Epilepsy Surgery: Who should be considered? How will patients do?

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Disclosures

- none
Self-assessment questions
Q1- Which qualify for drug resistance in focal epilepsy?

A. Failure of levetiracetam 3000 mg per day and lamotrigine 200 mg per day

B. Failure of lamotrigine 600 mg per day and combination of lamotrigine and levetiracetam 3000 mg per day

C. Failure of lamotrigine due to rash and levetiracetam 3000 mg per day

D. Failure of lamotrigine due to rash and levetiracetam due to irritability
Q2- Which are essential elements of the presurgical evaluation of epilepsy?

A. Video-EEG
B. MRI
C. Detailed history
D. Ictal SPECT
E. A, B, and C
F. All the above
Q3- Which epilepsy has the highest risk of drug resistance

A. Epilepsy secondary to stroke
B. Epilepsy secondary to Cortical dysplasia
C. Epilepsy with hippocampal sclerosis
D. Epilepsy with ganglioglioma and hippocampal sclerosis
Q4- Select incorrect indication

A. Depth electrodes are indicated for deep lesions
B. Subdural grids are indicated for bilateral lateral temporal foci
C. Foramen ovale electrodes are indicated for bilateral hippocampal sclerosis
D. Subdural strips are indicated for suspected bilateral lateral frontal foci
Outline

- Drug-resistant epilepsy
- Identification of candidates for surgery
- Surgical strategies
- Outcome of epilepsy surgery
- Other treatment options for drug-resistant epilepsy
Drug-Resistant Epilepsy - Definition

- Failure of adequate trials of two (or more) tolerated, appropriately chosen, and appropriately used antiepileptic drug regimens (whether administered as monotherapies or in combination) to achieve freedom from seizures.
Drug-Resistant Epilepsy-Course

- Drug resistance may “remit” over time (at a rate of 4% per year among adults and a higher rate among children).
- Seizure relapse is common, suggesting a fluctuating course.
Drug-Resistant Epilepsy - Clinical Predictors

- consistent clinical predictors of drug resistance include
  - high number or frequency of seizures in the early phase of the disorder
  - presence of a known, often structural cause of the epilepsy, particularly hippocampal sclerosis
Newly Treated Epilepsy - Outcome of AED treatment

Kwan and Brodie

- 470 patients with epilepsy who had never received AED treatment: 64% were seizure-free at follow-up
  - Response to 1st drug: 47%
  - Third drug: 1%
  - Second drug: 13%
  - Two drugs: 3%

- A large number of seizures before treatment was a poor prognostic sign:
  - >20 seizures: epilepsy uncontrolled in 51%
  - <20 seizures: epilepsy uncontrolled in 29%

- Those with structural abnormality 1.5 times as likely to be drug-resistant than those with idiopathic epilepsy
Etiology as a risk factor for drug resistance- Paris 1990-1997

26% generalized
76% localization-related
  66% temporal lobe epilepsy
  35% hippocampal atrophy on MRI

Seizure free for the past year
Generalized  82%
Stroke       54%
Dysgenetic   24%
Hippocampal atrophy 10%
Dual pathology 3%

Why is epilepsy surgery considered?

- Approximately 1/3 of patients with symptomatic/cryptogenic partial epilepsy continue to have seizures despite optimal medical therapy.

- Persistent uncontrolled seizures are associated with psychosocial dysfunction, increased morbidity, and increased mortality, including accident related mortality and sudden unexpected death (SUDEP).

- Some forms of epilepsy may be progressive.
Epilepsy Surgery - purpose

- Curative
  - Resective surgery
  - Multiple subpial transections
- Palliative
  - Corpus callosotomy
  - (vagus nerve stimulation)
  - Resective surgery under certain circumstances
Who are the best candidates for epilepsy surgery

- Any patient with refractory epilepsy should be considered
- The most surgically remediable syndromes include
  - Unilateral mesial temporal lobe epilepsy with hippocampal sclerosis
  - Lesional partial epilepsy
- Other partial epilepsies- with slightly lower rate of success
MRI- Hippocampal Sclerosis

T2-weighted
MRI- Cavernous angioma
MRI- left frontal gangliocytoma
MRI- DNET tumor
Presurgical Evaluation

- Purpose: localize the epileptogenic zone

- **Epileptogenic zone**: zone whose resection is necessary and sufficient to eliminate seizures

