Focused Ultrasound and Potential New Technologies for Difficult to Control Seizures

Brought to you by the Epilepsy Foundation and Hope for Hypothalamic Hamartomas
Moderator: Patricia Osborne Shafer, RN, MN
Epilepsy Foundation

Speakers:
Nathan Fountain MD, Professor of Neurology, Director of F.E. Dreifuss Comprehensive Epilepsy Program, University of Virginia

Travis Tierney MD, Pediatric Neurosurgeon, Nicklaus Children’s Hospital
Welcome and Instructions

- Tonight’s program includes presentations from 2 speakers.
- Followed by a question and answer time.
- During the presentations, lines will be muted.
- As questions arise, please write them in the chat box.
- After the speakers are done, we will answer these questions and people can ask others aloud.
• Refractory or “treatment resistant” epilepsy
• Conventional epilepsy surgery
• New and experimental technologies and treatments
• Focused ultrasound research
WHEN SEIZURES DON’T RESPOND TO MEDICINES
WHAT IS EPILEPSY

• Epilepsy: Underlying tendency to have spontaneous recurrent seizures

• Refractory = treatment resistant = pharmacoresistant: Seizures persist despite trials of at least 2 appropriate anti-seizure medications
EXAMPLES OF REFRACTORY EPILEPSY

• When seizures don’t respond to at least 2 appropriate trials of seizure medications
• Some epilepsy syndromes
• Epilepsy associated with a ‘lesion’ or structural change in brain - hamartoma, tumor, change in structure or development of area of brain tissue (dysplasia)
Example 1: Temporal Lobe Epilepsy
Temporal Lobe Epilepsy: Single Photon Emission Computerized Tomography (SPECT)

Interictal (between seizures)

Ictal (during a seizure)
TLE: Subtraction Ictal SPECT Co-registered with MRI (SISCOM)
Standard FDG-PET
PET Subtracted from comparison population co-registered with MRI
National Association of Epilepsy Centers (NAEC)

- 310 M Americans
- 31 M Seizure
- 3 M Epilepsy
- 12,295 Epilepsy patients per NAEC Epilepsy center
- 1 M Refractory Epilepsy
- 4,098 refractory patients per NAEC Epilepsy Center
WHAT IS THE NEED FOR EPILEPSY SURGERY?

• What are the numbers?
  • 50% of people respond 1-2 AEDs
  • 25% of people respond >2 AEDs
  • 25% of people refractory to many AEDs

• Focal epilepsy can be “cured” by removing the focus
  • Focal epilepsy from mesial temporal sclerosis is the single most common cause of surgically treated epilepsy (61% in 2015)
    • Standard treatment is anterior temporal lobectomy (ATL)
THANK YOU
Epilepsy Surgery

**Curative**
- Resective surgery
  - Lesion
  - No lesion

**Palliative**
- Neurostimulation
  - Disconnection
Why Surgery?

- Best chance for **CURE**
- Increasing evidence suggesting referral for surgery earlier in the course of epilepsy

  - Continued seizures may result in progressive neurologic damage over time → surgery is “neuroprotective” as opposed to seizure medications (Bernhardt et al, '09)

  - Becoming seizure-free at a younger age may lessen the cognitive, behavioral, and psychosocial problems experienced by epilepsy patients, potentially improving societal integration.

  - Even **one seizure** per year ~ **lower QOL** (Jacoby et al, 1992)
Surgery for Temporal Lobe Epilepsy

Wiebe, Blume, Girvin, Eliasziw. A Randomized Controlled Trial of Surgery for Temporal Lobe Epilepsy; NEJM, 2001
When to Consider Epilepsy Surgery

1. **SEIZURES ARE FOCAL**: Single seizure focus in non-eloquent region

2. **MEDS AREN’T WORKING**: Persistent focal seizures after “adequate” treatment attempts (at least 2 seizure medicines)

3. **AFFECTS QOL**: Impaired quality of life due to ongoing seizures

4. **STATUS EPILEPTICUS**: One of the few urgent indications for epilepsy surgery
Potential Outcome of Video EEG Monitoring:

1. Data from testing matches
   → Go directly to Surgery (TLE, lesionectomy)

2. Not enough data or doesn’t match
   → Need invasive monitoring

3. Not a candidate (seizures not focal)

4. Not epilepsy - PNES Psychogenic Non-Epileptic Seizures
   - PLEDs Periodic Lateralized Epileptiform Discharges
An example of open surgery: Localizing the Seizure Focus

- Phase II- subdural electrodes for monitoring EEG, placed on top of the brain and under the bone
Brain Mapping – Stimulating Critical Brain Areas to Guide Surgery Decisions

Person is under local anesthesia

Look for speech arrest or hesitation

(Golby lab)
Laser Interstitial Thermal Therapy

Risks/Complications

- Death < 0.002%
- Hemiplegia (perm:tx) 2%-4% - Underreported
- Psychiatric deterioration 2-20% - Usually transient
- Word finding problems > 20% - Usually transient
- Visual field problem < .005% - Closer to 1%
- Memory deficit 1%
- Infection, blood clot < 0.5%

In general, the surgical risks for well-executed seizure surgery fall within or below the risks of surgery for most other open intracranial procedures.
# Epilepsy Surgery Outcomes
(from Engel, 1993)

<table>
<thead>
<tr>
<th>Seizure Free</th>
<th>Temporal</th>
<th>Extratemporal</th>
<th>Lesional</th>
<th>Hemispheric</th>
<th>Callosotomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure Free</td>
<td>68</td>
<td>45</td>
<td>66</td>
<td>45</td>
<td>8</td>
</tr>
<tr>
<td>Improved</td>
<td>23</td>
<td>35</td>
<td>22</td>
<td>35</td>
<td>61</td>
</tr>
<tr>
<td>Not Improved</td>
<td>9</td>
<td>20</td>
<td>12</td>
<td>20</td>
<td>31</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
Ideal Case: Lesion in Middle of Brain

17 year old female with history of Tuberous Sclerosis Complex
Non-ideal: Cortical Dysplasia
NEW TECHNOLOGIES
TECHNOLOGIES BEING TESTED

• Laser ablation
• Radiosurgery (Gamma Knife)
• Responsive neurostimulation
• Deep brain stimulation
• Focused ultrasound
Medtronic Animation of Laser Ablation

Stereotactic frame placement

Slit incision, 3 mm drill hole

Laser probe introduced (1.65 mm)

Laser heated tissue

Performed inside MRI, near real-time MR thermography
LASER ABLATION FOR TEMPORAL LOBE EPILEPSY

• Laser Interstitial Thermal Therapy (LITT)
  • Minimally invasive; does not require craniotomy (removal of bone)

• Temporal lobe is perfectly shaped and located for laser ablation

• Some small studies show it might be as effective as standard surgery for some types of TLE
LASER LESION OVER TIME

1 Day  

1 month  

16 months
RADIOSURGERY – GAMMA KNIFE

The Rose Trial – Radiosurgery or Open Surgery in Epilepsy

• Method:
  • Randomized single-blind, controlled trial of RS vs. standard temporal lobectomy for mesial TLE
  • 250 subjects planned at 14 centers
  • Main outcome measure: Seizure-freedom between 2-3 years after treatment is

• Results:
  • Study stopped by NIH for slow recruitment after 3 years
  • 58 Randomized: 31 RS, 27 ATL
  • Seizure outcome, verbal memory, QOL: no difference

• Takes months to years to take full effect
RADIOSURGERY LESION OVER TIME

Preop 1 year 2 year 3 year
DEVICES: RESPONSIVE NEUROSTIMULATION

- FDA approval for use in adults as adjunctive therapy
  - For refractory focal seizures arising from 2 areas
  - For people who are not candidates for removal of focus
  - Procedure done at comprehensive epilepsy centers
Interrogating the RNS Device

Seizure Aborted by Stimulation
DEVICE: DEEP BRAIN STIMULATION

- Identical Medtronic system used in Parkinson’s disease
- Cyclical stimulation of the thalamus
- Intended to disrupt seizure spread through thalamus or prevent seizure from occurring
- Few side effects
- Low rate of device complications
- Not FDA cleared for epilepsy
FOCUSED ULTRASOUND
266,488 students trained through Take Charge of the Facts (FY08 – FY15)

