# Anticonvulsant Therapy

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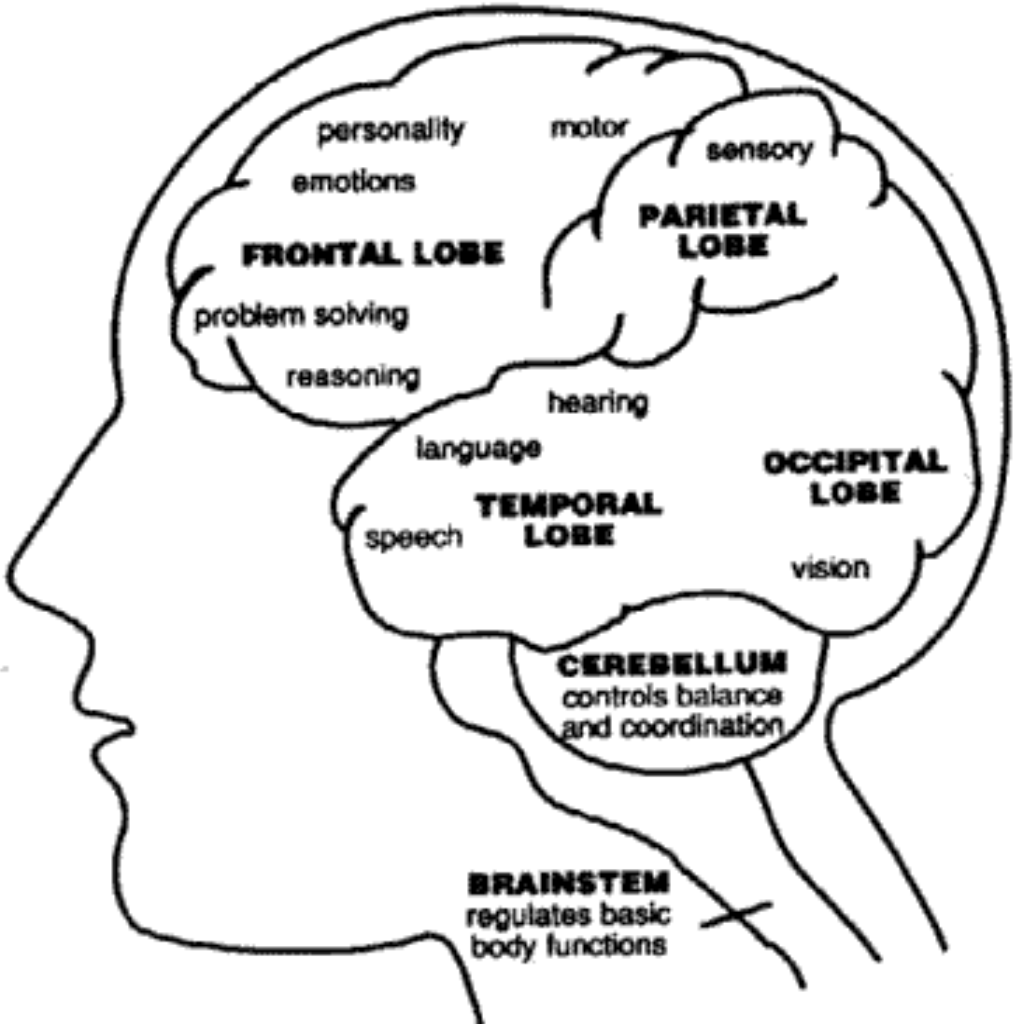
# Outline

