Disclosure and Disclaimer

- I have served on advisory boards for UCB Canada and Eisai Canada.
- I have received unrestricted educational support from both UCB Canada and Eisai Canada.

Objectives

- Seizures and Epilepsy
- Approach to First Seizure
- Management of Epilepsy
Seizure

- Epileptic Seizure
  - A transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain
  - **Transient** – demarcated in time with a clear start and finish (usually brief)
  - **A clinical event** – has signs and/or symptoms
  - **Abnormal enhanced synchrony** of neurons in the brain

http://www.ilae.org/

Seizures Can Cause Diverse Signs/Symptoms

- Depends on the location of onset and the pattern of propagation in the brain – can affect:
  - sensory functions
  - motor functions
  - autonomic functions
  - consciousness
  - emotional state
  - memory
  - cognition
  - behavior
Epilepsy

- A disease of the brain defined by any of the following conditions:
  - At least 2 *unprovoked seizures* occurring > 24 hours apart
  - One *unprovoked seizure* and a probability of *further seizures* similar to the recurrence risk after two unprovoked seizures (an enduring predisposition increasing the likelihood of future epileptic seizures)
  - Diagnosis of an *epilepsy syndrome*

http://www.ilae.org

Epileptic Seizures

- Brief
- Stereotyped – always the same
- Recurrent
- From the Brain

Prevalence and Incidence

- 1/100 – number of people in Canada living with epilepsy (~340,000)
- 15,500 new cases of epilepsy per year – based on an overall epilepsy incidence of 40–70/100,000
- ~42 people are diagnosed with epilepsy in Canada every day
- 60% of newly diagnosed patients with epilepsy will be either young children or seniors
- 10% of the population will experience a seizure in their lifetime

ILAE Classification of Seizures (1981)

I. Partial Seizures – beginning locally
   A. Simple Partial (consciousness not impaired)
   B. Complex Partial (impairment of consciousness)
   C. Partial Seizures that become Secondarily Generalized Seizures

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

III. Unclassified

Adapted from Commission on Classification and Terminology of the International League against Epilepsy, Epilepsia 1981; 22:48
ILAE Classification of Seizures (2010)

- Generalized Seizures
  - Originating in and engaging bilaterally distributed networks

- Focal Seizures
  - Originating within networks limited to one hemisphere

- Unknown
Focal Seizure

- Without dyscognitive features (remain aware) (SPS)
- With dyscognitive features (loss of awareness) (CPS)
- Evolving into a bilateral convulsive seizure (Secondarily Generalized)

Components of Assessment of First Seizure

- Correctly identify the spell in question
- Identify any provoking factors
- Identify any prior events
- Order appropriate tests
- Consider need for treatment with medication
- Council regarding lifestyle issues
Accurately Identifying the Spell

- **History is the key** – from the individual and from a witness to get an accurate detailed description of event
- Preceding symptoms are important
  - warning
- **Clinical features are important**
  - Cessation of activity, loss of interaction, staring, unresponsive, lip smacking, hand fumbling
  - Myoclonic jerks, absence spells
  - Stiff fall, eyes open and rolled back in head, stiff limbs or tonic-clonic movements, frothing, laboured breathing
- Post-ictal signs
  - deep snoring breathing, difficulty rousing or keeping awake, urine incontinence, tongue bite, post event exhaustion, muscle ache

Differential Diagnosis

- Syncope
- Psychogenic non-epileptic seizure (PNES)
- Transient ischemic attack
- Migraine
- Sleep disorder
- Cardiac arrhythmias/QT-syndrome
- Pancreatic attack
- Hyperventilation
- Hypoglycemia
- Transient global amnesia
- Paroxysmal movement disorders dyskinesia/dystonia
- Others

