Surgical Management for Difficult to Treat Epilepsy

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Treatment of Epilepsy

- **Primary Treatment:** Pharmacotherapy (AEDs)

- **Alternative Treatment**
  - **Surgery**
  - Ketogenic Diet & other diet therapy
  - Behavioral therapy
    - Avoidance or stimulation alteration in Reflex epilepsy
    - Alternative sensory stimulation
    - EEG biofeedback
    - Psychological treatment
  - Traditional or Folk medicine
Surgical Procedures in Epilepsy

♣ **Resective (or curative) Surgery**
  - Temporal lobectomy: standard or tailored ATL
  - Selective amygdalohippocampectomy
  - Corticectomy (or topectomy)
  - Multi-lobar resection
  - Hemispherectomy
  - Lesionectomy

♣ **Connective (or palliative) Surgery**
  - Corpus callosotomy
  - Multiple subpial transection (MST)

♣ **Neurostimulation (or neuromodulation)**
  - Vagal nerve stimulation (VNS)
  - DBS, Cortical stimulation, TMS, etc
  - Responsive electrical stimulation
Epilepsy Surgery (Resective)

Goal
- Seizure freedom and normalization of QOL
- In children: improve neurodevelopment

Principles
- Complete resection or disconnection of Epileptogenic zone
- No new neurological deficits (spare eloquent cortex)
Epilepsy Surgery: Indication & Timing

- SYNOPSIS -

I. Selection of Surgical Candidates
II. Presurgical Evaluation
III. Surgical Cases
IV. Timing of Patient Referral
I. Selection of Surgical candidates

“Selection of Surgical Candidates” is based on the Risk-Benefit Assessment in individual patients (no absolute contra-indications)

“Basic Criteria of Surgical Candidates”

- Accurate diagnosis of Epilepsy Syndromes
  - ILAE-Classification
  - Epilepsy Syndromes related to Epilepsy Surgery
- Medical Intractability
- Patient’s willingness to accept the process of presurgical evaluation and surgery
- Careful evaluation of underlying illnesses and psychiatric comorbidities, QOL, etc.
I. Selection of Surgical Candidates

- Process of Patient Selection -

(1) Patient referral to the Epilepsy Center (First Step)

Primary Care Physician → Epileptologists

✦ Reason for pt. referral
  - Failure of seizure control
  - Deterioration of clinical condition
  - Presence of a mass lesion
  - Others

✦ Diagnostic Reevaluation
  - Dx of epilepsy syndrome
  - Etiology of treatment failure

✦ Medical Intractability, confirmed?
  - Yes, consider surgery
  - No, Systemic AEDs therapy

✦ Psychosocial evaluation
I. Selection of Surgical Candidates

- Process of Patient Selection -

(2) Referral for the Presurgical Evaluation (Second Step)

**Selection Criteria for Surgical Candidates**

**Indications**
- Medical intractability
- Correct Dx of Epilepsy syndrome
  - SRES > Non-SRES
- Stable psychosocial status
- Patients having favorable predictive factors for surgery(?)

**Contra-indications**
- Degenerative or metabolic disorders
- Underlying serious medical illness
- Pseudo Sz or benign epilepsy syndrome
- Serious psychosocial handicaps*
  - Interictal psychosis
  - Personality disorder, depression, etc
  - Severe dysfunction of family dynamics

*only relative contraindications
Predictors of Surgical Candidacy
(Haque et al., Ped Neurol 2015:53:58-64)

- n=131 children with DREs who underwent in-patient VEEG
  - 69 patients were determined surgical candidates

