The Evaluation and Surgical Treatment of Medically Refractory Epilepsy

Carol M. Ulloa, MD
Geisinger Health System, PA
Overview

- What is medically refractory epilepsy (RE)?
- Why is its identification necessary?
  - QOL
  - Morbidity/mortality
- Resective epilepsy surgery
  - Pivotal temporal lobe epilepsy (TLE) trial
  - Risks
  - Benefits
- Pre-surgical evaluation
  - History
  - Scalp EEG
  - Imaging
  - Neuropsychological testing, Wada
  - Invasive recording
- Cases
Epidemiology

- 3% of Americans have epilepsy
- 200,000 new cases diagnosed each year
- 1/3 are medically refractory
- 2-3 failed AEDs
- 2 years duration

Success of AED regimens in newly diagnosed epilepsy

**Table 2. Success of Antiepileptic-Drug Regimens in 470 Patients with Previously Untreated Epilepsy.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response to first drug</td>
<td>222 (47)</td>
</tr>
<tr>
<td>Seizure-free during continued therapy with first drug</td>
<td>207 (44)</td>
</tr>
<tr>
<td>Remained seizure-free after discontinuation of first drug</td>
<td>15 (3)</td>
</tr>
<tr>
<td>Response to second drug</td>
<td>61 (13)</td>
</tr>
<tr>
<td>Seizure-free during monotherapy with second drug</td>
<td>41 (9)</td>
</tr>
<tr>
<td>Remained seizure-free after discontinuation of second drug</td>
<td>20 (4)</td>
</tr>
<tr>
<td>Response to third drug or multiple drugs</td>
<td>18 (4)</td>
</tr>
<tr>
<td>Seizure-free during monotherapy with third drug</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Seizure-free during therapy with two drugs</td>
<td>12 (3)</td>
</tr>
<tr>
<td>Total</td>
<td>301 (64)</td>
</tr>
</tbody>
</table>

Factors leading to RE

- Multifactorial
- Epilepsy syndrome
- Neuropathology
  - TLE with mesial temporal sclerosis
  - Cortical dysplasia
- Altered distribution, sensitivity of GLU/GABA receptors
- Channelopathies in genetic epilepsies
- Autoimmunity

Kwan, Brodie. Seizure. 2002 Mar;11(2):77-84
Pitfalls in determining RE

- Cannot just ask, “Any seizures?”

- Inaccuracy of self reported seizure rates
  - Blum et al
    - 30% were NEVER aware of any seizures
    - 50% of right temporal and 90% of left temporal lobe seizures were denied by patients
    - Those with the lowest self-reported rate had the highest proportion of unrecognized seizures

- Utilize video EEG monitoring

Dimensions of refractory epilepsy

- Intractable seizures
- Injuries
- Excessive drug burden
- Cognitive decline
- Psychosocial dysfunction
- Restricted lifestyle
- Unsatisfactory QOL
- Increased mortality

Kwan, Brodie. Seizure. 2002 Mar;11(2):77-84
Long-Term Mortality in Childhood-Onset Epilepsy

Matti Sillanpää, M.D., Ph.D., and Shlomo Shinnar, M.D., Ph.D.
Table 1. Mortality among Subjects with Childhood-Onset Epilepsy.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Subjects (N = 245)</th>
<th>Subjects with Idiopathic or Cryptogenic Epilepsy (N = 122)</th>
<th>Subjects with Epilepsy Due to Remote Symptomatic Causes (N = 123)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total deaths — no.</td>
<td>60</td>
<td>15</td>
<td>45</td>
</tr>
<tr>
<td>Age at death — yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>23</td>
<td>26</td>
<td>21</td>
</tr>
<tr>
<td>Range</td>
<td>1–50</td>
<td>11–50</td>
<td>1–49</td>
</tr>
<tr>
<td>No. of person-yr</td>
<td>8692</td>
<td>4638</td>
<td>4054</td>
</tr>
<tr>
<td>No. of deaths/1000 person-yr (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>6.90 (5.3–8.9)</td>
<td>3.23 (1.9–5.4)</td>
<td>11.10 (8.3–14.9)</td>
</tr>
<tr>
<td>Men</td>
<td>7.33 (5.2–10.2)</td>
<td>2.69 (1.2–6.0)</td>
<td>11.63 (8.0–16.8)</td>
</tr>
<tr>
<td>Women</td>
<td>6.41 (4.4–9.4)</td>
<td>3.74 (1.9–7.2)</td>
<td>10.33 (6.4–16.6)</td>
</tr>
<tr>
<td>Remission status at time of death‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not in remission — no./total no. of deaths (%)</td>
<td><strong>51/60 (85)</strong></td>
<td>11/15 (73)</td>
<td>40/45 (89)</td>
</tr>
<tr>
<td>In remission — no./total no. of deaths (%)</td>
<td>9/60 (15)</td>
<td>4/15 (27)</td>
<td>5/45 (11)</td>
</tr>
<tr>
<td>Receiving medication — no.</td>
<td>5</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Not receiving medication — no.</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

