REFRACTORY EPILEPSY AND PRESURGICAL EVALUATION

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DRUG RESISTANT EPILEPSY

- the ILAE defines drug-resistant as
- “Failure of adequate trials of two tolerated and appropriately chosen AED schedules (whether as monotherapies or in combination) to achieve seizure freedom”
- Seizure freedom means “Freedom from all types of seizures for 12 months or three times the preintervention interseizure interval, whichever is longer”

Is it true drug resistance epilepsy?

- Misdiagnosis
- Poor compliance
- Inappropriate AED

Outcome in Patients According to the Number of Seizures before Treatment.

“TIME IS BRAIN”

- How early should surgery be done in drug-resistant TLE? : Large cohort 664 patients ; 136 children and 528 adults

Level of recommendation

- **A** = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*

- **B** = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

- **C** = Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

- **U** = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.
AAN guideline 2004 in treatment of new onset epilepsy

Table 1  Summary of the 2004 American Academy of Neurology guideline Level A or B recommendations regarding the use of new antiepileptic drugs (AEDs) in treatment of new-onset epilepsy

<table>
<thead>
<tr>
<th>AED</th>
<th>Monotherapy focal/mixed (focal + IGE)</th>
<th>Childhood absence epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviation: IGE = idiopathic generalized epilepsy.
AAN guideline 2004 for treatment resistant epilepsy

Table 1 Summary of first guidelines on the use of antiepileptic drugs (AEDs) in treatment-resistant epilepsy, based on Level A and B recommendations

<table>
<thead>
<tr>
<th>AED</th>
<th>Adjunctive focal adult</th>
<th>Focal monotherapy</th>
<th>IGE</th>
<th>LGS</th>
<th>Adjunctive focal pediatric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (only in CAE)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Topiramate</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: CAE = childhood absence epilepsy; IGE = idiopathic generalized epilepsy; LGS = Lennox-Gastaut syndrome.
### Table 2  Mechanism of action of the 8 newly approved antiepileptic drugs (AEDs)

<table>
<thead>
<tr>
<th>AED</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clobazam</td>
<td>Binding to benzodiazepine at the GABA&lt;sub&gt;A&lt;/sub&gt; ligand-gated chloride channel complex</td>
</tr>
<tr>
<td>Eslicarbazepine</td>
<td>Use-dependent blockage of voltage-sensitive sodium channels</td>
</tr>
<tr>
<td>Ezogabine</td>
<td>Positive allosteric modulator of KCNQ2-5; positive allosteric modulator of GABA&lt;sub&gt;A&lt;/sub&gt; receptors</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>Slow inactivation of voltage-gated sodium channels; binds to CRMP-2</td>
</tr>
<tr>
<td>Perampanel</td>
<td>AMPA receptor antagonist</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Binding to the α2-δ protein subunit of voltage-gated calcium channels</td>
</tr>
<tr>
<td>Rufinamide</td>
<td>Use-dependent blockage of voltage-sensitive sodium channels</td>
</tr>
<tr>
<td>Vigabatin</td>
<td>Inactivation of GABA transaminase</td>
</tr>
</tbody>
</table>
Level A

- immediate-release pregabalin and perampanel for TR adult focal epilepsy (TRAFE);
- vigabatrin for TRAFE (not first-line treatment);
- rufinamide for Lennox-Gastaut syndrome (LGS) (add-on therapy).

Level B

- Lacosamide, eslicarbazepine, and extended-release topiramate for TRAFE (ezogabine production discontinued)
- Immediate- and extended-release lamotrigine for generalized epilepsy with TR generalized tonic-clonic (GTC) seizures in adults
- Levetiracetam (add-on therapy) for TR childhood focal epilepsy (TRCFE) (1 month-16 years), TR GTC seizures, and TR juvenile myoclonic epilepsy

Level B

- clobazam for LGS (add-on therapy)
- zonisamide for TRCFE (6-17 years)
- oxcarbazepine for TRCFE (1 month-4 years).