- The epileptogenic zone cannot be identified directly. It is a theoretical zone that can be estimated by a number of other "zones"
Zones in Partial Epilepsy

- **Ictal onset zone or pacemaker zone**: zone in which seizures are originating. This zone is always contained in the epileptogenic zone, but may be smaller than the epileptogenic zone.
- **Epileptogenic lesion**: lesion causing epilepsy.
- **Irritative zone**: zone in which interictal epileptiform discharges originate.
- **Symptomatogenic zone**: zone that produces the first ictal clinical manifestations.
- **Functional deficit zone**: zone responsible for functional deficits.
Presurgical Epilepsy Localization- history and PE

- History (etiologic factors, age at risk factor/injury) (association with specific pathology- epileptogenic lesion)
- Physical examination: focal/generalized deficits (functional deficit zone)
- Seizure description (description of aura, focal features during seizure progression, ororallimentary automatisms, language manifestations, postictal manifestations) (ictal symptomatogenic zone)
Presurgical Epilepsy Localization- EEG

- EEG, EEG-CCTV
  - Interictal slow activity, attenuation (functional deficit zone)
  - Interictal epileptiform discharges (irritative zone)
  - Ictal EEG onset (ictal onset zone)
  - Clinical seizure semiology: early head turning, oro-alimentary automatisms, dystonic posturing, ictal language, ictal vomiting/spitting, adversive head turning and focal tonic/clonic activity in transition to generalization, postical aphasia, postictal nose wiping (ictal symptomatogenic zone)
Presurgical Epilepsy Localization structural imaging

- MRI (epileptogenic lesion)
  - Focal structural “foreign tissue” lesions: tumors, cavernous angiomas, arteriovenous malformations
  - Hippocampal sclerosis
  - Developmental malformations: focal cortical dysplasia, heterotopias, other

Warning: some lesions usually have a weak association with epilepsy (venous angioma, arachnoid cyst)
Presurgical Epilepsy Localization

functional neuroimaging

- PET (interictal)
  - Hypometabolism zone (functional deficit zone)
- Ictal SPECT
  - Focal/regional hyperperfusion (ictal onset zone)
- Functional MRI?
  - Still a research application
  - Hyperperfusion associated with interictal activity or with ictal discharges
  - Functional connectivity
Presurgical Epilepsy Localization
Neuropsychology

- Neuropsychological testing *(functional deficit zone)*
- Intracarotid amobarbital procedure *(Wada test)* *(functional deficit zone for memory)*
Tests added to resolve conflicting or unclear data

- **Ictal SPECT** - must be combined with interictal SPECT scan (and possibly subtracted) for best interpretation - not useful to resolve bilateral independent foci, since one ictal SPECT reflects one seizure.

- **MEG/MSI** - most useful to resolve localization of epileptiform discharges with complex but consistent field.

- **MRS** - can help identify dysfunction in certain brain regions.
Functional Mapping/ Localization/ Lateralization

The tests below help determine if eloquent cortex is at risk from surgery:

- Wada test (lateralization of language and memory)
- Functional MRI (motor, sensory, language, ?memory)
- Magneto-encephalography (motor, sensory, language, ?memory)
Surgery without invasive testing

Surgery may proceed without invasive testing if

- Presurgical results are congruous
- There is a structural or clear functional lesion corresponding to consistent electrical localization
- There is no definite risk to eloquent cortex
When is invasive intracranial monitoring indicated?

- Epileptogenic zone well lateralized but not well localized (example: frontal versus temporal or postero-lateral temporal versus anterior-mesial temporal)
- Bitemporal epileptogenicity?
- Epileptogenic zone may overlap with functional cortex (example: language or motor)
- Extratemporal or neocortical non-lesional epilepsy
- Epileptogenic zone not well-defined or data non-congruent
  - Fishing expeditions not appropriate
  - May try to localize electrical abnormality from a zone defined with functional imaging (functional deficit or ictal onset zone)
Invasive EEG techniques

- Subdural grid electrodes
  - For better localization and functional mapping
- Depth electrodes
  - For lateralization, deep structures
- Subdural or epidural strip electrodes
  - For lateralization, wide coverage
- Foramen ovale electrodes
  - For lateralization of bilateral mesial temporal epilepsy
- Epidural peg electrodes
Language
- Mild Interference
- Moderate to Marked Interference

Motor Response
- Arm
- Finger
- Tongue
- Jaw
- Eye
- Negative

Sensory response

Auditory response
Indications

- **Subdural grid** - assumes a strong hypothesis regarding the lateralization of the epileptogenic zone - most useful for refining a broad localization and for localizing cortical functions with electrical stimulation.