Identify Risk or Provoking Factors

- Epilepsy risk factors
  - Complications of pregnancy, labour or delivery
  - Febrile convulsions
  - Meningitis/encephalitis
  - Brain injury
- Provoking factors
  - Pro-convulsive medications (Wellbutrin)
  - Excessive alcohol or alcohol withdrawal
  - Significant illness/fever
  - Significant metabolic derangements
  - Significant Sleep deprivation
Identify Prior Events
- Carefully question about any other previous or ongoing stereotypic, recurrent spells
  - Lost time
  - Staring spells
  - Déjà vu
  - Epigastric phenomenon
  - Brief recurrent spells of unexplained anxiety/fear
  - Sensory or motor recurrent events
  - Myoclonus
  - Nocturnal spells

Order Appropriate Tests
- If you suspect the spell was seizure
  - Clinical Examination
  - CT head or MRI (epilepsy protocol)
  - EEG (fax: 902-473-6351)
  - Screening labs
  - ECG

Consider Need for Treatment
- **Provoked Seizure**
  - No clear indication for antiepileptic medication. Correction or removal of provoking factor is indicated
  - Withdrawal from alcohol or drugs
  - Intoxication
  - Significant hypoglycemia or other significant metabolic derangement
  - Medications
  - Significant sleep deprivation
  - High fever
  - Acute brain insult (medication sometimes indicated)

- **Single Unprovoked Seizure**
  - Risk for further seizure after a single unprovoked seizure is ~30%
  - No clear indication for antiepileptic medication
Consider Need for Treatment

- Single Unprovoked Seizure with epileptiform discharges on EEG or causative lesion on CT/MRI
  - Consistent with a diagnosis of epilepsy (enduring predisposition for further seizure)
  - Risk for further seizures significantly higher ~60%
  - Antiepileptic medication recommended

- Other preceding spells determined to be seizures
  - Consistent with a diagnosis of epilepsy
  - Risk for further seizures significantly higher ~60%
  - Antiepileptic medication recommended

Counseling

- Explanation of what a seizure is (and isn’t)
- Possible etiology and prognosis
- Purpose and limitations of tests
- Lifestyle considerations (safety, occupation, seizure threshold)
- Driving
- Seizure first aid
- Role of medication (if appropriate)
- Medication action and side effects
- Psychological implications
- Next steps and when to call for help
Epilepsy...The Early Years

- Earliest detailed account of epilepsy is in the British Museum, London:
  - Babylonian text written before 1000 BCE (over 3000 years ago)
  - Provided remarkable descriptions of many of the seizure types (miqtu) that we recognize today, including what we would call tonic clonic seizures, absences, drop attacks, simple and complex partial seizures and even focal motor or gelastic attacks.

Translation and analysis of a cuneiform text forming part of a Babylonian treatise on epilepsy
J V Kinnier Wilson and E H Reynolds
Medical History / Volume 34 / Issue 02 / April 1990, pp 185-198
DOI: 10.1017/S0025727300050651, Published online: 16 August 2012
Link to this article: [http://journals.cambridge.org/abstract_S0025727300050651](http://journals.cambridge.org/abstract_S0025727300050651)

Epilepsy...The Early Years

- School of Hippocrates in 5th-century BCE Greece, which first suggested that the brain was the seat of this disorder:
  - "I do not believe that the Sacred Disease is any more divine than any other disease but, on the contrary, has specific characteristics and a definite cause. Nevertheless because it is completely different from other diseases it has been regarded as a divine visitation by those who, being only human, view it with ignorance and astonishment. .... The brain is the seat of this disease, as it is of other very violent diseases."

Causes of Epilepsy

- Genetic
- Structural/Metabolic
  - Brain tumor
  - Stroke
  - Brain trauma (more severe – more likely)
  - Injury, infection or illness of a mother during pregnancy
  - Brain injury to infant during delivery
  - Infection (encephalitis/ meningitis)
- Toxic effects
- Unknown
  - 50 - 60% - Unknown

Incidence of Epilepsy by Age


Antiepileptic Medications: Which Ones When?
Antiepileptic Medications (AEDs)

- AEDs are antiseizure not antiepileptic – they work to prevent seizures not to cure epilepsy
- Efficacy – regardless of AED choice
  - 50\(^\circ\) – 60\(^\circ\) of patients will achieve complete seizure freedom on their first AED
- 30% of patients with epilepsy will be medically refractory\(^4\)
- Little benefit obtained from 3rd or additional AED