<table>
<thead>
<tr>
<th>Variable</th>
<th>Surgical candidates if present</th>
<th>Surgical candidates if absent</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>One semiology at seizure onset</td>
<td>57/84 (68%)</td>
<td>2/47 (26%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Structural etiology</td>
<td>56/87 (64%)</td>
<td>13/44 (30%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Normal development (DQ &gt;70)</td>
<td>37/59 (63%)</td>
<td>32/72 (44%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Either single interictal focus of multiple foci but limited to one hemisphere on outpatient EEG</td>
<td>41/60 (68%)</td>
<td>28/71 (39%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Focal background EEG slowing on outpatient routine EEG</td>
<td>31/41 (76%)</td>
<td>38/90 (42%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Focal/hemispheric abnormality on MRI</td>
<td>49/59 (83%)</td>
<td>20/72 (28%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. Predictors</th>
<th>Surgical Candidates</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0/5 (0.0%)</td>
</tr>
<tr>
<td>1</td>
<td>2/16 (13%)</td>
</tr>
<tr>
<td>2</td>
<td>5/18 (28%)</td>
</tr>
<tr>
<td>3</td>
<td>8/26 (31%)</td>
</tr>
<tr>
<td>4</td>
<td>13/22 (59%)</td>
</tr>
<tr>
<td>5</td>
<td>21/23 (91%)</td>
</tr>
<tr>
<td>6</td>
<td>18/19 (95%)</td>
</tr>
<tr>
<td>7</td>
<td>2/2 (100%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Effect</th>
<th>Point Estimate</th>
<th>95% Wald Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI abnormality</td>
<td>12.798</td>
<td>(4.712, 34.763)</td>
</tr>
<tr>
<td>Single semiology at seizure Onset</td>
<td>4.834</td>
<td>(1.836, 12.726)</td>
</tr>
<tr>
<td>Male gender</td>
<td>4.326</td>
<td>(1.624, 11.527)</td>
</tr>
<tr>
<td>Number of additional predictors</td>
<td>2.902</td>
<td>(2.040, 4.129)</td>
</tr>
</tbody>
</table>

- Only 5% (3/56) of patients with focal MRI findings had non-congruent semiology and/or interictal EEG
I. Selection of Surgical Candidates

Medical Intractability: *A Key Issue*

- **Theoretical Definition**
  
  “Seizures not responding to adequate trials of all available AEDs in monotherapy and combination therapy”

- Is there any **“Unified Definition”** for practice? No!

- **Problems**
  
  - Epilepsy: heterogeneous condition having different etiology, natural courses, and prognosis
  - Great individual variation among same epilepsy syndrome
  - Different definition for purpose of investigations
Medical intractability
- Pharmacological definition -

♣ ILAE Consensus Proposal (Kwan et al., Epilepsia 2010)

• Failure of adequate trials of 2AEDs
  – Well tolerated
  – Appropriately chosen and used (either monotherapy or combination therapy)

• Failure to achieve sustained seizure freedom
  – $\geq 3$ times of the longest interseizure interval or $\geq 1$ year (choose the longer one)
1. Optimal AEDs Therapy

(4) AEDs Therapy after Failure to Two AEDs

♣ Berg et al. (Ann Neurol 65:510-519)
  ◇ n=128; f/u for 10.1yrs (med) after failure to first 2 AEDs.
  ◇ Sz remission ≥ 1yrs in 73(57%) patients
  →relapse in 50 of 73 pts (68%) but often regained remission
  →terminal 1yr remission in 48 (38%)
  →terminal 3yr remission in 28 (22%)
  →Prognostic factor : for ≥ 1yr remission : idiopathic epilepsy (RR 3.64, p<0.0001)
    low Sz frequency (RR 2.57, P=0.008)
  for ≥ 3yr remission : symptomatic epilepsy (RR 0.76, p=0.003)
    (33% vs. 11% : RR=0.76, p=0.003)

♣ Wirrell et al. (Epilepsia 2013:54:1056-1064)
  ◇ 79 of 381 children (19.7%) : "early medical intractability" defined as
    (i) Sz freq>1/6 mo, and (ii) failure to ≥ 2 AEDs within 2 yrs of diagnosis
  ◇ Long-term outcome (median f/u = 11.7 yrs)
    34(45.3%) remained medically intractable
    34(45.3%) SF with or without AEDs
    7(9.3%) rare Szs only
  ◇ Neuroimaging abnormality: Sz free in 9% (vs. 60% in normal NI)
    the single important predictor of enduring medical intractability (RR:7.0, 95% CI= 2.30-21.24, p=0.0006)
Medical Intractability

