EPILEPSY

PATHOPHYSIOLOGY & PRINCIPLES OF DRUG THERAPY

SEIZURES

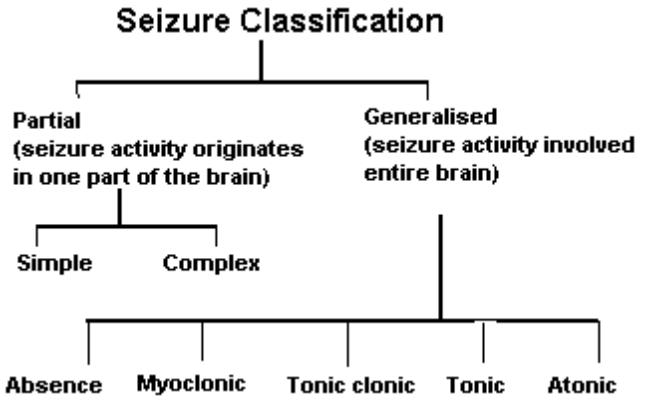
- **Electrical disturbance** in brain: abnormal, excessive, synchronous discharges of cortical neurons
- **Cellular events:** prolonged depolarization → recruitment → rapid firing → synchronized discharge of abnormally linked neurons → localized or generalized spread
- **Neurochemical causes:** imbalance between excitation & inhibition in CNS
  - Abnormal voltage/ligand gated ion channels
  - Ionic micro-environment changes
  - ↓GABA (inhibitory)
  - ↑Glutamate (excitatory)
- **Clinical manifestations:** changes in motor activity, sensation, autonomic function, consciousness

EPILEPSY

- **≥2 seizures** (unpredictable, intermittent) without known or provoked cause
- **Epidemiology:** most frequently precipitated in young children (<5) and the elderly (>65)
- **Etiology**
  - Mostly idiopathic, with genetic influences
  - Pediatric: congenital malformations, developmental disorders, metabolic defects, injury, infection
  - Adult: trauma, tumors, infection, AV malformations
  - Elderly: CVD, CNS degeneration, tumors
- **Diagnosis**
  - Confirm diagnosis & identify seizure type, epilepsy syndrome, and cause
  - History: med hx, family hx, seizure description
  - Physical/neurological exam
  - Lab testing: rule out other metabolic disorders
  - EEG: findings alone not sufficient to confirm/deny diagnosis
    - Absence: 3 Hz spike & wave complex
    - Minor motor seizures (tonic, atonic, atypical absence): slow spike & wave complex
    - Infantile spasms: hypsarrhythmia
    - Myoclonic: polyspike & wave complex
  - Neuroimaging studies: MRI, CT scan

SEIZURE TYPES

- **Partial:** localized involvement of brain
  - Two main types of partial seizures:
    - **Simple:** maintain consciousness
    - **Complex:** impaired consciousness
  - Partial seizures can spread
    - Simple partial → complex partial
    - Simple/complex partial → secondarily generalized tonic clonic
  - Can't always tell it started out as partial
- **Generalized:** whole brain involved
  - **Absence:** brief interruption of consciousness
  - **Myoclonic:** brief, jerky
  - **Tonic clonic:** rigid muscle contractions → tongue biting, incontinence, absence of breathing → rhythmic muscle contractions
  - **Clonic:** regularly repeating jerks
  - **Atonic:** lose all muscle tone, drop attacks
- **Epilepsy syndromes:** classified based on seizure type, etiology, age, etc.; useful to classify epilepsy syndrome (vs. just seizure type) particularly in children



AED THERAPY

- Important! Need to classify epilepsy syndrome or seizure type correctly
- Balance between seizure control and side effect profile
- **Avoid AED therapy if:** reversible cause, 1st unprovoked seizure, benign epilepsies (febrile seizures, rolandic)
- **Monitoring:** seizures, drug interactions, side effects, compliance
- **Avoid precipitating factors:** alcohol, sleep deprivation, stress, poor diet, fever, flickering lights
- **Selecting the appropriate AED**
  - **1st principle:** seizure type (for children, use epilepsy syndrome instead)
  - **2nd principle:** dose optimization & individualization
    - Start low, go slow! Until seizures controlled or SE are too much to handle

Well tolerated	Can start now	Gabapentin, levetiracetam, phenytoin, pregabalin, vigabatrin
CNS & GI effects	Taper up	Carbamazepine, ethosuximide, lamotrigine, oxcarbazepine, primidone, topiramate, valproate, zonisamide
Skin rash	Don't go too fast	Carbamazepine, lamotrigine

    - Select initial target dose → titrate to target dose → determine optimal maintenance dose
    - Initial target dose: usually low end of therapeutic range
    - Pharmacokinetic/pharmacodynamics considerations
      - Weight: mg/kg dosing needed
      - Age: mg/kg dose higher in children, dose lower in elderly
      - Concurrent drug therapy: may alter absorption, or may inhibit/induce metabolism
      - Other diseases: particularly hepatic disease or impaired renal function
    - Allow time to assess response: time for Css to be reached, time to assess seizure frequency
    - Dose adjustment: based on clinical response, plasma concentrations, PK
  - **3rd principle:** look at other options when treatment fails
    - Monotherapy > polytherapy
    - Polytherapy (if failed 2-3 mono), surgery, vagal nerve stimulation, ketogenic diet
  - **4th principle:** monitoring AED therapy
    - Level of control: frequency, change in type, time of occurrence
    - SE: type, severity, impact on life, time of occurrence
    - Changes in concurrent therapy
    - AED plasma concentration
    - Compliance, education
    - Can stop therapy if seizure free for 2-5 years!

Drugs of Choice

Seizure Type	First-Line Drugs	Second-Line Drugs
Simple or Complex Partial	Carbamazepine Lamotrigine Levetiracetam	Gabapentin Phenytoin Valproic Acid Oxcarbazepine Topiramate Zonisamide
Generalized Tonic-Clonic (primary or secondary)	Carbamazepine Lamotrigine Valproic Acid	Gabapentin Levetiracetam Oxcarbazepine Topiramate
Absence	Ethosuximide Valproic Acid	Lamotrigine Levetiracetam
Atypical absence, atonic, myoclonic	Valproic Acid Lamotrigine Topiramate (not myoclonic)	Clonazepam Levetiracetam Zonisamide