Current Epilepsy
Clinical Research

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What New Things Have Been Recently Learned about Epilepsy?

Recent key Studies
How Dangerous is Epilepsy?

- People with uncontrolled epilepsy are at risk for injuries and accidents
- Some have serious progressive underlying conditions, such as brain tumors
- People with uncontrolled epilepsy have a higher risk of sudden death (SUDEP)

The risk has been difficult to measure

- It is different with different types of epilepsy, and with different degrees of seizure control.
- Many studies have underestimated risk because of lack of longterm and complete followup.
Long-term Followup of Childhood Epilepsy

- All children (<16 years, 245) with epilepsy in Southwest Finland identified from 1961-1964.
- Followed for 40 years. Seizure control measured every 5 years; mortality determined from many sources, including national registry.
- Overall death rate 0.7%/year, most seizure related.
- Most common cause (30%) SUDEP.
- The only significant predictor of mortality was failure to control the seizures.
- Death rate for those with uncontrolled seizures: 1.6% per year.
- After successful surgery, mortality rate same as general population.

Does Epilepsy Damage the Brain?

- People with uncontrolled epilepsy, especially temporal lobe epilepsy, often have memory problems.
- They also sometimes have some signs of brain atrophy on MRI scans.
- Are these two things connected?
- Are seizures the cause of this brain atrophy and memory problems?
Part of an Answer:

People with Uncontrolled Temporal Lobe Epilepsy Have Progressive Brain Atrophy

- Repeated MRIs in people with temporal lobe epilepsy over 2.5 years show progressive, subtle thinning of the cortex (gray matter) in the frontal, temporal and parietal lobes.
- This progresses more rapidly in those with more frequent seizures.
- After epilepsy surgery, people who were seizure free had less atrophy than those who were not.

What Does This Mean?

- The risk of epilepsy to life, and its effects on the brain are small over the short term.
- The long-term risks and consequences of epilepsy can be significant, and worse in those with uncontrolled, more frequent seizures.
- Even if seizures cannot be controlled, that efforts to reduce seizures as much as possible are important.
- New and better treatments are needed.
New Therapies: Ezogabine:
The AED Formerly Known as Retigabine

- Approved by FDA on June 13, 2011 under name Potiga as add-on treatment for adult focal epilepsy
- Unique mechanism: Neuronal potassium channel opener, opens KCNQ2 channel, activating M-current
- Effective in all animal seizure models tested
- Most common adverse effects in clinical trials: somnolence, dizziness, confusion, headache
- Effective adult dose 900-1200 mg/day
- Metabolism: half life, 8 hr
New Therapies: Other New Antiepileptic Medications

- Ganaxolone: Neuroactive steroid, works on GABA receptor, tested for focal seizures and infantile spasms.
- Brivaracetam: Related to levetiracetam (Keppra)
- Perampanel: Selective antagonist for the AMPA glutamate receptor, tested for focal seizures and Parkinson’s disease.
- Clobazam: Benzodiazepine, used in many other countries, licensed in U.S. on October 25, 2011, for the treatment of the Lennox-Gastaut Syndrome.
New Therapies: RNS

- Responsive neural stimulation: recording electrodes implanted directly over seizure focus.
- Microchip programmed to detect seizures, and respond to give electrical shocks to interrupt seizures.
- Electrodes permanently implanted over brain.
- Submitted to FDA for approval.
- Most promising for seizures coming from brain areas that cannot be safely taken out.
New Therapies: Thalamic Stimulation

- Deep brain stimulation: Electrodes implanted in the anterior thalamus to give periodic electrical pulses.
- Submitted to FDA for review.
- Improvement in seizure control in clinical trials compared to control group was modest.
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VS

RS

ATL

ROS

Radiosurgery or Open Surgery for Epilepsy
Background: Radiosurgery for Mesial Temporal Epilepsy

- Régis et al, Epilepsia. 2004; 45(5):504-15
  - 21 patients with mesial temporal epilepsy, treated with 24 Gy radiosurgery
  - At 2 years, 65% seizure free
  - 5 had short term adverse effects of depression, headache, nausea, vomiting, or imbalance
  - No permanent neurological adverse effects except visual field changes