Pre-surgical evaluation in Epilepsy
Epilepsy surgery: issues to consider

- Misdiagnosis: non epileptic
- Seizure type
- Focal or generalized epilepsy?
- If focal→ temporal VS extratemporal
- Causes of epilepsy: structural, metabolic, immune, infection, genetic, unknown

Luder H. Textbook of Epilepsy Surgery. Informa UK
Fundamental principles

- Identify focus of medically refractory epilepsy
- To remove focus in order to render seizure free
- To avoid permanent postoperative deficit
- If 1-3 are not possible, to reduce seizure burden as possible
Epilepsy surgery: indication

- Drug resistance epilepsy

- Failure to achieve sustained seizure freedom with adequate trials of at least 2 appropriately chosen and used AED regimens (whether administered as monotherapies or in combination)

- Issue: inappropriate, inadequate, poor tolerability, seizure freedom—free from all seizure types
Presurgical evaluation in epilepsy

- Semiology
- Electroencephalography (EEG)
- SPECT: ictal, interictal, subtraction (SISCOM)
- PET scan
- MEG
- Neuroimaging
- fMRI
- Wada test
- Neuropsychology
- Genetic test
- Invasive EEG: grid, strip, depth electrode, Stereo-EEG
Semiology

- Analysis of seizure symptom and sign
- To lateralize and localize the seizure
Electroencephalography

- 21 electrode scalp EEG recording
  - Limited spatial resolution
  - Relatively low cost and global accessibility

- 256 channel dense array EEG
  - Higher localization value

- Ambulatory EEG, Video – AEEG

- Amplitude integrated EEG (C3/P3, C4/P4)
Neuroimaging
Neuroimaging

- MRI 3 Tesla, 7 Tesla
- SWI, gradient echo
- fMRI
- Diffusion tensor imaging (DTI)
- Tractography: image white matter tract
- Voxel based analysis (VBM) of MRI scan
MRI

- 1.5 T, 3 T, 7 Tesla (in few centers)
- High soft tissue contrast
- Fine cut 1-2 mm
- 3 dimensional volumetric T1-weighted sequences, T2, FLAIR
- Three planes (sagittal, coronal, axial)

Serial MRI

- Infant and young children during second year of life after complete myelination
- Rasmussen encephalitis, Sturge-Weber syndrome
Neuroimaging

- Susceptibility-weighted image (SWI)
  - Provide additional information in epileptogenic lesions containing blood products: cavernoma, certain posttraumatic epilepsy, Sturge-weber syndrome
  - High resolution three-dimensional gradient-echo technique
  - Superior to gradient echo (GRE) in detection of remote hemorrhage

DTI

- DTI: connection of different region of brain
MRI post processing

- Carries significant advantages for detection of subtle lesions

- Have consistently shown abnormalities beyond visually perceptible lesion and may offer measure of extent of cortical disruption
Voxel-based morphometry (VBM)

- Most popular post processing algorithm
- Automated technique that extracts gray matter and white matter maps from individuals to make statistical comparisons with a normal control database
Functional MRI

- Principle of cerebral blood oxygen level-dependent (BOLD) signal changes in response to activation of specific brain areas
- Language, motor & sensory cortex
Wada test

- Intracarotid amobarbital test, pharmacologic inactivation of cortex supplied by anterior and middle cerebral arteries in each hemisphere via left and right intracarotid injection of sodium amobarbital

- To lateralize language and test memory function
Neuropsychological test

- A test battery contains a personality inventory, intelligence quotient tests, memory and language function tests, other tests

- Earlier rationale for such testing to help localize an epileptogenic focus on basis that subtle deficits in cognitive functioning are not so valid now with increased availability of better imaging modalities

- However, certain tests and abnormal findings have value in demonstrating lateralization of dysfunction