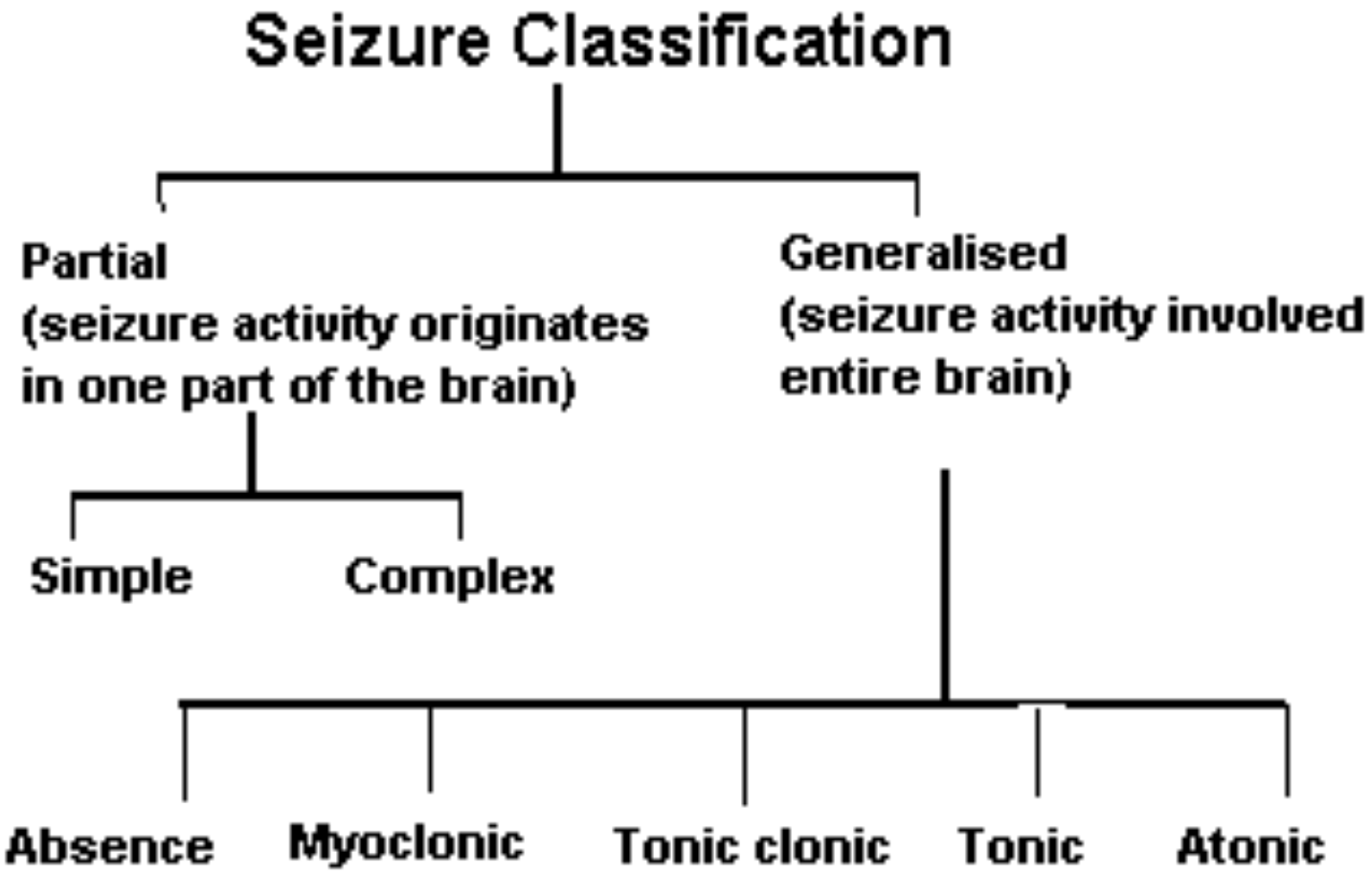
- Introduction
- Why do we treat seizures
- How do we select anticonvulsant medications
- Adverse Effects
- Drug Interactions
- Anticonvulsants and Pregnancy

# Epidemiology of Epilepsy

- 1- 2 % of Canadians
  - 40, 000 people in BC
    - Cerebral Palsy – 20%
    - Autism – 20-30%
    - Developmental Delay - >20%
- 3rd most common neurologic disorder
  - After Stroke and Alzheimer's

# Seizure Manifestations




Seizure Classification
Partial
(seizure activity originates
in one part of the brain)
Generalised
(seizure activity involved
entire brain)
Simple
Complex
Absence
Myoclonic
Tonic clonic
Tonic
Atonic

# Seizure Occurrence

- Up to 10% of the population will experience a single seizure during their lifetime
  - majority due to an acute reversible cause: fever, metabolic changes, drug intoxication/withdrawal.