* CI denotes confidence interval.
† A remote symptomatic cause of epilepsy indicates epilepsy associated with a major neurologic abnormality or insult.
‡ A total of 107 subjects in the study cohort were not in 5-year terminal remission, and 138 were in 5-year terminal remission; of the 138 subjects in 5-year terminal remission, 35 were receiving medication and 103 were not.
## Causes of Death

### Table 2. Causes of Death.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Subjects (N = 245)</th>
<th>Subjects with Idiopathic or Cryptogenic Epilepsy (N = 122)</th>
<th>Subjects with Epilepsy Due to Remote Symptomatic Causes (N = 123)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total deaths — no.</td>
<td>60</td>
<td>15</td>
<td>45</td>
</tr>
<tr>
<td>Death related to epilepsy — no./total no. of deaths (%)</td>
<td>33/60 (55)</td>
<td>9/15 (60)</td>
<td>24/45 (53)</td>
</tr>
<tr>
<td>Witnessed seizure — no.</td>
<td>6</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Status epilepticus — no.</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Probable seizure — no.</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Drowning — no.</td>
<td>6</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Sudden, unexplained death — no.</td>
<td>18</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Death not related to epilepsy — no./total no. of deaths (%)</td>
<td>26 (43)</td>
<td>6 (40)</td>
<td>20 (44)</td>
</tr>
<tr>
<td>Pneumonia — no.</td>
<td>12</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Cardiovascular disease — no.</td>
<td>8</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Suicide — no.</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Other cause of death — no.</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cause of death unknown — no.</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

* A remote symptomatic cause of epilepsy indicates epilepsy associated with a major neurologic abnormality or insult.
# Predictors of Death

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>All deaths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence of 5-yr terminal remission</td>
<td>5.3 (2.6–11.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Remote symptomatic cause of epilepsy</td>
<td>3.4 (1.9–6.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior status epilepticus</td>
<td>1.9 (1.2–3.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Age at onset &lt;2 yr</td>
<td>1.4 (0.8–2.3)</td>
<td>0.20</td>
</tr>
<tr>
<td>Epilepsy-related deaths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence of 5-yr terminal remission</td>
<td>6.4 (2.2–18.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Remote symptomatic cause of epilepsy</td>
<td>3.1 (1.4–6.7)</td>
<td>0.004</td>
</tr>
<tr>
<td>Prior status epilepticus</td>
<td>2.1 (1.1–4.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>Age at onset &lt;2 yr</td>
<td>1.9 (0.96–3.8)</td>
<td>0.06</td>
</tr>
<tr>
<td>Sudden, unexplained deaths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence of 5-yr terminal remission</td>
<td>5.2 (1.4–18.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Prior status epilepticus</td>
<td>2.8 (1.1–7.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Age at onset &lt;2 yr</td>
<td>2.1 (0.8–5.5)</td>
<td>0.11</td>
</tr>
<tr>
<td>Remote symptomatic cause of epilepsy</td>
<td>1.9 (0.7–4.8)</td>
<td>0.20</td>
</tr>
<tr>
<td>Localization-related epilepsy</td>
<td>0.8 (0.3–2.0)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

