What Are Epileptic Seizures?

“Occasional, sudden, excessive, rapid and local discharges of gray matter”

John Hughlings Jackson
1835-1911

How Likely are Seizures and Epilepsy?

- ~9% of the population will have seizure at some point, but that does not constitute epilepsy. Any acute brain injury, trauma, anoxia, high fever etc. can cause an acute seizure. Most do not recur.
- Epilepsy is the habitual unprovoked recurrence of seizures, because of electrically irritable brain. About ½% of the population has epilepsy.
Seizures at the Neuronal Level

- Excitatory synapses generate EPSPs by depolarization making action potentials more likely. Esp. Glutamate
  - Some anti-epileptic drugs block release of glutamate (lamotrigine), or are glutamate receptor antagonists (topiramate).
- Inhibitory synapses generate IPSPs by hyperpolarization, making action potentials less likely. Esp. GABA
  - Some anti-epileptic drugs, benzodiazepines and barbiturates, are agonists at GABA receptors.
- If excitation substantially exceeds inhibition, repetitive action potentials result in seizures.

Glutamate Mediates Excitation

- Glutamate binding to its receptors opens Na+ and Ca++ channels that depolarize the cell, making neuronal firing and seizures more likely.
- Some anti-epileptic drugs block release of glutamate (lamotrigine), or are glutamate receptor antagonists (topiramate).
- There are many glutamate receptor sub-types.

Glutamate excitotoxicity is a potential mechanism of production of epilepsy
**GABA (gamma-amino butyric acid) Mediates Inhibition**

- GABA binding to its receptor opens a chloride channel that hyperpolarizes the cell. This makes neuronal firing and seizures less likely.
- Some anti-epileptic drugs, benzodiazepines and barbiturates, are agonists at GABA receptors.
- Different receptor subtypes may mediate different functions.

**Neuroinflammation**

- Epilepsy has been considered mainly a neuronal disease, without much attention to non-neuronal cells.
- Growing evidence suggest that astrocytes, microglia, blood leukocytes and blood-brain barrier breakdown are involved in the pathogenesis of epilepsy.
- Leukocyte-endothelium interactions and eventually subsequent leukocyte recruitment in the brain parenchyma seem to represent key players in the epileptogenic cascade.
  - Chemokines are chemotactic factors controlling leukocyte migration.

**Channelopathies**

- Mutations in a number of genes encoding voltage-gated sodium channels cause a variety of epilepsy syndromes
- Genetic (generalized) epilepsy with febrile seizures plus (GEFS+) and severe myoclonic epilepsy of infancy (Dravet syndrome).
- Mutations of the SCN1A gene; dominantly inherited
- A wide range of seizure types and severities
- Primary effect of both GEFS+ and DS mutations is to decrease the activity of GABAergic inhibitory neurons


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**Channelopathies**

- Among the implicated gene mutations, a number of GABAA receptor subunit mutations have been recently identified that contribute to several idiopathic epilepsies, febrile seizures, and rarely to certain types of symptomatic epilepsies, like the severe myoclonic epilepsy of infancy.
  - Deletion of GABAA receptor genes has also been linked to Angelman syndrome.
- Also, mutations of proteins controlling chloride balance, which indirectly defines the functional consequences of GABAA signaling, have been identified.
  - These include the chloride channel 2 (CLCN2) and the potassium chloride cotransporter KCC3.

Causes of Epilepsy

Genetic Causes of Epilepsy

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene Locus</th>
<th>Function</th>
</tr>
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<tbody>
<tr>
<td>Generalized epilepsy with febrile seizures plus (FS+)</td>
<td>19q12.1</td>
<td>Results in mutation in the regulatory β1 subunit of the voltage-gated sodium channel. Loss of this allele could lead to hyperexcitability by facilitating an inward depolarizing Na⁺ current.</td>
</tr>
<tr>
<td>Autosomal dominant nocturnal frontal lobe epilepsy</td>
<td>20q13.2 and 15q24</td>
<td>2 different mutations have been described in the G4 subunit of the neuronal nicotinic acetylcholine receptor on chromosome 20q13.2</td>
</tr>
<tr>
<td>Febrile seizures</td>
<td>2q23-24</td>
<td>Not known</td>
</tr>
<tr>
<td>Absence seizures</td>
<td>21q22.1 and 8q24</td>
<td>21q22.1 codes for the kainate-selective GluR5 receptor</td>
</tr>
<tr>
<td>Unverricht-Lundborg disease</td>
<td>21q23.3</td>
<td>Gene codes for a protein called cystatin B, a noncaspase cysteine protease inhibitor</td>
</tr>
<tr>
<td>Lefora body disease</td>
<td>6p23-25</td>
<td>Gene encodes a protein tyrosine phosphatase termed laforin</td>
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Classification of Seizures

