Pathophysiology of Epilepsy
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Objectives:
1) To overview the natural history of seizures and epilepsy
2) To provide an update on definition of terms
3) To discuss the mechanisms of first seizure generation. Epileptogenesis and Ictogenesis

Disclosures
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Natural History of Epilepsy

- No Seizures
- First Seizure
- First AED
- Second Seizure
  - 47% Seizures are controlled
  - 13% Seizures recur
  - 4% Seizures continue
- Second AED
- More AEDs
- Pharmaco-resistant Epilepsy
Update on Definition of Terms

- Epilepsy
- Unprovoked Seizure
- Provoked Seizure
- Epileptogenic abnormality
- Epileptogenesis
- Ictogenesis

“A seizure that is provoked by a transient factor acting on an otherwise normal brain to temporarily lower the seizure threshold does not count toward a diagnosis of epilepsy”

At least two unprovoked (or reflex) seizures occurring >24 hours apart

“The condition of recurrent reflex seizures, for instance in response to photic stimuli, represents provoked seizures that are defined as epilepsy. Even though the seizures are provoked, the tendency to respond repeatedly to such stimuli with seizures meets the conceptual definition of epilepsy, in that reflex epilepsies are associated with an enduring abnormal predisposition to have such seizures.”
One unprovoked (or reflex) seizure and a probability of further seizures similar to the general occurrence risk (at least 60%) after 2 unprovoked seizures over the next 10 years. "Its intent is to encompass circumstances for which some practitioners and expert epileptologists manage patients as if epilepsy is present after a single unprovoked seizure, because of a very high risk of recurrence. Such examples may include patients with a single seizure occurring at least a month after a stroke or a child with a single seizure conjoined with a structural or remote symptomatic etiology and an epileptiform electroencephalography (EEG) study".

The term "unprovoked" implies absence of a temporary or reversible factor lowering the threshold and producing a seizure at that point in time. Unprovoked is, however, an imprecise term because we can never be sure that there was no provocative factor. Conversely, identification of a provocative factor does not necessarily contradict the presence of an enduring epileptogenic abnormality.

What are some of the “enduring epileptogenic” abnormalities?
Epileptogenesis and Ictogenesis

- **Epileptogenesis:**
  - The process(es) involved in transforming a “normal” or “pro-epileptic” brain into a seizure-prone brain
  - These mechanisms make epilepsy a progressive disease

- **Ictogenesis:**
  - Mechanisms involved in initiation of seizures: distinct, transient occurrences caused by abnormal, excessive, or synchronous neuronal activity in the brain

Seizures can be induced in any "normal" animal

- Kainic acid model
- Pilocarpine model
- Pentylenetetrazole (PTZ) model
- Direct cortical stimulation model...

These are models of acute seizure induction in otherwise normal brains: These are PROVOKED seizures!

Can a single seizure occur in a "normal" human brain?
21 y o RH male
IDDM
No FHx of epilepsy
No risk factors for epilepsy
Normal examination
Recent episodes of confusion
Blood glucose: 105
Rule out seizures

Episode of confusion
Blood glucose: 32

Severe hypoglycemia may induce a seizure in a non epileptic human brain

Seizures can be induced/provoked in a “normal” human brain

Triggers for the development of seizures in the human brain

1. Febrile illness in children
2. Trauma
3. CNS infections
4. Stroke
5. Other acute metabolic disturbances

These conditions may be associated with provoked seizures in humans
A first seizure…

**may be induced/provoked in any brain**

- Multiple metabolic, endocrinologic, endogenous/exogenous excitatory conditions, electrical stimulations… induce a seizure in a normal brain

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Does epilepsy always develop after one single provoked seizure?

**NO**

- But the presence of a lesion and/or EEG epileptic abnormality increases the risk for recurrent seizures

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Does epilepsy develop in all patients with pro-epileptic lesions?

**No, only some patients with potentially “epileptogenic abnormalities” develop epilepsy**

- Examples: hemorrhagic infarcts, severe head trauma…

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If epilepsy is to develop… Does it develop at the same age in all patients with pro-epileptic lesions?

NO...

Patients with FCD exhibit their first seizure at different and variable ages

One-way Analysis of Age of Onset By Pathology Classification, F=5.003

Is the presence of a lesion enough for the generation of epilepsy?