- **Subdural strips** - useful to sample various brain regions with wide coverage.

- **Foramen ovale electrodes** - useful to resolve lateralization in patients with apparent bitemporal independent seizure onsets on scalp EEG - assumes that seizures are mesial temporal in origin.
Indications

- **Depth electrodes** - useful for recording from deep difficult to access regions, such as insula, depth of sulci, heterotopias, hippocampi, amygdala, mesial frontal region.

- **Epidural PEG electrodes** - can be used a “semi-invasive” electrodes to explore EEG from various regions without the interference of muscle artifact.

- **Combinations of above** - the most common are combinations of subdural grids and strips.
Who is the best candidate for focal resection?

- Partial (focal) epilepsy
  - All zones congruent
  - Epileptogenic zone outside eloquent cortex
  - Epileptogenic zone dysfunctional
  - Associated focal structural lesion, or unilateral mesial temporal localization with associated hippocampal sclerosis
Modalities of Surgical Therapy and Indications

Lesionectomy
- Focal lesion associated with single epileptogenic zone

Temporal lobectomy
- Well localized temporal lobe focus, particularly non-dominant

Selective amygdalohippocampectomy
- Well localized mesial temporal focus, particularly if associated with hippocampal sclerosis
- Was reserved for dominant foci, but no longer so

Tailored neocortical resection
- Localized neocortical epileptogenic zone
Standard Temporal Lobectomy
Selective Amygdalo-hippocampectomy

Approach corridor
Sel AH vs St ATL for mesial TLE
Tanriverdi et al, J Neurosurg 2008

- Seizure outcomes compared at the 5-year follow-up in 100 patients with unilateral mesial TLE due to hippocampal sclerosis (HS)- 50 had a standard ATL and 50 had a selective AH.

- Favorable (Engel Classes I and II) seizure outcomes were noted in 82 and 90% of patients who had undergone St ATL and SelAH, respectively.
  - 40% of ATL and 58% of SelAH patients were seizure free (Engel Class Ia).

- There was no statistically significant difference between the 2 surgical approaches in terms of seizure outcome at the 5-year follow up (p = 0.38).
Modalities of Surgical Therapy & Indications - cont

- Hemispherectomy
  - Well-lateralized widespread epileptogenic zone and severe associated or anticipated motor deficit (e.g., Rasmussen syndrome) - if there are no independent finger movements, no significant worsening in motor function will be expected in the long-term

- Multiple subpial transections
  - Neocortical epileptogenic zone well localized over functional (eloquent) cortex
  - Most often used with motor, sensory or language cortex
  - May be combined with resection
Functional Hemispherectomy

- Temporal + Centro-parietal resection
- Frontal and occipital disconnection with preservation of vascular supply
MRI post hemispherectomy
Multiple Sub-pial Transections
Multiple Sub-pial Transections
Classification of Postoperative Outcome

- **Class I- Free of disabling seizures**
  - A- Completely seizure-free since surgery
  - B- Non disabling simple partial seizures only since surgery
  - C- Some disabling seizures after surgery, but free of disabling seizures for at least 2 years
  - D- Generalized convulsion with antiepileptic drug withdrawal only

- **Class II- Rare disabling seizures ("almost seizure-free")**
  - A- Initially free of disabling seizures, but has rare seizures now
  - B- Rare disabling seizures since surgery
  - C- More than rare disabling seizures after surgery, but rare seizures for at least 2 years
  - D- Nocturnal seizures only
Classification of Postoperative Outcome

- Class III- Worthwhile improvement
  - A- Worthwhile seizure reduction
  - B- Prolonged seizure-free intervals amounting to greater than half the follow-up period, but not less than 2 years

- Class IV- No worthwhile improvement
  - A- significant seizure reduction
  - B- No appreciable change
  - C- Seizures worse
Outcome from epilepsy surgery - Pooled studies from 100 facilities