- Conclusion -

- Failure to adequate trials of 2 AEDs
  - **Recommended Criteria** for referral to Surgery in Lesional Epilepsy
  - **Minimal Criteria** for Refractory Epilepsy for their referral to Epilepsy Center

- **Conventional Criteria** for Refractory Epilepsy; failure to 6-7 AEDs
II. Presurgical Evaluation

1. Purpose

- **Localize the “Epileptogenic Zone (EZ)”**
  - brain area essential and sufficient for generation of Sz
  - hypothetical zone
    - Usually identified by convergence of independent investigating modalities or related zones
    - confirmed only after surgery

- **Determine the extent of resection**
  - the extent of EZ and its relation to the eloquent cortex
**How to Localize “Epileptogenic Zone”?**

- **Related Zones** -

<table>
<thead>
<tr>
<th>Descriptions of Zones and lesions of the cortex (Lüders and Awad, 1992)</th>
</tr>
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<tbody>
<tr>
<td><strong>Epileptogenic zone</strong></td>
</tr>
<tr>
<td><strong>Irritative zone</strong></td>
</tr>
<tr>
<td><strong>Seizure onset zone</strong></td>
</tr>
<tr>
<td><strong>Epileptogenic lesion</strong></td>
</tr>
<tr>
<td><strong>Ictal symptomatic zone</strong></td>
</tr>
<tr>
<td><strong>Functional deficit zone</strong></td>
</tr>
<tr>
<td><strong>Eloquent cortex</strong></td>
</tr>
</tbody>
</table>
II. Presurgical Evaluation

2. General Concepts

- electrical stimulation
- symptomatic zone
- ictal semiology

**f-MRI, PET, MEG**

- eloquent cortex
- WADA

**fMRI**

- functional deficit zone
- N/E, PET, N-Psych
- interictal SPECT
- EEG, MRS, WADA

**MRI/CT**

**Epileptogenic Zone**

- irritative zone
- ictal zone
- ictal onset zone

**Interictal EEG & MEG**

**Interictal EEG/fMRI**

**Ictal EEG & SPECT**

**Ictal EEG/fMRI**

**Epileptogenic lesion**
Pathway of Epilepsy Surgery

Referral of Surgical Candidates

Hx and Neuro Exam, EEG, ED-MRI
neuropsychological Evaluation

Phase I Evaluation (non-invasive)

CCTV-EEG: (1) ictal and interictal EEG
(2) semiology
± PET/SPECT (SISCOM)/MRS (or other advanced MR)
± Wada test, fMRI
± Source Localization (MSI or ESI)

“No Surgery”

TEAM conference

Phase II Evaluation (invasive)

Subdural Electrodes/depth (or stereoEEG)
Cortical mapping

“Surgery”
Surgical Outcomes

- Literature Review Published since 1995
  - Tellez-Zentano et al. (Epilepsy Res. 2010:89;310-318)
    - 40 articles, Non-lesional (n=697) vs Lesional (n=2860) cases
    - SFR based on presurgical MRI

<table>
<thead>
<tr>
<th>Categories</th>
<th>Non-lesional</th>
<th></th>
<th>Lesional</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>SF(%)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>226</td>
<td>51</td>
<td>45-57</td>
</tr>
<tr>
<td>Ext-TLE</td>
<td>124</td>
<td>35</td>
<td>27-42</td>
</tr>
<tr>
<td>TLE+Ex TLE</td>
<td>398</td>
<td>46</td>
<td>41-51</td>
</tr>
</tbody>
</table>

- the odds of being Sz free after surgery was 2.5 times higher in patients with LE.
Overview of all presurgically evaluated patients and their outcomes

Bien et al., Arch Neurol 2009;66:1491-1499
Neuroimaging Modalities for Epilepsy Surgery