Generalized Epilepsy with Convulsive Seizures

- Epilepsy with generalized convulsive seizures, but no other brain problems, is usually an idiopathic or genetic disorder with good prognosis. It usually begins in childhood or adolescence.
Generalized EEG abnormality in Epilepsy with Grand Mal Seizures

- Patients with juvenile myoclonic epilepsy have convulsive seizures and diffuse EEG abnormalities.
- This is a form of generalized epilepsy with prominent motor cortex involvement. It is often due to mutated GABA receptor.

Movie of Grand Mal Seizure

- Note bilateral stiffening. That is the tonic part, and reflects rapid repetitive neuronal firing.
- Note bilateral jerking. The jerks are really relaxation, and reflect brief cessation of neuronal firing.
- After the seizure the patient is flaccid, which reflects neuronal inhibition or exhaustion.
Generalized Epilepsy with Non-convulsive Seizures: Childhood Petit Mal

Childhood petit mal is a genetic disorder that begins with staring spells around school age. It has a good prognosis though some children can also develop convulsive seizures.

Generalized EEG Abnormality in Petit Mal Seizure

- EEG abnormalities are quite diffuse.
- Even though clinical signs are minor this is classified as a form of generalized epilepsy. In some kindred there is a mutated glutamate or GABA receptor.
- Not every neuron is involved in a seizure. Motor cortex discharge would cause a convulsion.
Focal Epilepsy

- Focal epilepsy is associated with focal brain lesions, and seizures that begin in one region. There may be variable degrees of spread leading to secondary generalization of seizures. When there is diffuse brain disease, the distinction between focal and generalized epilepsy can get blurred.

Cerebral Hemorrhage

- Acute trauma causes seizures, and is a cause of subsequent epilepsy.
- The degradation products of hemoglobin are very epileptogenic.
Mesial Temporal Sclerosis

- Mesial temporal sclerosis is a common cause of epilepsy.
- This may be due to trauma, infection, congenital malformation, or prolonged febrile convulsion.

EEG of Temporal Lobe Epilepsy

- Focal sharp discharge is seen in the bottom 4 channels, corresponding to the right temporal lobe.
- Such abnormalities are seen in patients with mesial temporal sclerosis.
Movie of Complex Partial Seizure

• Complex is a technical term and means that consciousness is impaired.
• Partial means that the whole brain is not involved. In a simple partial seizure there might be focal muscle jerks with fully preserved consciousness.
• Note that the patient remains alert, but is confused and behaving peculiarly.

Clinical Approach to Epilepsy

• History is the key
  1. Family and observers often know more than the patient.
  2. Is there a family history, and are there risk factors such as trauma and meningitis?
  3. What is the seizure frequency? Is there more than one kind of seizure?
  4. Is there an aura?
     #Gastric/olfactory/gustatory sensations, déjà vu: Mesial temporal.
     #Auditory: Lateral temporal.
     #Lateralized parasthesias: Frontal, Parietal.
     #Visual changes: Occipital.
     #Vague feelings in the head: Frontal or Generalized.
  5. Tongue biting and incontinence suggest generalized seizures, but do not distinguish between primary and secondary generalization.
Clinical Approach to Epilepsy

- Physical examination may not help
  1. Often the neurological exam is normal.
  2. Look for neurocutaneous disorders.
  3. Occasionally one finds a subtle hemiparesis or hemiatrophy.
  4. Examination may give clues to other diseases in the differential diagnosis, e.g., a carotid bruit, orthostatic hypotension, cardiac murmur or arrhythmia.

Clinical Approach to Epilepsy

- Differential diagnosis
  1. Is it a fit or a faint? Vasovagal syncope can mimic generalized epilepsy. So can orthostasis, cardiac arrhythmia, aortic stenosis. Global ischemia can produce loss of consciousness and even convulsive movements.