Test material-specific memory and abilities among patients with suspected TLE

- Deficits in verbal memory and other verbal abilities (object naming, word list generation) are common when seizure focus lies in left temporal lobe in a right-handed patient
- Deficits in nonverbal memory and abilities suggest right temporal lobe epilepsy in a right-handed patient

PET and SPECT

- Both are prone to effects of seizure propagation and thus areas of abnormality be more extensive than epileptogenic region

PET scan

- To identify functional deficit zone, area of hypometabolism during interictal period in non-lesional patient

- FDG-PET is most useful for defining epileptogenic region lateralization, and to a lesser extent localization, but not necessarily its extent

Ictal and interictal SPECT

- Technitium 99m radiolabelled tracer used to identify area of increased cerebral blood flow or hyperperfusion

- Timing of injection is critical
  - Injection within seconds of seizure onset
  - Within 10 sec of start of seizure more likely to indicate area of seizure onset
  - Late injections may provide false localizing or lateralizing data in patients with complex seizure propagation patterns

- Subtraction of ictal and interictal SPECT help localization

Magnetoencephaligraphy (MEG)

- MEG record weak magnetic field generated by brain
- Superconducting quantum interference device (SQUID) technique operates at very low temperature
- Required a bath of liquid helium to cool the sensors, 100-300 SQUID magnetic sensors
- High cost, limited availability

MEG VS EEG

- MEG being more sensitive to tangential sources and EEG to radially oriented sources
- Define smaller foci (4–8 cm²) compared to EEG (10–15 cm²)
- Magnetic field is not influenced by inhomogeneity of conductivity, in patients with lesions, skull defects, asymmetries, malformations
- MEG is suited for foci in neocortical areas oriented tangentially, basal or interhemispheric region, or in postoperative cases

USE of MEG to define irritative zone

- TLE
  - Spike in anterior temporal neocortex; temporal tip with horizontal to temporal lobe and superior or basal temporal neocortex with vertical orientation are relatively specific to mesial TLE
  - Spike vertically in posterior temporal region seen with seizure originate from lateral temporal lobe

- Extratemporal lobe epilepsy: good agreement between MEG and invasive EEG for spike localization
  - Spike tightly-clustered in small area suggest seizure onset zone
  - Loosely distributed spike tend to be associated with nonlocalizable seizure onset

Invasive monitoring

- Extraoperative invasive EEG monitoring (IEM)
  - Gold standard for ER localization
  - Has its own limitations, including potential for adverse events
- Subdural, depth, or a combination of electrodes

Stereoelectroencephalography (SEEG)

- Stereotactic depth placement (SEEG) methodology permits accurate 3D in vivo electroclinical recordings of epileptiform activity.

- SEEG plan required clear formulation of specific anatomo-electro-functional hypothesis to be tested.

- Hypothesis based on results of various noninvasive evaluation.

- Generally feasible only above age of 3 years.

## SEEG

<table>
<thead>
<tr>
<th>Advantage</th>
<th>Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access to recording from deep cortical structures</td>
<td>More challenging to map plane continuously over an eloquent region of interest by using spaced SEEG electrodes</td>
</tr>
<tr>
<td>depths of sulci, mesial temporal lobe, cingulate gyrus, posterior orbitofrontal region, insula</td>
<td>Need for sophisticated equipment, including a stereotactic frame or robotic system</td>
</tr>
<tr>
<td>Ability to localize epileptogenic zone when subdural grids have failed to do</td>
<td>Costly disposable electrodes and skull anchor bolts</td>
</tr>
<tr>
<td>Possible multifocal seizure onsets, need for bihemispheric explorations</td>
<td>Neurosurgeon's experience</td>
</tr>
<tr>
<td>Capability in mapping 3D aspect of epileptic networks (limbic system, F/T, F/P) in non-leisonal MRI</td>
<td>Steep learning curve associated with learning the technique</td>
</tr>
</tbody>
</table>