- Class I outcome in:
  - 56% of 2,336 anterior temporal lobectomies before 1986
  - 68% of 3,579 anterior temporal lobectomies after 1986
  - 69% of 413 amygdalol hippocampectomies after 1986
Surgery versus medical therapy

- 80 patients with temporal lobe epilepsy, randomized to best medical treatment while surgery is delayed one year (40 pts) versus immediate evaluation then surgery (40 pts- 36 operated)

- Free of seizures affecting consciousness at one year:
  - Medical group: 8%
  - Surgical group: 58% (64% of operated pts)  P<0.001

- Free of all seizures (including auras):
  - Medical group: 3%
  - Surgical group: 38%  P<0.001
7 center prospective observational study of resective epilepsy surgery in patients aged >12 years. Of 396 operated patients, 339 (297 medial temporal, 42 other) were followed over 2 years.

- Seizure remission was defined as 2 years completely seizure-free after hospital discharge with or without auras.
- Relapse was defined as any seizures after 2-year remission.

223 (66%) experienced a 2-year remission

- medial temporal- 68%; neocortical- 50%
- Only absence of GTCS and presence of hippocampal atrophy were significantly and independently associated with remission, and only in the medial temporal resection group.

55 patients relapsed after 2-year remission

- medial temporal- 25%; neocortical- 19%
- Only delay to remission predicted relapse, and only in medial temporal patients.
396 patients who underwent resective epilepsy surgery completed QOLIE-89 before surgery, within 6 months, and at ~ yearly intervals after surgery.

QOLIE-89 scores increased significantly at the first postoperative measurement (within 6 months after surgery) in the cohort overall.

Subsequent changes over time were sensitive to seizure-free and aura-free status.

- QOLIE-89 overall and four dimension scores increased as a function of square root of time seizure-free, and independently as a function of square root of time aura free, leveling by 2 years of stable seizure (aura) status.

HRQOL was not independently related to duration of epilepsy, duration of intractable epilepsy, or continuation of medications.
Late seizure relapse after surgery - Schiller et al, 2000

- 210 patients seizure-free after epilepsy surgery
- Follow-up at 5 years post-op
  - 7% relapse with no AED change
  - 14% relapse with partial AED reduction
  - 36% relapse with full AED withdrawal
- Surgery may render refractory epilepsy responsive to AEDs, without a cure
Recurrent refractory seizures after epilepsy surgery - incidence, predictors

Recurrent (refractory) seizures most likely within 2 years, but may continue after 2 years. Late recurrences have different predictors than early recurrences.

McIntosh et al, Brain 2004: In 325 patients who underwent anterior temporal lobectomy between 1978 and 1998 (mean follow-up 9.6 +/- 4.2 years), the probability of complete seizure freedom post-surgery was 55.3% at 2 years; 47.7% at 5 years, and 41% at 10 years.

Patients with 2 seizure-free postoperative years had a 74% probability of seizure freedom by 10 years. Late seizure recurrence was not associated with any identified risk factors.

Janszky et al, Brain 2005: In 171 patients with MTS and epilepsy surgery, longer epilepsy duration predicted a poor 5-year outcome, while secondarily generalized seizures and ictal dystonia predictor an unfavorable 2 year outcome.
Thirty-nine (68%) of 57 patients who discontinued AED therapy remained seizure-free.

Patients remaining seizure-free had a younger age at surgery than the group with seizure recurrence (p = 0.01).

Earlier surgery may be a favorable predictor for seizure freedom after AED discontinuation.

- Medications were withdrawn in 68 of 97 patients, seizure free (or with rare nondisabling auras) for >6 months after surgery;
  - 57 (84%) remained seizure free
  - 11 (16%) had seizure recurrence after 68 months (median).
    - Seizure recurrence was controlled with medication in 7 of the 11 patients (3 have rare seizures, 1 frequent auras).
- Discontinuing medications at <6 mo, compared with later or no withdrawal, had significant risk for seizure recurrence.
- Of 29 patients who continued drugs, 28 (97%) remained seizure free after a median of 37 months.
- Freedom from seizures 6 months after surgery predicted good outcome (95% seizure free, with or without medication).
How soon should surgery be offered after seizures become refractory?
Early Randomized Surgical Epilepsy Trial (ERSET)

- Multicenter randomized controlled trial of early surgical intervention for mesial temporal lobe epilepsy
- 19 surgical centers evenly spaced across the country
ERSET- Subjects