  2. Transient ischemia from carotid disease can mimic focal seizures and Todd’s paralysis.

  3. Visual and sensory phenomena in migraine can mimic epileptic auras, but are usually more prolonged.

  4. It is easy to be deceived by non-epileptic psychogenic (hysterical) events.
Clinical approach to epilepsy

• Evaluation
  – In the emergency room get a CT scan. Electively get an MRI scan. CT scans often miss brain tumors.
  – Check CBC, chemistry, glucose, and liver profiles. Obtain EKG and chest X-ray.
  – Do spinal tap if there is any suspicion of infection.
  – Electively, get an EEG.
Clinical approach to epilepsy

• **Principles of Acute treatment**
  – Status epilepticus has high mortality.
  – To stop seizures IV lorazepam is best. It is just as fast and longer lasting than IV diazepam. Give 3mg IV to adults.
  – It is reasonable to load a drug for long term therapy. IV phenytoin or fosphenytoin 1gm (for an adult; 10-20 mg/kg) is standard, but IV valproate 1.5 gm (20 mg/kg) and IV levetiracetam 1.5 gm are reasonable.
  – For refractory status epilepticus, IV phenobarbital 500 mg (10-20 mg/kg) is best, but IV propofol, midazolam and pentobarbital titrated to effect) are all reasonable. Intubation is necessary at this stage.

Clinical approach to epilepsy.

• **Principles of Chronic Treatment**
  – First seizures are often not treated, because only 50% recur.
  – Provoked seizures, e.g. with trauma, high fever, or alcohol withdrawal, are acutely treated for a few days but not long term.
  – Recurrent seizures are treated on a long term basis. Medications can be successfully withdrawn after several years in about 50% of patients
Choosing Anti-Epileptic Drugs is Simpler than You Think

Therapy of Generalized Epilepsy

- Valproate is the single most effective drug (80% control). Drawbacks include obesity, alopecia, polycystic ovaries, and neural tube defects.
- Ethosuximide is good only for pure absence seizures in children (50-80% control). Sedation and GI problems can occur.
- Other reasonable choices are lamotrigine (preferred drug for child-bearing women), topiramate, and levetiracetam (50-75% control).
- Phenytoin, carbamazepine and phenobarbital are less desirable.
Therapy of Focal Epilepsy

- Focal epilepsy is harder to control than generalized epilepsy. ~50% seizure free.
- Phenytoin and carbamazepine somewhat more effective and better tolerated than phenobarbital and primidone, in study of VA patients.
- Range of effectiveness 45-65%, and not all patients who were counted as successful were seizure free.

Therapy of Focal Epilepsy:
Comparison of carbamazepine and valproate

- Drugs that block sodium channels seem best for focal epilepsy.
- Carbamazepine and valproate are equally effective for secondarily generalized seizures.
- Carbamazepine is somewhat more effective for focal seizures. Other reasonable options are phenytoin, valproate, lamotrigine, topiramate, and levetiracetam.
Gabapentin Add-on Therapy
Efficacy in Refractory Patients

- Responder means less than you might think. It is not someone who becomes seizure free. Between the drug companies and the FDA, it means someone who has 50% fewer seizures. Clinically that does not mean much.
- In refractory epilepsy, each successive drug has only a 5-10% chance of making a patient seizure free.
- Gabapentin is easy to load, gentle, and has no drug interactions. It makes people obese and sleepy.

Lamotrigine Add-on Therapy
Efficacy in Refractory Patients

- Lamotrigine is a bit more effective than gabapentin for focal (partial) seizures and much better for generalized forms of epilepsy which are exacerbated by gabapentin.
- Lamotrigine has the best CNS side-effect profile.
- Inability to load rapidly because of increased risk of allergic rash is a drawback.
Lamotrigine vs. Carbamazepine

• The drugs are about equal in efficacy.
• In the elderly lamotrigine is better tolerated.
• Lamotrigine is not a liver enzyme inducer, so it has fewer drug interactions.
• Lamotrigine costs 4x as much, so in a young person not taking 6 other medications it is better to start with carbamazepine.