* A Cox proportional-hazards model was used to assess the risk of death associated with an absence of 5-year terminal remission, with remission status treated as a time-dependent covariate. A remote symptomatic cause of epilepsy indicates epilepsy associated with a major neurologic abnormality or insult. CI denotes confidence interval.
A RANDOMIZED, CONTROLLED TRIAL OF SURGERY FOR TEMPORAL-LOBE EPILEPSY

SAMUEL WIEBE, M.D., WARREN T. BLUME, M.D., JOHN P. GIRVIN, M.D., PH.D., AND MICHAEL ELIASZIW, PH.D.,
FOR THE EFFECTIVENESS AND EFFICIENCY OF SURGERY FOR TEMPORAL LOBE EPILEPSY STUDY GROUP*
Resection for TLE

Results

A

Percentage without Seizures Impairing Awareness

Months

Surgical group (n=40) 58%

Medical group (n=40) 8%

Practice parameter: Temporal lobe and localized neocortical resections for epilepsy

Report of the Quality Standards Subcommittee of the American Academy of Neurology, in Association with the American Epilepsy Society and the American Association of Neurological Surgeons

J. Engel, Jr., MD, PhD; S. Wiebe, MD; J. French, MD; M. Sperling, MD; P. Williamson, MD; D. Spencer, MD; R. Gummit, MD; C. Zahn, MD; E. Westbrook, MD; and B. Enos, MD, PhD
“Patients with disabling CPS, with or without secondarily generalized seizures, who have failed appropriate trials of first-line antiepileptic drugs should be considered for referral to an epilepsy surgery center.”
Evaluation of duration of epilepsy prior to TLE surgery during the past two decades

- 213 patients with temporal lobe resection between 1996 and 2007:
  - 1996-1999
  - 2000-2003
  - 2004-2007

### Table 2
Mean Values (SD) for Duration of Epilepsy Prior to Temporal Lobe Epilepsy Surgery According to Year of Surgery

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean duration in years (S.D.)</td>
<td>22.6 (12.7)</td>
<td>22.4 (15.4)</td>
<td>21.1 (14.2)</td>
<td>0.54*</td>
</tr>
</tbody>
</table>

* ANOVA
“VNS is not more effective than AEDs and has a very low chance of achieving seizure freedom in drug-resistant epilepsy, so it should NOT be considered before resective surgery, and should be reserved for patients who are poor candidates or who refuse surgery.”

Risks

- 1-3% risk of infection, hematoma, infarct
- Naming deficits in 30-40%
- Verbal memory decline in 10-50%
  - Subjective vs objective memory (Sawrie et al. 1999)
  - Progressive deterioration with uncontrolled seizures
  - Post-op improvement in memory
- “Double winners” or “Double losers”
- Visual field defect

Helmstaedter et al. Epilepsia. 2006;47(supp 2);96-98
### Subjective vs Objective Memory

<table>
<thead>
<tr>
<th>Measure</th>
<th>Improvement</th>
<th>No change</th>
<th>Decline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left ATL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QOLIE-89 Memory</td>
<td>11.1</td>
<td>86.1</td>
<td>2.8</td>
</tr>
<tr>
<td>CVLT SDFR</td>
<td>5.0</td>
<td>40.0</td>
<td>55.0</td>
</tr>
<tr>
<td>CVLT LDFR</td>
<td>10.0</td>
<td>45.0</td>
<td>45.0</td>
</tr>
<tr>
<td><strong>Right ATL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QOLIE-89 Memory</td>
<td>13.8</td>
<td>79.3</td>
<td>6.9</td>
</tr>
<tr>
<td>CVLT SDFR</td>
<td>26.1</td>
<td>43.5</td>
<td>30.4</td>
</tr>
<tr>
<td>CVLT LDFR</td>
<td>13.0</td>
<td>60.9</td>
<td>26.1</td>
</tr>
</tbody>
</table>

ATL = anterior temporal lobectomy; QOLIE-89 Memory = Quality of Life in Epilepsy–89 Memory subscale; CVLT SDFR/LDFR = California Verbal Learning Test Short Delay Free Recall/Long Delay Free Recall.
Predictors of postsurgical memory