1. Kwan and Brodie, Epilepsy 2001
2. Collaborative Group for the Study of Epilepsy, Epilepsy 1992
3. Camfield et al., J Paediatrics 1997

Treatment in new-onset epilepsy

"Hospital-based", follow-up
Classes of AED – Primary Action

**Sodium Channel Action**
- Carbamazepine
- Phenytoin
- Lamotrigine
- Oxcarbazepine
- Lacosamide
- Zonisamide
- Rufinamide

**GABA Related Action**
- Phenobarbital
- Primidone
- Vigabatrin
- Tiagabine
- Benzodiazepines

**Calcium Channel Action**
- Gabapentin
- Pregabalin
- Ethosuximide

**Multiple Mechanisms**
- Valproate
- Topiramate
- Felbamate

**Unknown Mechanism**
- Levetiracetam

**Glutamate Mechanism**
- Perampanel

Considerations for AED Choice

- Syndrome (focal/ generalized/specific syndrome)
- Efficacy
- Safety profile
- Tolerability
- Drug interaction profile
- Co-morbidities
- Speed of action
- Age / gender
- Special issues (weight, cognition)
- Drug cost/ coverage

AED Choice by Seizure Type

**All Seizure Types**
- Lamotrigine
- Levetiracetam
- Phenobarbital
- Primidone

**All Seizure Types Except Absence**
- Lamotrigine
- Levetiracetam
- Phenobarbital
- Primidone

**Focal Seizures +/- SGTC**
- Carbamazepine
- Gabapentin
- Tiagabine
- Lacosamide
- Oxcarbazepine
- Perampanel
- Pregabalin

**Absence Seizures Only**
- Ethosuximide
- Lamotrigine

**Lennox-Gastaut Only**
- Rufinamide
Common Side Effects

- Weight gain – valproate, carbamazepine, perampanel
- Hair loss – valproate
- Tremor – valproate
- Hair growth – phenytoin
- Gingival hyperplasia - phenytoin
- Weight loss – topiramate
- Cognitive slowing – topiramate
- Speech and language impairment - topiramate
- Irreversible visual field defect – vigabatrin
- Irritability, mood and behavioral change – levetiracetam
Special Considerations: Oral Contraception Use

- Enhances metabolism of oral contraception reducing their effectiveness
  - Carbamazepine
  - Oxcarbazepine
  - Perampanel
  - Phenobarbital
  - Phenytoin
  - Primidone
  - Rufinamide
  - Topiramate
- Little effect on contraception effectiveness
  - Ethosuximide
  - Lacosamide
  - Lamotrigine*
  - Levetiracetam
  - Pregabalin
  - Valproate
  - Vigabatrin
  - Zonisamide

* Can affect progesterone-only agents

Special Considerations: The Elderly

- Physiologic changes of aging
  - Decrease in renal clearance
  - Lower plasma protein and albumin levels
  - Decrease in hepatic metabolism
- Polypharmacy and drug interactions
- Increased impact of common side effects
  - Drowsiness, light-headedness, dizziness, ataxia, fatigue, diplopia
- Fixed income
- Want an AED with minimal drug-drug interactions and minimal side effect profile.

Antiepileptic drug Advantage Disadvantage Doses / day
---|---|---|---
Gabapentin | No drug interaction. Excellent tolerability, rapid titration | Weak antiepileptic drug. Strongly dependent on renal function | 2–3
Levetiracetam | Strong AED, no drug interaction. Excellent tolerability, rapid titration. Low doses sufficient | Rarely insomnia, behavioural disturbances Add-on only coverage | 2
Lamotrigine | Well proven minor neuropsychological improvement, few drug interactions | Slow titration, allergic reactions, | 2
Topiramate | Strong AED, well tolerated in low doses, few drug interactions | Renal and hepatic excretion, weight loss, cognitive impairment, titration within 3–4 wks | 2
Valproate acid | Broad spectrum. No enzyme induction | 90% protein binding enzyme inhibitor, tremor, thrombocytopeny | 1-2
Most AED are FDA risk category C
Few are FDA risk category D
Valproate, Primidone, Phenobarbital, Phenytoin

Pregnancy

Special Considerations:
Renal and Liver Considerations

Almost all AEDs have some component of renal excretion so this must be considered in patients with impaired renal function.