1,035,055 served through our local network with education services, support groups, social support and networking opportunities

48,211 school nurses trained through Managing Students with Seizures (FY08 – FY15)

50,292 school personnel trained (includes teachers, guidance counselors, bus drivers, cafeteria workers, health aides, and other professionals in school settings)

FUS FOR TREATING THE BRAIN

FOCUSED ULTRASOUND – HOW IS IT DONE?

- Performed inside an MRI so focal point can be seen
- Sends beams from helmet array to common focal point
- CT corrects beams for bone thickness
- MR monitors temperature in real time
- Cold water pillow to cool scalp
- Reversible lesion to confirm target
- Temperature controlled thermal ablation
- Approved in the US for treatment of essential tremor
FOCUSED ULTRASOUND: ADVANTAGES

• Non-invasive (Minimally)
  • Does not need open brain surgery
  • Does not require anesthesia
  • Immediate effect of the lesion

• Sound wave energy focused in one area
  • Heat destroys the abnormal brain tissue
  • Tightly controlled and monitored

• Ideal for deep lesions
AN EXAMPLE OF SUBCORTICAL EPILEPSY: HYPOTHALAMIC HAMARTOMA
SUBCORTICAL EPILEPSY: TUMOR OF TUBEROUS SCLEROSIS
PERIVENTRICULAR NODULAR HETEROTOPIA (PVNH)
INSIGHTEC’S TECHNOLOGY

- Treatment can be performed in the intact head
- 1024 beams individually corrected based on local bone thickness to a common focal point
- Focal point can be controlled electronically in size and location
- Real-time MR monitoring of temperature
- Resultant lesion is very sharp
Procedure allows assessment of outcome and side effects before final treatment.
FOCUSED ULTRASOUND: RESEARCH IN CHILDREN

“A Feasibility Safety Study Using the ExAblate 4000 System in the Management of Benign Centrally-Located Intracranial Tumors Which Require Clinical Intervention in Pediatric and Young Adult Subjects.”

(FDA IDE no: G160189)
FOCUSED ULTRASOUND IN CHILDREN:
Rationale

• No incisions, quicker recovery

• Safer alternative or added treatment to:
  ▪ Conventional surgery
  ▪ Laser thermal therapy
  ▪ Conventional radiotherapy
FOCUSED ULTRASOUND IN CHILDREN: Some Inclusions for Children with Epilepsy

- 10 pts, 8-22yrs
- Subcortical lesion, grade 1
- Ideally, asymptomatic with some slow growth
- A child able to be considered for surgery
FOCUSED ULTRASOUND: Some Exclusions

• Children at risk for bleeding
• Large tumor, prior shunt, history of headache
• Cancer risk
• Any child that should be followed in clinic
• Technical issues, for example VNS, RNS
YOUNG ADULT WITH GELASTIC SEIZURES AND HAMARTOMA
FOCUSED ULTRASOUND FOR SUBCORTICAL EPILEPSY (FUSE STUDY)

- Open label safety and feasibility
- Pilot study
- Up to 15 adults
- Subcortical lesions causing epilepsy
  - Hypothalamic hamartoma
  - DNET
  - Periventricular nodular heterotopia
  - Focal “cortical” dysplasia
  - Tuberous sclerosis
FOCUSED ULTRASOUND FOR SUBCORTICAL EPILEPSY (FUSE STUDY)

- Single MR guided ultrasound treatment session over 2-4 hours
- Person may be sedated
- Model on where to target made in advance
- Low temperature treatment to visually confirm temperature change at target
- High temperature lesion created
FUSE STUDY: MAIN CRITERIA

• Age 18-80 years
• At least 3 seizures per month
• Currently taking 2 seizure medicines
• Previously failed 2 seizure medicines
• Intractable epilepsy due to a subcortical lesion indicated for ablation
• Lesion
  • Located within the treatment envelope
Discussion