  - 9 of 15 patients (60%) were seizure free
  - Seizures stop after 12 months on average, often preceded by increase aura or seizures (6 patients)
Background: Radiosurgery for Mesial Temporal Epilepsy

- Multicenter trial comparing 20 and 24 Gy radiosurgery targeting hippocampus, amygdala and parahippocampal gyrus.
- 24 Gy patients had higher risk of transient headaches and steroid use.
- Seizure freedom for prior year at 36 months: 24 Gy 10/13 (77%); 20 Gy 10/17 (59%).
- In this uncontrolled study, the risk of verbal memory decline with dominant side radiosurgery less than half of what is reported for anterior temporal lobectomy.

ROSE: Hypotheses

- Radiosurgery seizure freedom at 25-36 months no worse than temporal lobectomy
- With speech dominant procedures, risk of verbal memory decline greater with temporal lobectomy than radiosurgery
- Similar quality of life improvements with both methods
- Radiosurgery cost effective compared to temporal lobectomy
ROSE: Criteria for Enrollment

- Refractory epilepsy with mesial temporal sclerosis, with concordant EEG and MRI who would otherwise be offered surgery.
- ≥ 3 complex partial seizures in 3 months on stable AEDs.
- Age ≥ 18; IQ ≥ 70; no visual field deficits; no other MRI abnormalities; no severe medical or progressive neurological condition.
- No severe psychiatric or substance abuse condition or active nonepileptic seizures.
Focal Cooling

- Preliminary evidence in experimental animals that cortical cooling can block seizures in a model of chronic focal epilepsy.
- Purpose of subproject to determine the degree of intraoperative surface cooling necessary to achieve ~1.2°C cooling 5 to 10 mm into human neocortex.
- Joint project with Washington University in St. Louis.
- UW: 4-5 patients where planned resections include the entire region cooled.
Managing Epilepsy Well

- Purpose is to develop an epilepsy self-management intervention and test it on patients
- 1. Needs assessment to tailor a self-management program specific to the medical and psychosocial needs of patients with epilepsy.
- 2. Randomized, controlled trial of effectiveness of epilepsy self-management intervention.
- 3. Determine variables predicting the effectiveness of this intervention.
- 4. Disseminate the epilepsy self-management program.
NEAD

Neurodevelopmental Effects of AEDs

- Identify pregnant women on monotherapy with phenytoin, carbamazepine, valproate, lamotrigine.
- Assess and follow offspring prospectively.
- Main findings:
  - Serious adverse fetal outcomes: carbamazepine 8.2%, lamotrigine 1.0%, phenytoin 10.7%, and valproate 20.3%
  - IQ at age 3 compared to children exposed lamotrigine:
    - Valproate 9 points lower (P=0.009)
    - Phenytoin 2 points lower
    - Carbamazepine 3 points lower
**MONEAD proposal:**
*Maternal Outcomes and Neurodevelopmental Effects of AEDs*

- **Candidate women:**
  - Pregnant with epilepsy on levetiracetam, lamotrigine, or carbamazepine
  - Pregnant with epilepsy on polytherapy, or any monotherapy
  - Pregnant with epilepsy on no AED
  - Not pregnant with epilepsy on any therapy
  - Pregnant without epilepsy on no AEDs

- **Studied in women during pregnancy:**
  - seizures, AED levels, OB complications, depression

- **Studied in the offspring:**
  - VIQ and other neurodevelopmental effects
  - adverse neonatal outcomes, especially small for gestational age
  - % AED transfer via placenta, in breast milk and to nursing child
  - additional effects of nursing on IQ of offspring
Epilepsy Phenome Genome Project

- To create a database of phenotype and genotype data from patients with epilepsy and to investigate the genetics of common and rare forms of epilepsy and pharmacoresistance.

- Recruitment:
  - Sibling pairs with generalized or focal epilepsy
  - Triads (pt + both parents)
    - infantile spasms or LGS that is cryptogenic or due to FCD
    - epilepsy due to polymicrogyria or bilateral periventricular nodular heterotopia

- Data:
  - Clinical history, EEG/LTM samples, MRI images and blood

- Childrens Hospital leads study
Your Help is Needed