- Since seizures don't recur in these patients after the provoking factor has been corrected, they don't have a diagnosis of epilepsy.

- A **<u>diagnosis of epilepsy</u>** is made after a patient has had 2 or more **<u>unprovoked</u>** seizures

# What was the cause of the seizure?

- Epileptic seizures are symptoms due to a variety of causes
- Determining the underlying cause has implications for both treatment and prognosis

# Causes epileptic seizures

**Idiopathic (Genetic) - 50% of cases**

- Childhood and Juvenile absence epilepsy
- Benign rolandic epilepsy of childhood
- Juvenile myoclonic epilepsy (JME)

**Symptomatic - 50% of cases**

- Malformations of brain developmental
- Tuberous Sclerosis
- Brain Infection
- Stroke
- Traumatic brain injury
- Tumor

# Clinical Factors Associated With Genetic Versus Symptomatic Epilepsy

**Idiopathic Epilepsy**

1. Normal development
2. Normal neurological examination
3. Family history of epilepsy
4. No history of brain injury

   (e.g. head trauma, meningitis)

- Characteristic EEG abnormalities

**Symptomatic Epilepsy**

- Developmental Delay
- History of brain injury
- Abnormal Neurological Exam
- Other congenital malformations

# Why Do We Treat Seizures?

- Prevent Falls & Injuries
- Employment & Education
- Psychosocial well-being
  - Anxiety
  - Embarrassment
  - Loss of self-control
  - Driving
  - Life-style restriction

# Medications

- Very Old
  - Bromides (1861)
- Old
  - Phenobarbital (1912)
  - Phenytoin (Dilantin$^{R}$)(1936)
  - Diazepam (Valium$^{R}$)(1960's)
  - Carbamazepine (Tegratol$^{R}$) (1974)
  - Valproic Acid (Depakote$^{R}$) (1978)
- **New**
  - Clobazam (Frisium$^{R}$)
  - Lamotrigine (Lamictal$^{R}$)
  - Topiramate (Topamax$^{R}$)
  - Vigabatrin (Sabril$^{R}$)
- **Even Newer**
  - Levetiracetam (Keppra$^{R}$)
  - Oxcarbazepine (Trileptal$^{R}$)
- **The Newest**
  - Lacosamide (Vimpat$^{R}$)
  - Rufinamide (Banzel$^{R}$)
  - Ezogabine (Potiga$^{R}$)
    - (Retigabine in Europe)

# When do you consider starting treatment?

- After first unprovoked seizure 50% of patients will have a 2nd seizure. This needs to be balanced against the potential side-effects and cost of medication.

- In general treatment is started after the 2nd seizure.

# How effective are medications?

- 70% of patients will respond
  - (1st or 2nd drug)
- If 2 appropriate drugs fail
  - 3rd drug:  approximate 5% success rate
- If 3rd drug fails:  " refractory epilepsy"
  - Other treatments
    - Ketogenic diet
    - Epilepsy Surgery

# Goals of Treatment

- Complete Suppression of Seizures
  - with NO side-effects
- Maintain/Restore patients lifestyle

# Case #1

- Mark is an 7 year boy seen in the neurology clinic accompanied by his mom. Teachers have noticed “staring spells” at school.