**Structural NI**
- Epilepsy-dedicated MRI
  - 3D-volume imaging

**Advanced MR technology**
- Mechanics: 3T/7T MRI, surface coils
- MR-Contrasts: DTI, MTI, DIRI, etc.

**Neurotransmitters & Receptors**
- FMZ, AMT, Opioid, serotonin, etc.

**Functional NI**
- PET/SPECT: CBF/CMRgluc
- MRS: biochemicals
- fMRI/EEG-fMRI

**Post-imaging Analysis**
- Volumetry/T₂-relaxometry
- 3D surface rendering
- MPR/CR текстуalo analysis
- SPM & Voxel-based analysis
- Coregistration of multimodality imagings

**Epileptogenic Zone**

**Focal lesion**
- Focal abnormalities
  - Eloquent cortex & Irritative zone
Ictal (A) and interictal (B) SPECT and SISCOM (C) images from a patient with intractable seizures with a normal seizure-protocol MRI. Ictal SPECT showed a number of high-intensity areas, including those in the left frontal, right frontal, and left parietal regions. Using the traditional visual method of reviewing SPECT images, blinded reviewers determined the scans to be nonlocalizing. However, using SISCOM images, the reviewers localized the focus of hyperfusion to the left frontal area. Left frontal lobectomy was performed after confirmation of the site of seizure onset with intracranial EEG. The patient was seizure free at 22 months after surgery.

(O'Brien et al., Neurology 1998; 50: 445-454)
Examples of difficult-to-identify type 1 cortical dysplasia from two patients with epilepsy

(Salamon et al. Neurology 2008;71:1594-1601)
High-frequency oscillations in human

Worrell et al., (Brain 2008;131:928-937)
**High-frequency Oscillation (HFO)**

- **Fast Ripples --- A biomarker of epileptogenic zone?**
  - Found only in Rats exhibiting spontaneous seizures after epileptogenic insult (SE models)
  - Associated with sites of Sz onset
  - A greater number of FR-generating sites correlates with a higher rate of Sz.
  (Bragin et al., current opinion in Neurology 2010; 23: 151-156)

- **Fast Ripples and Epilepsy Surgery**
  - Removal of brain tissue exhibiting preoperatively recorded HFOs was associated with better surgical outcomes
  (Jacobs et al., Ann Neurol 2010;51:573-582)
  - Residual FRs in post-resection ECoG were associated with higher seizure recurrence rate after surgery, but not with ripples, interictal spikes, and ictiform spikes
  ( von’t Klooster et al., Neurology 2015; 85: 120-128)

- **Is it time to replace epileptic spikes with fast ripples?**
  (Jobst and Engel, Neurology 2015;85:114-115)
An integral part of pre-surgical evaluation
- Each patient presents unique management situations
- Multi-disciplinary team approach to synthesize complex objective and subjective data
- Concordance of independent data (seminology, imaging, EEG)
  - Key for determination of Epileptogenic Zone

Basic Issues
- Is the EZ well localized?
  - If yes (i) can the EZ be resected safely?
    (ii) any risks for its complete resection?
  - If not, what is the next step? Synthesis of hypothesis
    (i) can phase II investigation reliably localize the EZ?
    (ii) what is the hypothesis for the choice and placement of intracranial electrodes?
Surgery of Non-lesional Partial Epilepsies

SK Lee et al. (Ann Neurol, 2005)
n=89, Sz free rate : 47% at f/u ≥ 2yrs

<table>
<thead>
<tr>
<th>Concordance (number of patients)</th>
<th>Sz-free (42)</th>
<th>not Sz-free (47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>four modalities (5)</td>
<td>4 (80%)</td>
<td>1</td>
</tr>
<tr>
<td>three modalities (18)</td>
<td>10 (56%)</td>
<td>8</td>
</tr>
<tr>
<td>two modalities (25)</td>
<td>15 (60%)</td>
<td>10</td>
</tr>
<tr>
<td>one modality (28)</td>
<td>9 (32%)</td>
<td>19</td>
</tr>
<tr>
<td>all non-localizing (13)</td>
<td>4 (31%)</td>
<td>9</td>
</tr>
</tbody>
</table>
MRI-based Algorithm of Epilepsy Surgery