- Kainic acid-induced hippocampal sclerosis leads to chronic/recurrent spontaneous seizures
- Pilocarpine-induced hippocampal lesions lead to chronic/recurrent spontaneous seizures
- Radiation-induced cortical dysplasia in utero leads to spontaneous seizures

Not all animals with lesions become spontaneously epileptic
Animals with pro-epileptic lesions (enduring epileptogenic abnormalities) have a lower threshold for the development of acute seizures (second hit) and later on may easily develop spontaneous seizures (epilepsy).

Rats with cortical dysplasia have lower threshold for spontaneous and PTZ induced seizures.

10% of dysplastic rats exhibit spontaneous seizures.
70% of animals exhibit status after subthreshold dose of PTZ.

Kunieda et al, 2002
Oghlakian et al, 2009

Epileptogenesis in more prevalent after TBI in animals with preexisting pathology (CD).

Nemes et al, 2016
Epilepsy is defined as the occurrence of TWO or more unprovoked “epileptic” seizures, or…

One unprovoked (or reflex) seizure and a probability of further seizures similar to the general occurrence risk (at least 60%)

What does it take to transform a non epileptic brain/lesion into an epileptic one?

A possible second hit history in patients with pharmacoresistant FCD

145 patients
- Febrile seizures: 17 (12%)
- CNS infection 11 (7%)
- Head trauma 31 (21%)
- Family history 36 (25%)
- Perinatal adverse events 48 (33%)

Widdess-Walsh et al, 2005

Dysplastic (but not yet epileptic) cortex expresses pro-growth and anti-apoptotic genes

Hiremath et al, Epileptic Disorders, 2009
Congenitally abnormal hippocampus develop sprouting following one single generalized seizure.

Timm’s staining

Control after PTZ GTC

Sprouting

CD after PTZ GTC

Synaptogenesis increases after a second hit in animals with cortical dysplasia.

What about human pathology?
Synaptogenesis in FCD type II

Ying et al, 2014

Synaptogenesis in FCD type II is epilepsy duration dependent

New synapse formation is proportional to epilepsy duration

Ying et al, 2014

Other factors may play a role in the expression of epilepsy in some but not all patients with "pro-epileptic" (Enduring epileptogenic) abnormalities

Mesial TLE
Neocortical epilepsy due to FCD, tumor...

Family
Single "Major" Gene
Multiple "Minor" Genes
Environmental Factors ("second hit effect")

Sporadic

Courtesy of Jocelyn Bautista, MD (Modified)
What happens after a single seizure? A “second” hit?

NORMAL BRAIN  →  NOTHING
BRAIN with PRO-EPILEPTIC LESION  →  EPILEPTOGENESIS: NEW CONNECTIONS NEW SYNAPSES OTHER CHANGES…

Can epileptogenesis be prevented?

Prevention of Epileptogenesis

• Clinically:
  - No AED has been shown to work as an antiepileptogenic agent

• Animal models:
  - Levetiracetam delayed the expression of spontaneous seizures in the kindling model of epilepsy development

Pitkanen, Epilepsia 2010
Pretreatment with levetiracetam prevents the development of sprouting following second hits (PTZ induced seizures in rats with cortical dysplasia). O’Dwyer et al, Unpublished Data

What are the molecular mechanisms of epileptogenicity (ictogenesis)?

Excitatory mechanisms of ictogenesis:
- Increase in NMDA receptors
- Change in the subunit composition
- Increase in AMPA receptors
- Change in the subunit composition
- Increase in Ca++ channels
- SV2
- Presynaptic composition change
Inhibitory mechanisms of ictogenesis:
Decrease in GABAergic inhibition

- Low glutamic acid decarboxylase levels in kindled rats and in excised human epileptic tissue (2)
- Reduced GABA levels in CSF (1)
- Reduced GABA receptors in human brain tissue (2)

ICTOGENESIS:
Increase in Excitatory mechanisms
Decrease in Inhibitory mechanisms
Failure in glial buffering
Other systemic changes (electrolytes)

EPILEPTOGENESIS:
NEW CONNECTIONS
NEW SYNAPSES

Pathophysiology of Epilepsy

- No Seizures
- Epileptogenesis starts
- Seizures recur
- Seizures continue
- EPILEPTOGENESIS continues
- Seizures are controlled
- Seizures continue
- Pharmacoresistant Epilepsy