# VIDEO

Panayiotopoulos CP.  Typical Absence.  Neurology Medlink. June 2007

# Principles of AED therapy

1. Select most appropriate drug
   - Seizure type
   - Epilepsy Syndrome
   - Individual patient factors
     - adverse effect, cost, patient-lifestyle
     - dosing schedule
     - Co-morbidities

# Principles of AED therapy

2. Optimize Dosage
   - start low dose, titrate up to maximum dose
   - Minimize initiation related side-effects
   - End Point:
     - seizures controlled or side-effects occur

# Principles of AED therapy

- Drug level monitoring
  - Target blood drug level
    - Helpful in guiding dose adjustments
  - Treat the INDIVIDUAL
    - NOT  the therapeutic range

# Adverse Effects

# Adverse Effects

- Initiation & Dose related adverse effects
- Idiosyncratic “allergic” reactions

# Case #1 continued

- Mark's mom calls your office 2 weeks later.  Patient has been increasing the medication every 5 days but noticing that she is more "sleepy" during the day.

# Adverse Effects

- Initiation & Dose related adverse effects
  - Important to recognize
  - Seldom are serious – reversible
    - Decreasing medication
    - Discontinuing medication

# Valproic Acid (Depakote$^{R}$)

- Advantages
  - Well tolerated
  - Broad spectrum
  - No effect on BCP
- Disadvantages
  - Weight gain
  - Tremor
  - Hair thinning
  - Platelet dysfunction
  - Drug interactions
  - “allergic” reactions
  - Avoid in Pregnancy

# Case # 2

- Sarah 14 year old girl.  She has experience 2 brief generalized tonic-clonic seizures.
- Decision is made start anticonvulsant medication.
- She is started on lamotrigine (Lamictal$^{R}$)

# Lamotrigine (Lamictal$^{R}$)

- Advantages
  - Effective
  - Well-tolerated
  - Twice daily
- Disadvantages
  - Allergic Rash
  - Titrate Slowly

# Case #2 continued

- Sarah returns to your office 3 weeks later.
- She has developed a rash and fever.

# Idiosyncratic “allergic” reactions

- Unpredictable
- NOT dose-dependent
- Usually occur early in the course of treatment
- Range:  Mild-> severe
- Rare:  1 in 20,000 – 50,000

# Idiosyncratic “allergic” reactions

- Skin Rash
  - Usually within 4 – 6 weeks
  - Titrate dose up slowly
  - Mild - Severe
    - Reversible if discontinued early!!
  - AED:  lamotrigine 1:1000-2000
  - Others:  phenytoin, carbamazepine, phenobarbital

# Idiosyncratic “allergic” reactions

- Liver
  - Usually occurs early in treatment
  - Can be reversible if medication is stopped early
- Blood
  - Symptoms:
    - Bleeding, bruising, persistent infections

# Carbamazepine (Tegratol$^{R}$)

- Advantages
  - Effective
  - Well tolerated
- Disadvantages
  - Dizziness/unsteady
  - “allergic” reaction
  - Drug Interactions
  - May exacerbate seizures
    - Myoclonic, absence

# Carbamazepine

- Rare serious & potentially fatal skin reactions:
  - 1 to 6 per 10, 000 patient
- Asian Ancestry:  risk 10 times higher

# Carbamazepine

- Genetic Marker
  - Inherited variant of a gene (HLA-B 1502 allele), an immune system gene
  - Patients with this variant are at a higher risk
  - It is possible to screen:  blood test

- Asian Ancestry:  prevalence of this allele
  - High Risk: (10-15%)
    - China (Han Chinese), Thailand, Malaysia, Indonesia, Philippines, Taiwan
  - Moderate  Risk: (5-10%)
    - South Asia
  - Low Risk: ( <1%)
    - Japanese or Korean

# Carbamazepine

- Note:
  - If already on carbamazepine for months
    - Unlikely to experience serious reaction
  - Patients with positive results may not get this reaction
  - Serious skin reactions can still occur in patients who test negative
  - Regardless of ethnicity
    - Monitor for signs and symptoms