No: MRI

Yes: EEG, Clinical, Semiology, Neuropsych

Not-concordant: PET/SPECT

Intracranial EEG

Congruent: Functional Mapping SDE, fMRI

Surgery
Presurgical Evaluation in Non-lesional Epilepsy

Non-Lesional Epilepsy

- Functional NI
  - No
  - Yes
    - Not-concordant
    - Congruent

Scalp EEG

Clinical & Semiology

Phase II Investigation
CASES(1-3)
IV. Time to Epilepsy Surgery

- No specific Guidelines for optimal timing for surgery
- Expert’s opinions are centered at avoidance of unnecessary time delay in patient’s referral to surgery
- Early surgery of MTLE (≤ 2 yrs after failure of 2 AEDs) were found to be effective
## IV. Time to Epilepsy Surgery

### 1. Current status

Duration between Age at onset and Presurgical evaluation

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sites</th>
<th>n</th>
<th>Age at surgery</th>
<th>Epilepsy duration (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spencer et al. (2005)</td>
<td>(Multicenter)</td>
<td>396</td>
<td>37</td>
<td>22</td>
</tr>
<tr>
<td>Gilliam et al. (1999)</td>
<td>University of Alabama, Brimingham</td>
<td>196</td>
<td>32</td>
<td>19</td>
</tr>
<tr>
<td>Wiebe et al. (2001)</td>
<td>Ontario</td>
<td>80</td>
<td>35</td>
<td>22</td>
</tr>
<tr>
<td>Choi et al. (2009)</td>
<td>New York</td>
<td>213</td>
<td>35</td>
<td>22</td>
</tr>
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*Gilliam & Albertson, Epilepsy Behav 2011;20:156-159*
Any changes in referral patterns since the publication of AAN practice Parameter (2003)?

Haneef et al. (Neurology 2010;75:699-704)

- Analysis of patients with TLE referred for 1995 to 1998 (group 1, n=83) and 2005 to 2008 (group 2, n=102)
- No difference between Group 1 vs Group 2
  - Duration of illness: 17.1±10.0 yrs vs 18.6±12.6 yrs (p=0.39)
  - Age of evaluation: 34.1±10.3 yrs vs 37.0±11.8 yrs (p=0.08)

- Conclusion: (i) No impact of AAN practice parameter on the practice of patients referral for surgery
  (ii) Need more efforts for communications with primary physicians about epilepsy surgery
IV. Time to Epilepsy Surgery

2. Barriers to Earlier Patient’s Referral

- Shortages of Evidence for the advantage of Early Surgery
- Time delay until confirm the “Medical Intractability”
- Attitude of Stakeholders
  - Referring physicians
  - Epilepsy Experts
  - Patients and family
- Others
2. Barriers to Earlier Patient’s Referral

(1) Early Surgery in MTLE

Engel et al., JAMA 2012;307:422-430

- n=38 (23 pts: med Rx, 15 pts: ATL)
  - MTLE within 2 yrs after the failure of adequate trials of 2 AEDs
  - In all, both MRI and PET were diagnostic of MTLE
  - Mean duration of epilepsy: 5.2 yrs (3.2 – 15.8 yrs)

- Results
  - None in medical group and 11 of 15 pts in surgical group were SF during 2 yrs of f/u (p < 0.001)
  - Memory decline in 4 pts (36%) after surgery
  - Transient deficit in 1 pts after surgery (MRI-identified stroke) and SE in 3 pts in medical group
  - QOL: higher in the surgical group but NS (p=0.08)

- Conclusion
  - Surgery soon after failure of 2 AEDs offers better chance of preventing a lifetime disability
  - No evidence for long-term outcomes of QOL, cognition, and psycho-social function, etc.
2. Barriers to Earlier Patient’s Referral