MRI- Unilateral MTS
FDG-PET hypometabolism
Lower baseline memory scores
WADA memory scores

Better Memory Outcome
The pre-surgical evaluation

- Define the “epileptogenic zone”
- The cortical area capable of generating seizures, and whose removal or disconnection will result in seizure freedom

Epilepsy Surgery 2nd ed. Luders, Lippincott, Nov 2000
- History and Examination
  - Seizure semiology (*symptomatogenic zone*)
  - Epilepsy risk factors
- Scalp EEG
  - Interictal activity (*irritative zone*)
  - Seizure (*ictal onset zone*)
- High resolution MRI (*epileptogenic lesion*)
- FDG-PET (*functional deficit zone*)
  - Cerebral glucose metabolism
- Neuropsychological testing
  - Lateralization/localization
  - Risk for post-op cognitive decline
- Wada test
MEG
- Dipoles created by dendritic membrane potentials produce a magnetic field

Ictal SPECT
- Images cerebral blood flow with radioactive tracer

Indications:
- Normal MRI
- Extratemporal epilepsy
- Discordant findings
- Multifocal lesions
- Guide placement of intracranial electrodes

Invasive monitoring
- Subdural strips/grids
- Depth electrodes
- Cortical mapping
Case 1

- 40 year old LH male
- Epilepsy since about age 36
- Severe MVA 1991 (hit by drunk driver)--collapsed lung, splenic injury, facial fractures
- Typical event: no aura; unresponsive staring with no automatisms
- NEVER aware of his seizures
- 5 seizures per month
- Failed 3 AEDs
Left anterior temporal spike
Left temporal seizure
Left hippocampal sclerosis
<table>
<thead>
<tr>
<th>Brain Structure</th>
<th>LH Volume (cm$^3$)</th>
<th>LH Volume (% of ICV)</th>
<th>RH Volume (cm$^3$)</th>
<th>RH Volume (% of ICV)</th>
<th>Asymmetry Index (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forebrain Parenchyma</td>
<td>499.83</td>
<td>32.81</td>
<td>496.85</td>
<td>32.62</td>
<td>0.60</td>
</tr>
<tr>
<td>Cortical Gray Matter</td>
<td>257.44</td>
<td>16.90</td>
<td>256.11</td>
<td>16.81</td>
<td>0.52</td>
</tr>
<tr>
<td>Lateral Ventricle</td>
<td>5.87</td>
<td>0.39</td>
<td>5.92</td>
<td>0.39</td>
<td>-0.76</td>
</tr>
<tr>
<td>Inferior Lateral Ventricle</td>
<td>0.92</td>
<td>0.06</td>
<td>0.74</td>
<td>0.05</td>
<td>20.61</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>2.79</td>
<td>0.18</td>
<td>3.47</td>
<td>0.23</td>
<td>-21.73</td>
</tr>
<tr>
<td>Amygdala</td>
<td>1.48</td>
<td>0.10</td>
<td>1.55</td>
<td>0.10</td>
<td>-4.81</td>
</tr>
<tr>
<td>Caudate</td>
<td>3.68</td>
<td>0.24</td>
<td>3.77</td>
<td>0.25</td>
<td>-2.44</td>
</tr>
<tr>
<td>Putamen</td>
<td>5.23</td>
<td>0.34</td>
<td>5.10</td>
<td>0.33</td>
<td>2.58</td>
</tr>
<tr>
<td>Pallidum</td>
<td>0.84</td>
<td>0.05</td>
<td>0.96</td>
<td>0.06</td>
<td>-13.91</td>
</tr>
<tr>
<td>Thalamus</td>
<td>7.65</td>
<td>0.50</td>
<td>7.76</td>
<td>0.51</td>
<td>-1.39</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>71.76</td>
<td>4.71</td>
<td>74.68</td>
<td>4.90</td>
<td>-3.98</td>
</tr>
</tbody>
</table>

*The Asymmetry Index is defined as the difference between left and right volumes divided by their mean (in percent)*
FDG-PET
Left mesial temporal hypometabolism
fMRI word generation task
Case 1