# Review of Drugs

# Phenytoin (Dilantin$^{R}$)

- Advantages
  - Effective
  - Broadspectrum
  - Chew tabs, capsules
  - Intravenous
  - Inexpensive
  - Once daily
- Disadvantages
  - Therapeutic levels
  - Drug interactions
  - “Allergic” reactions

# Topiramate (Topamax$^{R}$)

- Advantages
  - Effective
  - “off label”
    - Migraine
  - No “allergic” reactions
  - Twice daily
- Disadvantages
  - Cognitive effects
  - Kidney Stones
  - Weight Loss

# Levetiracetam (Keppra$^{R}$)

- Advantages
  - Effective
  - No drug interactions
    - Including OCP
  - Well tolerated
    - No “allergic” reactions
  - Can titrate fast
- Disadvantages
  - Mild fatigue
  - Psychosis (0.6%)
  - Cost

# Clobazam (Frisium$^{R}$)

- Advantages
  - Effective
  - Well tolerated
  - Once or twice daily
- Disadvantages
  - Drowsiness
  - Unsteadiness
  - Rare
    - Behavior changes

# Lacosamide (Vimpat$^{R}$)

- Advantages
  - Effective for focal seizures
  - Well tolerated
- Disadvantages
  - Drowsiness
  - Headache
  - Unsteadiness
  - Rare
    - Heart arrhythmia
    - Rash
    - Suicidal behavior

# Rufinamide (Banzel$^{R}$)

- Advantages
  - Effective in Lennox-Gastaut Syndrome
  - Well tolerated
- Disadvantages
  - Drowsiness
  - Headache
  - Unsteadiness
  - Loss of appetite
  - Rare
    - Heart arrhythmia
    - Rash
    - Suicidal behavior

# Ezogabine (Potiga$^{R}$)

- Advantages
  - Effective for focal seizures
  - Well tolerated
- Disadvantages
  - Three times daily dosing
  - Drowsiness
  - Dizziness
  - Urinary Retention
  - Rare
    - Bluish Pigmentation
      - Skin
      - Sclera
      - Retina

# Drug Interactions

# Why do drug interactions occur?

- Increase breakdown of other drugs
- Decrease breakdown of other drugs

# Drug Interactions:  Birth Control Pill

- Reduce Effectiveness
  - Carbamazepine
  - Oxcarbazepine
  - Phenobarbital
  - Phenytoin
  - Topiramate
- Lamotrigine
- No Effect
  - Clobazam
  - Clonazepam
  - Ethosuximide
  - Gabapentin
  - Levetiracetam
  - Valproic Acid

# Stopping AED Therapy

- Need to continue AED therapy should be re-evaluated after 2 years seizures free.
- Factors favoring low risk recurrence
  - Minimum 2 years seizure free
  - Normal EEG
  - Normal Neurological Examination
  - Ease of controlling seizures
- Slow withdrawal of medications:
  - over 2-3 months

# Anticonvulsant Medication and Pregnancy

# Anticonvulsants and Pregnancy

- **> 90% of women with epilepsy will have a healthy baby**

- Slightly higher risk for congenital malformations
  - General population: 2-3%
  - Untreated epilepsy:  2-5%
  - All anticonvulsant drugs: 4-7%

# Anticonvulsants and Pregnancy

- Planned Pregnancy
  - Talk to doctor
- Ideally one drug at lowest possible dose
  - Monotherapy: 4.5% vs polytherapy 7%
- Folic Acid
  - 0.4mg/day all women of child baring age
  - Higher dose (4-5mg/day): women with epilepsy of child baring age

# Conclusion

- Epilepsy is common
- We treat seizures to prevent injury and maintain active lifestyle
- We select anticonvulsant medications
  - Seizure types, drug profile, individual factors
- Adverse Effects
- Drug Interactions
- Anticonvulsants and Pregnancy