(2) Time Delay until Confirm of Medical Intractability

- Natural courses of epilepsy are often variable and repeat remissions and relapses
  - *Sillanpaa and Schmidt (Brain, 2006):* n = 144 (children)
    - late remission (mean 9 years) in 50%
    - remission and relapses in 33%
  - *Borodie et al. (Neurology, 2012):* n = 1098 (mixed)
    - delayed remission in 22%
    - remissions and relapses in 16%
2. Barriers to Earlier Patient’s Referral

* Berg et al., Neurology 2003;60:186-190 *

- n= 333: A Multicenter Study of Surgical outcomes
- Criteria of Intractability
  - ≥ 20 CPS during the 24 mo prior to presurgical evaluation
  - Failure of ≥ 2 first-line AEDs
- Result :
  - Latency time from Sz onset to the Dx of RE: 9.1 years (0 to 48 yrs)
  - 26% reported a prior remission (≥ 1yr) before the Dx of RE with Remission ≥ 5yrs in 85%
  - Young age of onset has associated with longer latency time (p<0.0001) and higher probability of past remission (p<0.001)

Fig. Distribution of time from second unprovoked seizure to failure of second medication (intractability) in 333 surgical patients
Pharmacotherapy in Drug Resistant Epilepsy

Luciano and Shorvon (Ann Neurol. 2007)
- N=155; ≥ 1 Sz/mo; Sz duration ≥ 5yrs
- 265 trials of drug addition (new AEDs)
  - SFR in 28% of all patients
  - SFR of 16% of all drug introduction
- Predictors of SF: number of failed drug (<5 drugs), IGE, duration of epilepsy (<10yrs)

Schiller and Najjar (Neurology 2008;70:54-65)
- N=478; newly treated; f/u: 1.5 to 7.5 yrs
- SFR: 61.8% for the first drug
  - 41.7% for the 2nd drug
  - 16.6% for 3rd-6th drug
  - 0 % for 7th drug or more
- Predictors of SF: number of failed drug, IGE
duration of epilepsy, No of Sz prior to AED therapy
IV. Time to Epilepsy Surgery

2. Barriers to Earlier Patient’s Referral

(3) Attitudes of Stakeholders

- Survey of Neurologists *(Hakimi et al., Epilepsy & Behav 2008;13:96-101)*
  - N=84 (Michigan, USA)
  - Results: 3 major factors for delay in patients referral

(i) more conservative definition of medical intractability
  - Failure of ≥ 3 drugs for monotherapy and combination therapy

(ii) Knowledge on Surgical outcomes
  - Only 27% reported Sz. Free rate > 70%, while 60% reported the complication rate is > 5%
  - 31% reported that patients experienced serious post-op complications

(iii) Lack of Communications from the Epilepsy Centers
  - 47% reported no appropriate feedback from the epilepsy center about their patients
  - 38% reported no return of their patients in a timely manner
IV. Time to Epilepsy Surgery

3. Competing Factors for the “Decision of Epilepsy Surgery”

Defining Epilepsy Severity

Perceived Benefit \[\uparrow\]

Perceived Risk \[\downarrow\]

Considering Surgery?

Chance for Success \[\uparrow\]

SRES

(MTLE, Lesional Epilepsy)

Defining Epilepsy Severity

Perceived Benefit \[\uparrow\]

Perceived Risk \[\downarrow\]

Considering Surgery?

Chance for Success \[\downarrow\]

Non-SRES

(Non-lesional epilepsy, Multifocal lesion, etc)

Modified from Gilliam & Albertson, Epilepsy Behav 2011;20:156-159
In situations where surgery can produce a high remission rate,
- It is advisable to recommend a surgical procedure
- ATL or lesionectomy

In situations of normal MRI and a probable extrahippocampal origin
- Not best served by immediate surgery after failure of only two medications
- It is advisable to recommend further trials of AED therapy
- Higher surgical risk
- Low chance (25%) of inducing long-lasting seizure remission
Thanks for your attention