Exception – Valproate – renal disease has little or no impact

Almost all AED’s undergo some hepatic metabolism and doses must be adjusted in hepatic impairment

Exceptions – Levetiracetam, Gabapentin, Vigabatrin

Other Oral Formulations

Carbamazepine – suspension, chew tab
Phenobarbital – elixir
Phenytoin – chew tab, suspension
Valproic Acid - syrup
Topiramate – sprinkle capsule
Lamotrigine – chew tab, suspension
Vigabatrin – sachets
Ethosuximide – syrup
Oxcarbazepine - liquid

ANTIEPILEPTIC DRUG
PREGNANCY REGISTRY
http://www.aedpregnancyregistry.org/
Phone: 888-233-2334 (TOLL FREE)
IV formulations

- Lacosamide
- Phenytoin
- Phenobarbital

- Phenytoin - Intravenous administration should be accompanied by continuous monitoring of the electrocardiogram and of blood pressure and respiratory depression; cardiac resuscitation equipment should be available

- Lacosamide - The solution for infusion and the tablets are bioequivalent and, therefore, can be used interchangeably. When using infusion, administer intravenously over 15-30 minutes twice daily

Advantages of Newer AEDs

- Generally lower side effect rates
- Little or no need for serum monitoring
- One or twice daily dosing
- Fewer drug interactions

Other Considerations of Newer AEDs

- No clear evidence for increased efficacy
- No evidence for improved QoL over older agents
- Significant increased cost

Practical Considerations

- Driving
  - CCMTA (Canadian Council of Motor Transport Administrators) guidelines
  - CMA (Canadian Medical Association) Guidelines
- Safety
  - heights, heavy machinery, open water, bathing
- Situations the Lower Seizure Threshold
  - Sleep deprivation, alcohol, social drugs
Goals Of Treatment

- Maximize Seizure Control
- Minimize Adverse Events
- Individualized for each and every patient

Referral and Contact Info

- Referrals:
  - Neurology – First Seizure Clinic
  - Neurology – Epilepsy
  - Fax to: 902-473-4438

- My contact info:
  - Karen Legg - phone: 902-473-7661
  - Karen.legg@nshealth.ca

Is it a Seizure? What kind? Is it Epilepsy?

- Healthy young woman. Her partner awakens to noise and sees her having rhythmic jerking of limbs. Non-responsive, eyes open and rolled back, frothing mouth and laboured breathing. No warning, tongue bite, post event exhaustion. Report of significant lack of sleep (2 hours only) and alcohol intake the night before.

- Further history reveals brief jerking of arms 3-4 times/month, only in the morning, for past 7 years. Drops objects, has to wait to brush teeth and drink coffee.

- Tonic-Clonic Seizure – unclear if generalized onset or focal onset
- Epilepsy - no, single event only
- Myoclonic Jerks – together these are most in keeping with generalized seizures
- Epilepsy - yes, specifically JME
Is it a Seizure? What kind? Is it Epilepsy?

- 71 y/o man presenting with sudden onset of non-responsiveness, staring, confusion, doing non-sense things. Spell lasts 1 to 2 minutes. Occurs 6 - 8/month.
  - Focal Seizure with dyscognitive features – focal involvement only and impaired awareness
  - Epilepsy – yes, recurrent seizures
  - Focal onset epilepsy of uncertain etiology

- 58 yo woman. Witnessed spell. Suddenly stopped interacting with those around her. Staring, twitching of left side of face and left arm noted and forced head turn to the left. Then rhythmic jerking of all limbs eyes open and rolled back, frothing mouth and labored breathing.
  - Focal Seizure that evolved to a Bilateral Convulsive Seizure – focal involvement and impaired awareness then convolution

- Scan done - tumor present
  - Epilepsy – yes, single event only
  - Epilepsy - yes, single event only but in the setting of a lesion causing an enduring predisposition for seizure
  - Focal onset structural epilepsy

THE END