Method of choice for invasive monitoring

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Method of Choice</th>
<th>Second Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesional MRI: Potential epileptogenic lesion is superficially located, near or in the proximity of eloquent cortex. Nonlesional MRI: Hypothetical EZ located in the proximity of eloquent cortex.</td>
<td>SDG</td>
<td>SEEG</td>
</tr>
<tr>
<td>Lesional MRI: Potential epileptogenic lesion is located in deep cortical and subcortical areas. Nonlesional MRI: Hypothetical EZ is deeply located or located in noneloquent areas.</td>
<td>SEEG</td>
<td>SDG with depths</td>
</tr>
<tr>
<td>Need for bilateral explorations and or reoperations.</td>
<td>SEEG</td>
<td>SDG with depths</td>
</tr>
<tr>
<td>After subdural grids failure</td>
<td>SEEG</td>
<td>SDG with depths</td>
</tr>
<tr>
<td>When the AEC hypothesis suggest the involvement of a more extensive, multilobar epileptic network.</td>
<td>SEEG</td>
<td>SDG with depths</td>
</tr>
<tr>
<td>Suspected frontal lobe epilepsy in nonlesional MRI scenario</td>
<td>SEEG</td>
<td>SEEG</td>
</tr>
</tbody>
</table>

Abbreviations: AEC, anatomoelectroclinical correlations; EZ, epileptogenic zone; SDG, subdural grid; SEEG, Stereo-electroencephalography.

Outcome and Complication

**TABLE 2: Surgical and medical complications in 200 patients undergoing a total of 2663 SEEG electrode implantations**

<table>
<thead>
<tr>
<th>Nature of Complication</th>
<th>No. of Patients</th>
<th>Complication Rate per Electrode (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>surgical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>wound infection</td>
<td>2</td>
<td>0.08</td>
</tr>
<tr>
<td>hematoma</td>
<td>2</td>
<td>0.08</td>
</tr>
<tr>
<td>transient speech deficit</td>
<td>1</td>
<td>0.04</td>
</tr>
<tr>
<td>medical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cardiac</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>DVT/PE</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>urinary infection</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>C. difficile gastroenteritis</td>
<td>1</td>
<td>NA</td>
</tr>
</tbody>
</table>

* DVT = deep venous thrombosis; NA = not applicable; PE = pulmonary embolism.

Genetic test

- Genetic factor account for about 40% of etiology causes of epilepsy

- Phenotype heterogeneity and genetic heterogeneity

- Genetic testing in patients with intractable epilepsy and developmental delay
  - Metabolic testing for inborn error of metabolism
    - Neonates with in utero seizure, myoclonic epilepsy in infants, IS, atypical absence, EPC, episodic decompensation, hypsarrhythmia, burst suppression, MRI with metabolic pattern
  - Vitamin dependent conditions (B6, folinic, biotin)
  - Genetic test

Genetic test

- Karyotype
- Chromosomal microarray: higher resolution than chromosome
  - Miss balanced inversion, translocation, triplet repeat, point mutation
- Specific gene or gene panel sequencing (20->400 genes)
- Whole exome sequencing: sequence all protein-coding exons (1-1.5% of human genome)
  - Dealing with uncertainty of variants of unknown significance
  - Not detect mutation in noncoding area and intron, triplet repeats, abnormal methylation, some large insertion, deletion and duplication
- High cost
- Whole genome sequencing

## Syndromes and some of the more commonly associated genes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign familial neonatal convulsions</td>
<td>KCNQ2, KCNQ3</td>
</tr>
<tr>
<td>X-linked infantile spasms</td>
<td>CDKL5, ARX</td>
</tr>
<tr>
<td>Dravet syndrome</td>
<td>SCN1A, SCN2A, GABRG2, GABRA1, PCDH19, STXBP1, HCN1</td>
</tr>
</tbody>
</table>
Thank you