- Memory scores higher than expected for dominant TLE and patient is left handed
- Wada revealed left hemisphere language, and memory function primarily supported by right hemisphere
- s/p left mesial/basal temporal resection 1/2013
- Path consistent with hippocampal sclerosis
- Seizure free
- No deficits reported
Case 2

- 48 year old RH female with epilepsy since age 45
- Risk factors:
  - Possible meningitis in 1995
  - Mother with epilepsy
- Typical event: no aura; speaks nonsense; lip smacking; right hand automatisms
- Ictal bradyarrhythmia/asystole
  - Episodes would progress to syncope/collapse, cyanosis
  - Diagnosed as cardiac issue and emergent pacemaker placed
  - After the PPM, no longer had syncope but continued with CPS
- Daily seizures
- Failed 4 AEDs
Left anterior temporal spikes
Left temporal seizure

Rubbing leg
Seizure onset
Initial EEG change
Oral automatisms

[Graph showing EEG waveform changes]
No definite hippocampal asymmetry
Left > right temporal hypometabolism
Case 2

- Semiology consistent with TLE (CPS, ictal asystole)
  - RUE automatisms suggestive of right TLE
- Scalp EEG suggestive of left TLE
- PET with left > right temporal hypometabolism
- MRI normal
- Invasive monitoring with bilateral occipital approach hippocampal depth electrodes
Case 2

- 10 days of invasive EEG
- 8 complex partial seizures with onset at the anterior contacts of the left depth electrode
- The study supported a diagnosis of left mesial temporal lobe epilepsy
- s/p left mesial/basal resection 7/20/2013
- Pathology consistent with hippocampal sclerosis
- Seizure free thus far
- Mild naming difficulty
Case 3

- 42 year old LH female
- Macrocephaly noted at 4 weeks of age
- Cystic parasagittal mass s/p resection at age 12 weeks
- Shunt placement complicated by meningitis
- Epilepsy since age 12
- Seizure-free for 17 years until age 40
- Exam: mild right hemiparesis
- Failed 7 AEDs
- History, EEG and imaging suggestive of two active epileptogenic zones
Type I semiology (extratemporal)

- **Right foot spasm** => visual illusions (things look distorted like monsters) => GTC => prolonged post-ictal right hemiparesis and dysarthria

- **Right hemianesthesia** (beginning in RUE, then RLE) => involuntary right hand movement => GTC => post-ictal right hemiparesis and dysarthria
Cystic lesion w/ surrounding abnormal cortex
Cystic lesion w/ surrounding abnormal cortex
FDG-PET
Seizure type one, Cz onset
Seizure type 1, evolution
Clinical

- Right foot spasm (right foot appears to dorsiflex) => tonic extension of right arm and leg => head/eye version right => GTC
Type II semiology (temporal)

- Dizziness/diaphoresis + visual hallucination (slot machine) => lip smacking => able to speak prior to generalization => GTC
Left hippocampal sclerosis
Left mesial/basal temporal hypometabolism
Seizure type 2, left temporal onset
Seizure type 2, evolution
Clinical, seizure 2

- Complained of feeling hot and blurred vision. Able to answer questions and read key phrase =>
- Oral automatisms. Could still answer questions =>
- Unresponsive with clonic activity of right face and right arm => Head version right
Case 3

- Wada: language and memory supported on the RIGHT hemisphere

- Hypothesis: Two epileptogenic zones
  - Temporal lobe (? Mesial vs neocortical)
  - Perilesional

- Requires intracranial monitoring
Ictal Onsets

Frequent Interictal
Continuous slowing in left temporal grid
Subtemporal spike
Polyspikes left temporal grid
Seizure, subtemporal onset with rapid spread to grid
Case 3

- Implantation complicated by significant blood loss
- s/p left (non-dominant) temporal lobe resection 1/2013
- Wound infection
- Transient post-op worsening of baseline right hemiparesis
- Subquadrantic right superior visual field deficit
- Doing well and will be driving soon
Conclusions

- It is imperative to identify patients with medically refractory epilepsy in order to provide the appropriate work-up and treatment
- 1/3 are pharmacoresistant
- Inaccuracy of self-reported seizure rates
- Early referral to epilepsy surgery center
- Hypothesis-driven approach