Topiramate

• Effective for generalized and focal forms of epilepsy.
• Potent, but tends to sedate and have cognitive side effects.
• Effective for migraine prophylaxis. Has some effect on neuropathic pain.
• Promotes weight loss. So if an obese diabetic patient with headaches and neuropathy has a stroke, and then develops epilepsy, topiramate may be the drug of choice.
Topiramate Add-on Therapy
Efficacy in Refractory Patients

- The efficacy is somewhat higher than with other drugs, but side-effects are worse too. Patients are sleepy, dysphasic, and have paraesthesias.
- Keep in mind that all add-on drugs can be used in monotherapy and have fewer side-effects when used alone.

Levetiracetam (Keppra®)

- Effective across the board, for focal and generalized epilepsy. Rapid GI absorption. Plasma protein binding <10%. Not extensively metabolized, and metabolite is pharmacologically inactive. Renal excretion, 66% unchanged. IV and oral dose equivalence. Useful for acute seizures and transition to oral therapy.
- Pharmacokinetic drug interactions are unlikely. It has no effect on an oral contraceptives, digoxin, warfarin or chemotherapy. Oncologists favor it, and it is very useful in the ICU.
- Not a sedating drug, but 13.3% of Keppra® patients, vs. 6.2% placebo patients, experienced behavioral symptoms, reported as aggression, agitation, anger, anxiety, apathy, depersonalization, depression, etc.
Keppra Add-on Therapy: Patients with Refractory Epilepsy Responding by Randomized Dose

STUDY 1

- 39.5% seizure reduction
- 37.1% seizure reduction
- 19.3% seizure reduction
- 13.4% seizure reduction
- 10.9% seizure reduction
- 8.3% seizure reduction
- 6.9% seizure reduction
- 4.1% seizure reduction

% of Patients

≥50% seizure reduction
≥75% seizure reduction
≥90% seizure reduction
Seizure freedom (100% seizure reduction)

*P < 0.001 vs. placebo
†P < 0.01 vs. placebo
‡P < 0.05 vs. placebo

Therapy of Epilepsy with Old and New Drugs

Conclusions:

- Generalized epilepsy is easier to control than focal epilepsy, unless there is diffuse brain disease. Valproate is the most effective drug. Lamotrigine is best for women. 80-90% of patients do well.
- Focal epilepsy is more common than generalized epilepsy (70:30), and treatment is only about 60-70% effective. Carbamazepine is probably the best drug. Lamotrigine is another good choice.
- ~50% of patients with focal epilepsy respond well to the first drug, and another 20% to subsequent drug trials. ~30% are medically refractory. New drugs show efficacy similar to old drugs, but may be more effective for some people, and vice versa.
- New drugs are more likely to be tested for effectiveness in focal epilepsy, but many are effective for generalized epilepsy as well.
- Once a patient has failed 2-3 drugs, each successive drug has less than 5% chance of making a patient seizure-free, and about a 50% chance of producing a 50% improvement.
The device is implanted like a cardiac pacemaker, except the wire runs to the left vagus nerve. The left side is preferred because stimulation of the left vagus nerve is less likely than the right to cause a cardiac arrhythmia.
Vagus Nerve Stimulation

Animal studies showed that electrical stimulation of the vagus nerve produced various changes in the EEG that were likely to be anti-epileptic. Seizures emerge from voltage spikes and hypersynchrony, and vagal stimulation seems to reduce both.

Intra-cranial EEG recording in cats showing seizures. Lower tracing shows ongoing seizure. Upper tracing shows seizure aborted by vagal stimulation.

In humans it is hard to deliver a stimulus before the seizure has spread widely. So intermittent stimulation, usual 30 seconds every 5 minutes, is used. Over a period of time seizure activity is down-regulated.
Vagus Nerve Stimulation

- Efficacy is shown in several trials all demonstrating that intermittent stimulation, usually for 30 seconds every five minutes, reduces seizures by ~50% over a period of 1-2 years. This is a bit better than most new drugs, and mood and alertness also improve. The device is also approved for the treatment of refractory depression.

Vagus Nerve Stimulation

- Most side effects are mild and well-tolerated. Occasionally seizures can worsen. Sleep apnea can be a complication of treatment.
Cerebral Stimulation

Can Responsive Cortical Stimulation Treat Seizures?

- Animal data suggest that electrographic seizures can be terminated with applied cortical stimulation.
- Clinical human data provide safety data and suggest efficacy in terminating electrographic discharges.
- These data supported the commencement of the RNS System Clinical Investigations.