- Age 12 or older
- Seizures that have not responded to 2 drugs
- Disabling seizures for not more than 2 consecutive years
- Rigid diagnostic criteria for MTLE (MRI, PET, ictal EEG, neurocognitive function)
ERSET- patient population

38 Randomized

23 Randomized to medical group
   16 Received treatment as randomized
   7 Received surgery

5 Withdrew prematurely
   3 Lost to follow-up
   2 Requested surgery

23 Included in analysis

15 Randomized to surgical group
   14 Received surgery as randomized
   1 Did not receive surgery (withdrew consent)

1 Withdrew prematurely (withdrew consent)

15 Included in analysis
ERSET- Results

- 0/23 in the medical group and 11 of 15 (73%) in the surgical group were seizure free during year 2 of follow-up (odds ratio=; 95% CI, 11.8 to ; $P.001$).

- The effect of surgery on QOL was significant after excluding patients who crossed over (12.8 vs 2.8 points; treatment effect=9.9; 95% CI, 2.2 to 17.7; $P=.01$).
Adjusted Mean QOLIE-89 Score

![Graph showing adjusted mean QOLIE-89 scores over time for surgical and medical treatment groups.](image-url)
ERSET- Conclusions

- Benefit of surgery in newly intractable epilepsy is very large.
- Patients who continue pharmacotherapy at this early stage of intractability have a very low likelihood of being seizure free during the second year.
More medical therapy?
Luciano & Shorvon, Ann Neurol 2007

- 265 drug additions in 155 adult patients with chronic epilepsy active at least 5 yrs after initiation of therapy.
- ~ 16% of all drug introductions resulted in seizure freedom at last follow-up for >12 months; further 21% produced 50 to 99% seizure reduction.
- 28% were rendered seizure free by a drug introduction.
- Clinical factors associated with a better effect were fewer previously used antiepileptic drugs, shorter duration epilepsy, and idiopathic epilepsy.
- “The application of a systematic protocol to the treatment of chronic epilepsy will improve seizure control in a substantial proportion of cases.”
More medical therapy?
Callaghan et al, Ann Neurol 2007

- 246 patients with refractory epilepsy (> 1 seizure/m, failed ≥ 2 AEDs) followed for 3 yrs.
- Estimated 6-m terminal seizure remission rate:
  - 14% when limited to those treated only with medication.
- Negative predictors for remission included
  - history of status epilepticus, younger age at intractability, number of failed drug therapies, and presence of mental retardation.
- No specific drug was significantly associated with remission, and frequently, no clear intervention led to terminal remission.
Long follow up after more medical therapy - Callaghan et al 2011

- 246 patients indentified with drug-resistant epilepsy in 2003 at a single center.
- Estimated cumulative probability of 12-month seizure remission was 33.4% at 7 years in those without surgery.
- The risk for relapse after a 12-month period of seizure remission was 71.2% at 5 years.
Long follow up after more medical therapy- Callaghan et al 2011

- Negative predictors of seizure remission:
  - developmental delay
  - symptomatic generalized epilepsy
  - duration of intractability
  - number of antiepileptic drugs failed

- Negative predictor of relapse: localization-related epilepsy.
Among patients with drug-resistant epilepsy, 5% per year enter seizure remission even with a follow-up of 6 years.

However, a substantial proportion of these patients relapse after the first year following a remission.

The large proportion of patients entering a significant remission gives these patients hope; however, caution should be advised when discussing the likelihood of future seizures.
All patients with a diagnosis of intractable (drug-resistant) epilepsy were considered for referral for a neurologic evaluation of appropriateness for surgical therapy and the consideration was documented in the medical record within the past three years.
Options for patients who are not candidates for surgery

- Vagus Nerve Stimulation
- Dietary therapy
  - Ketogenic Diet
  - Modified Atkins; Low Glycemic Index Diet
- Future stimulation options
  - Deep brain stimulation
  - Responsive neurostimulation
Summary

- Drug-resistant epilepsy should be identified early.
- Patients with drug-resistant epilepsy should be evaluated for possible surgery.
- Epilepsy surgery has a high success rate in eliminating disabling seizures and improving quality of life.
- The best candidates are those with mesial temporal sclerosis or lesional epilepsy.
Self-assessment questions
Q1- Which qualify for drug resistance in focal epilepsy?

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