until patient has failed two monotherapy trials
- Monitor patients closely for effectiveness, side-effects, and compliance

Overview of AEDs

- Narrow Spectrum (focal and secondarily generalized)
  - Felbamate (Felbatol)
  - Gabapentin (Neurontin) - adjunctive
  - Lacosamide (Vimpat) - adjunctive
  - Pregabalin (Lyrica) - adjunctive
  - Primidone (Mysoline)
  - Tiagabine (Gabitril) - adjunctive
  - Vigabatrin (Sabril) - adjunctive
Overview of AEDs

- Special seizure types
  - Felbamate (Felbatol) – Lennox-Gastaut Syndrome
  - Rufinamide (Banzel) – Lennox-Gastaut Syndrome
  - Ethosuximide (Zarontin) – absence seizures only
  - Vigabatrin (Sabril) – Infantile spasms

Overview of AEDs

- Common toxicities with AEDs
  - Suicidality – twice the risk with AEDs compared to placebos
  - Neurotoxicities – ataxia, dizziness, somnolence, fatigue, headache
  - Rash – wide-spectrum from simple maculopapular rashes to Stevens-Johnson Syndrome
  - Liver enzyme induction or inhibition

First Generation AEDs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Seizure type</th>
<th>Side effects</th>
<th>Monitoring</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin (Dilantin)</td>
<td>Focal and Secondarily Generalized</td>
<td>Ataxia, diplopia, nystagmus, slurred speech</td>
<td>Blood levels</td>
<td>$</td>
</tr>
<tr>
<td>Valproic Acid (Depakene)</td>
<td>All seizure types</td>
<td>Tremors, N/V, somnolence, weight gain</td>
<td>Blood levels</td>
<td>$5</td>
</tr>
<tr>
<td>Carbamazepine (Tegretol)</td>
<td>Focal and Secondarily Generalized</td>
<td>Ataxia, N/V, rash, hyponatremia, aplastic anemia</td>
<td>Blood levels</td>
<td>$</td>
</tr>
<tr>
<td>Ethosuximide (Zarontin)</td>
<td>Absence only</td>
<td>Rash, N/V, hyperactivity, ataxia</td>
<td>Blood levels</td>
<td>$</td>
</tr>
<tr>
<td>Phenobarbital/Primidone</td>
<td>Focal and Secondarily Generalized</td>
<td>Rash, sedation, hyperactivity, ataxia</td>
<td>Blood levels</td>
<td>$</td>
</tr>
</tbody>
</table>

Second Generation AEDs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Seizure type</th>
<th>Side effects</th>
<th>Monitoring</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxcarbazepine (Trileptal)</td>
<td>Focal and Secondarily Generalized</td>
<td>Ataxia, rash, GI, hyponatremia, sedation</td>
<td>Few drug interactions</td>
<td>$$$</td>
</tr>
<tr>
<td>Gabapentin (Neurontin)</td>
<td>Focal and Secondarily Generalized</td>
<td>Fatigue, ataxia, weight gain, nystagmus</td>
<td>Few drug interactions, best safety profile</td>
<td>$$</td>
</tr>
<tr>
<td>Lamotrigine (Lamictal)</td>
<td>All seizure types</td>
<td>Ataxia, tremor, Stevens-Johnson Syndrome, N/V</td>
<td>Interacts with valproic acid</td>
<td>$$$</td>
</tr>
<tr>
<td>Topiramate (Topamax)</td>
<td>All seizure types</td>
<td>Memory, weight loss, depression, nephrolithiasis</td>
<td>Interacts with other AEDs</td>
<td>$$$</td>
</tr>
<tr>
<td>Levetiracetam (Keppra)</td>
<td>Adjunctive - Generalized</td>
<td>Somnolence, anxiety, weight loss, pancytopenia</td>
<td>Few drug interactions</td>
<td>$$</td>
</tr>
</tbody>
</table>

Second Generation AEDs

- Adjunctive (combination) therapy only
  - Tiagabine (Gabitril) - partial seizures
  - Pregabalin (Lyrica) - partial seizures
  - Zonisamide (Zonegran) – All seizure types
  - Felbamate (Felbatol) – All seizure types

Which AED Is Best???

- Not much evidence and few head-to-head trials
- Standard and New Antiepileptic Drugs (SANAD) trial in UK
  - 1721 patients with partial seizures and 716 with generalized seizures
  - Measured time to treatment failure
  - Lamotrigine best for partial seizures
  - Valproate best for generalized seizures
  - Not blinded trial

Status Epilepticus

- A single unremitting seizure lasting longer than 5-10 minutes, or recurrent seizures without interictal return to baseline
- Overall mortality rate of first episode is 20%
  - Metabolic stress of repeated muscular convulsions
  - Neuronal death after 30-60 minutes of continuous seizure activity

5. Which of the following should be given intravenously in the initial treatment of status epilepticus?

A. Propofol
B. Lorazepam
C. Phenobarbital
D. Midazolam

Epilepsy and Pregnancy

- Hormonal contraception failure on AEDs that stimulate cytochrome P450 system:
  - Carbamazepine
  - Phenytoin
  - Phenobarbital/primidone
  - Topiramate
  - Oxcarbazepine
6. A 23-year-old female comes to you for pre-conception counseling. She has idiopathic epilepsy, but has been seizure-free on valproic acid. You would recommend:

