Seizures in Rett syndrome

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Definitions

- **Epileptic seizure**: brief episode of abnormal excessive or synchronous neuronal activity in the brain
- **Epilepsy**: recurrent, unprovoked epileptic seizures
Where do epileptic seizures come from?
Seizures are created by large groups of neurons (nerve cells)
Human cerebral cortex
Cortical neurons 1 - glutamate

CB - Cell Body
D - Dendrite

Cortical neurons 2 - GABA
How neurons talk to each other

- Synaptic connections using chemical messengers: neurotransmitters
- Two main types of transmitter molecules: excitatory – glutamic acid; acetylcholine; inhibitory – gamma-aminobutyric acid (GABA); glycine
Synapse

Pre-Synaptic Terminal

GABA Molecule
Glutamate Molecule
Synaptic Vesicle

Post-Synaptic Site

Ligand-Gated Chloride Channel
Ligand-Gated Sodium Channel

Cl⁻ Ion
Na⁺ Ion

What a synapse really looks like
Recording cortical electrical activity
Normal EEG recording
Neurons that produce seizures

A. Normal Neuron

B. Epileptic Neuron

Why do epileptic seizures occur?

- Presence of *focal brain injury or malformation*, most often in the cerebral cortex
- Presence of a *low threshold* for the spontaneous occurrence of seizures, typically of hereditary origin
- *Both factors* may be present in the same individual
Examples of focal seizure patterns

- Brief twitching of fingers of one hand or one side of the face
- Episode of seeing exactly the same pattern of shapes in one visual field
- Abrupt deviation of head and eyes to one side with stiffening of limbs
- Sudden loss of awareness, staring, smacking of lips, flushing for 1-2 minutes followed by confusion
Low threshold

- Seizures occur in all cerebral cortical regions simultaneously rather than starting in an area of focal pathology.
- Patterns of epileptic seizures are therefore **generalized**: tonic-clonic (grand mal), tonic, clonic, myoclonic (shock-like jerks), absence (petit mal).
- If a focal seizure becomes generalized, patient has low threshold.
What makes generalized seizures possible?
Absence seizure (generalized)
What about Rett syndrome?

- Epileptic seizures are commonly observed in many mouse models of Rett syndrome (RTT).
- Seizures have been observed in specific knockout models in which *mecp2* has been selectively silenced in a sub-population of cortex neurons expressing GABA (Ito-Ishida et al 2015) or glutamate (Zhang et al 2014).
What kind of seizures occur in Rett syndrome?

- Nissenkorn et al 2015 (n=298)
  
  **Generalized tonic-clonic:** 46.3%
  
  **Partial onset:** 26.8%
  
  **“Absence”:** 14.4%
  
  **Myoclonic:** 12.1%
  
  **Tonic:** 9.1%
  
  **Atonic:** 4.02%
  
  **Multiple seizure types:** 29.4%
Generalized convulsion of focal origin in 5 year-old girl with RTT
How difficult is the diagnosis of epilepsy in RTT?

- Often a major problem! RTT patients often have epilepsy-like behaviors that are not seizures on EEG: breath-holding, cyanosis, hyperventilation, staring, rolling eye movements, stereotyped facial grimaces, toneless laughing, freezing spells, irregular limb jerks

- If in doubt, EEG/video recording of episodic behaviors is essential
Incidence of epilepsy in RTT

- Jian et al 2006: 81% (223/275)
- Glaze et al 2010: 59% (317/540)
- Pintaudi et al 2010: 71.4% (105/147)
- Cardoza et al 2011: 67% (60/89)
- Bao et al 2013: 60% (357/595)
- Nissenkorn et al 2015: 68.1% (850/1248)
Seizure medications

- Some epilepsy medications work best against generalized patterns of seizures: valproic acid, lamotrigine, ethosuximide, phenytoin, phenobarbital, clonazepam etc.
- Some work well against seizures of focal origin: carbamazepine, oxcarbazepine, levetiracetam, lacosamide etc.
- Some work well against both patterns
Drug treatment of epilepsy in RTT

- Many published series concerning antiepileptic drug (AED) use in RTT but small numbers of cases on individual agents
- Tendency to use “broad-spectrum” AEDs in RTT because of common presence of both generalized and focal seizures, e.g. valproic acid, lamotrigine
Most commonly used AEDs

- In the USA: levetiracetam, valproic acid, lamotrigine, oxcarbazepine, zonisamide, clonazepam
- Most other countries: valproic acid, lamotrigine, levetiracetam, oxcarbazepine, clonazepam, zonisamide (Bao et al 2013)
- Italy: valproic acid, carbamazepine, phenobarbital (Pintaudi et al 2016)
Results of AED treatment

- Nissenkorn et al 2015 (n=736):
  - no treatment – 3.6%
  - well-controlled – 63.7%
  - uncontrolled – 32.6%

- Pintaudi et al 2016 (n=118):
  - seizure free – 28%
  - >50% decrease – 41.5%
  - uncontrolled – 30.5%
Other options if AEDs not effective

- **Classic ketogenic diet** – few published cases but significant improvements in seizure control in all + improved social interaction and motor function
- KG diet well suited for RTT patients with gastrostomy feeding
- **Vagus nerve stimulator** – 1 study reporting >50% ↓ in seizure frequency over 1 year in 6/7 (Wilfong et al 2006)
What is needed

• Better understanding of the mechanism(s) involved in the production of seizures in RTT – may lead to the eventual development of “designer” drugs

• Large, multicenter, blinded, comparison trials of specific anti-epileptic drugs in RTT