Cerebral Stimulation

Clinical Observation

Applied cortical stimulation disrupts afterdischarge induced during functional mapping.
Cerebral Stimulation

The RNS™ Neurostimulator System

Cerebral Stimulation

Theory of Operation
Spontaneous epileptiform activity can be terminated acutely in humans by applied cortical stimulation

Transform of EEG

Transform of EEG
When All Else Fails: Open the Head and Remove Some Brain

- Trephination of the skull was a well-established treatment for epilepsy.
- Lifting a depressed skull fracture could even be helpful.
- Among the 25-30% of patients who are medically refractory, half can be helped with surgery. Half cannot be helped by anything at present.

MRI Scan Showing Mesial Temporal Sclerosis

- Mesial temporal sclerosis is a common cause of temporal lobe epilepsy.
- Often refractory to medications.
- Surgical treatment is very effective.
Outcome of Temporal Lobectomy

- **Engel Classification**
  - Class I = Seizure free
  - Class II = Rare seizures
  - Class III = Persistent seizures, worthwhile improvement
  - Class IV = No improvement

- **Results of one surgical series (22 patients):**
  - Class I: 18/22
  - Class II: 2/22
  - Class IV: 2/22

- **Outcome in Terms of IQ:**
  - Pre-surgery full scale (range) | Class I: 91 (69-117) | Class II: 90 (73-107) | Class IV: 94 (81-107)
  - Post-surgery full scale (range) | Class I: 97 (71-126) | Class II: 90 (74-106) | Class IV: 93 (84-101)

- **Conclusion:** Not only can we cure epilepsy, but bad brain is worse than no brain. Cure rates from temporal lobectomy are 60-70%. Outside the temporal lobes the cure rate is 50-60%.

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Functional Imaging in Non-lesional Epilepsy: SPECT Scan

- Epilepsy surgery is possible even when there is no obvious structural lesion.
- Technetium isotope is distributed proportional to blood flow.
- In the inter-ictal and post-ictal phases the seizure focus tends to be hypo-perfused.
- In the ictal state the focus of seizure onset is hyper-perfused.
- Injection must be done within a few seconds of seizure onset. Scanning can be done later.
Functional Imaging
SPECT Scan

- Ictal SPECT scan in patient with normal anatomy showing left frontal hyperperfusion.
- Nurse sitting with patient for injected isotope within 10 seconds of seizure onset.

Functional Imaging
SPECT Scan

- To heighten contrast, and bring out seizure focus, interictal image can be subtracted from ictal image.
- Then difference between the two is superimposed on a structural MRI study.
- Resection of left frontal seizure focus in this case produced a cure.
Functional Imaging

PET Scan

- Fluoro-deoxy glucose distribution is proportional to metabolism.
- Seizure foci tend to hypometabolic even when anatomically normal.
- This study shows left temporal hypometabolism corresponding to a seizure focus.

Intra-cranial Electrode Array

- Scalp EEG, structural imaging and functional imaging may give only lobar localization of the seizure focus.
- Fine localization down to 1 cm accuracy is achieved with intracranial EEG.
Multi-channel Intracranial EEG

- This slide shows focal seizure onset in the left frontal convexity. The seizure begins in 2 contacts only 1 cm apart.

Correlation of ictal SPECT and EEG data with surgical outcome

- Conclusion: surgical outcome is better when imaging and EEG data co-localize the seizure focus.
Callosotomy

- Cutting the corpus callosum is a palliative procedure.
- It prevents secondary generalization of seizures.
- It stops drop-attack seizures.
- It sometimes reduces seizure frequency.

Analysis of Outcome

- Most data suggest that patients who become seizure-free, with medical or surgical therapy, have a significant improvement in quality of life.
- Those who are almost seizure-free show only slight improvements. This demonstrates the importance of achieving complete seizure control, and the need for quantitative outcome studies.

It is not enough to know whether a radical surgical procedure has stopped attacks or not. We must know its effect upon the patient’s ability to work, to hold a job, to study; the effect on physical and mental function, the effect on behaviour and on the happiness of the patient and friends... In the opinion of the patient and of those who love him, was the operation a success or failure?

— Wilder Penfield, 1954
What Are Epileptic Seizures?

“Occasional, sudden, excessive, rapid and local discharges of gray matter”

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1835-1911