A. She should stop all AEDs
B. She never get pregnant since seizure disorder is a contraindication to pregnancy
C. She should supplement with Folic Acid 4 mg per day prior to conception
D. She should not breastfeed

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Epilepsy and Pregnancy

- Consider withdrawing AEDs 6 months prior to conception if patient has been seizure-free >2 years
- Do not change AEDs in pregnancy if patient well-controlled
- Supplement Folic Acid 4 mg per day if patient on carbamazepine or valproic acid

Epilepsy and Pregnancy

- Monitor both total and free drug levels of AEDs at 6 weeks, 10 weeks, then once a trimester, then first or second postpartum week.
- Vitamin K supplementation 10-20 mg/day in last month of pregnancy if on phenobarbital, carbamazepine, phenytoin, topiramate, oxcarbazepine.
- May breastfeed on AEDs except lamotrigine

7. A 36-year-old female comes to you for a complaint of headache that she has had for years and occurs 8-10 times a year. They have not changed and start with flashing lights in her eyes, followed by left-sided throbbing headaches associated with nausea and vomiting. She has taken OTC meds but wants to get better relief and not miss work so much.

A. Order a brain MRI
B. Prescribe a sublingual ergotamine
C. Prescribe propranolol
D. Prescribe sumatriptan

7. A 36-year-old female comes to you for a complaint of headache that she has had for years and occurs 8-10 times a year. They have not changed and start with flashing lights in her eyes, followed by left-sided throbbing headaches associated with nausea and vomiting. She has taken OTC meds but wants to get better relief and not miss work so much.

A. Order a brain MRI
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C. Prescribe propranolol
D. Prescribe sumatriptan
Migraine Headache

- Affects 12% of the population, female predominance
- Pathophysiology - unclear
  - Cellular and blood-brain permeability changes leading to inflammation of meninges and vasodilation
  - Genetic factors play a major role.
- Recurrent attacks in four phases
  - Prodrome – euphoria, depression, irritability, yawning
  - Aura
  - Headache
  - Postdrome – sudden head movement causes head pain

International Headache Society Diagnostic Criteria for Migraine

- Migraine without aura
  - Headaches last 4-72 hours
  - Two of the following:
    - Unilateral
    - Throbbing
    - Moderate to severe intensity
    - Worsened by usual physical activity
  - At least one of the following
    - Photophobia
    - Phonophobia
    - Nausea/vomiting
  - No evidence of other underlying disease

- Migraine with aura
  - Transient neurologic symptoms
    - Start gradually over 5-20 min
    - Last less than 60 min
    - Headache as above starts within 60 min
  - Types of aura
    - Visual – flickering lights, spots or lines
    - Sensory – pins and needles, numbness
    - Dysphasic speech
    - Fully reversible symptoms
  - At least two attacks of headache with aura

Migraine Variants

- Menstrual migraine
- Basilar-type migraine
  - Tinnitus, vertigo, ataxia, diplopia
- Familial hemiplegic migraine
  - Motor weakness that is fully reversible
  - At least one first- or second-degree relative
- Rare types
  - Aura without headache
  - Ocular migraines
  - Ophthalmoplegic migraines

Diagnosis of Migraine Headache

- Clinical diagnosis – primarily history
- Negative neurological examination
- Neuroimaging unnecessary, except with
  - Unexplained abnormal neuro findings
  - Headaches that do not fit the strict definition
- Headache “red flags”
  - Rapidly increasing headache frequency
  - History of lack of coordination
  - History of localized neurological signs
  - Headaches that awaken from sleep

Acute Treatment of Migraine

- Triptans – serotonin 1b/1d agonists
  - All triptans have been found to be effective and well-tolerated – currently first-line
  - Few head-to-head trials – individualized choice
  - Sumatriptan offers most delivery options
  - Prompt treatment is best predictor of success
  - Avoid triptans in
    - Familial hemiplegic migraine
    - Basilar migraine
    - Ischemic stroke
    - Ischemic heart disease, Prinzmetal’s angina, uncontrolled hypertension
    - Pregnancy
Acute Treatment of Migraine

- **Ergots**
  - Sublingual ergotamine
  - Dihydroergotamine (DHE 45)
    - Primary agents in ED setting
    - IV, IM, SQ, IN delivery
    - Contraindicated with hypertension, ischemic heart disease, MAO inhibitors, and the elderly

- **Antiemetics**
  - Used in combination with DHE 45 in emergency setting
  - Phenothiazines – chlorpromazine, prochlorperazine
  - Metoclopramide – usually used with DHE 45

Preventive Treatment of Migraine

- **Indications**
  - Headaches significantly interfere with usual activities
  - Overuse of acute therapies
  - Adverse events with acute therapies
  - Patient preference
  - Certain migraine variants
    - Hemiplegic migraines
    - Basilar migraines
    - Prolonged aura

- **Antihypertensives**
  - Beta blockers
  - Calcium channel blockers
  - ACEI/ARBs

- **Antidepressants**
  - Amitriptyline
  - Venlafaxine

- **Anticonvulsants**
  - Valproate
  - Gabapentin
  - Topiramate

Answers

1. B
2. A
3. C
4. D
5. B
6. C
7. D

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