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"

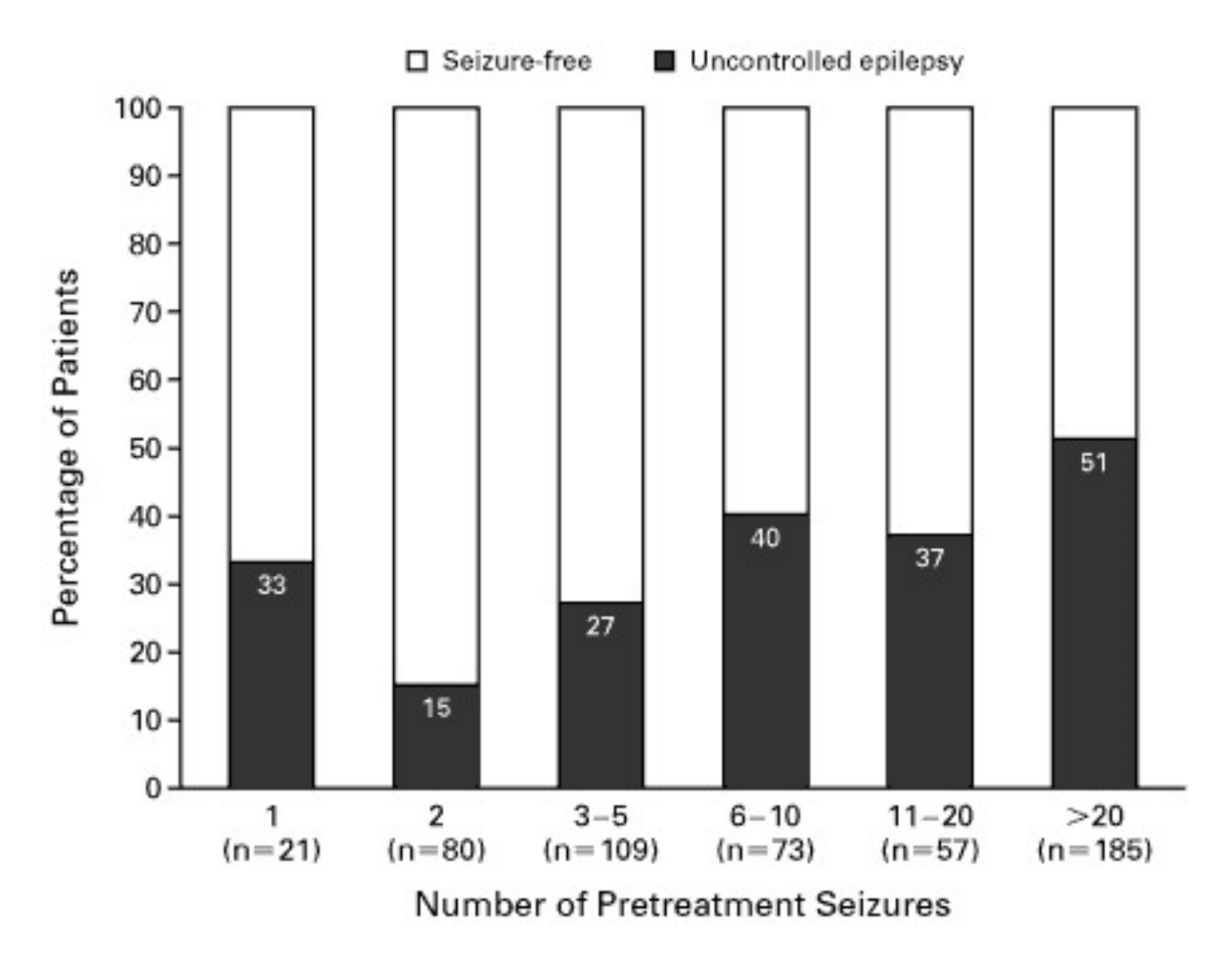
Kwan P, Arzimanoglou A, Berg AT et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010 Jun;51(6):1069-77.

Is it true drug resistance epilepsy ?

- Misdiagnosis
- Poor compliance
- Inappropriate AED

Kwan P, Arzimanoglou A, Berg AT et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010 Jun;51(6):1069-77.

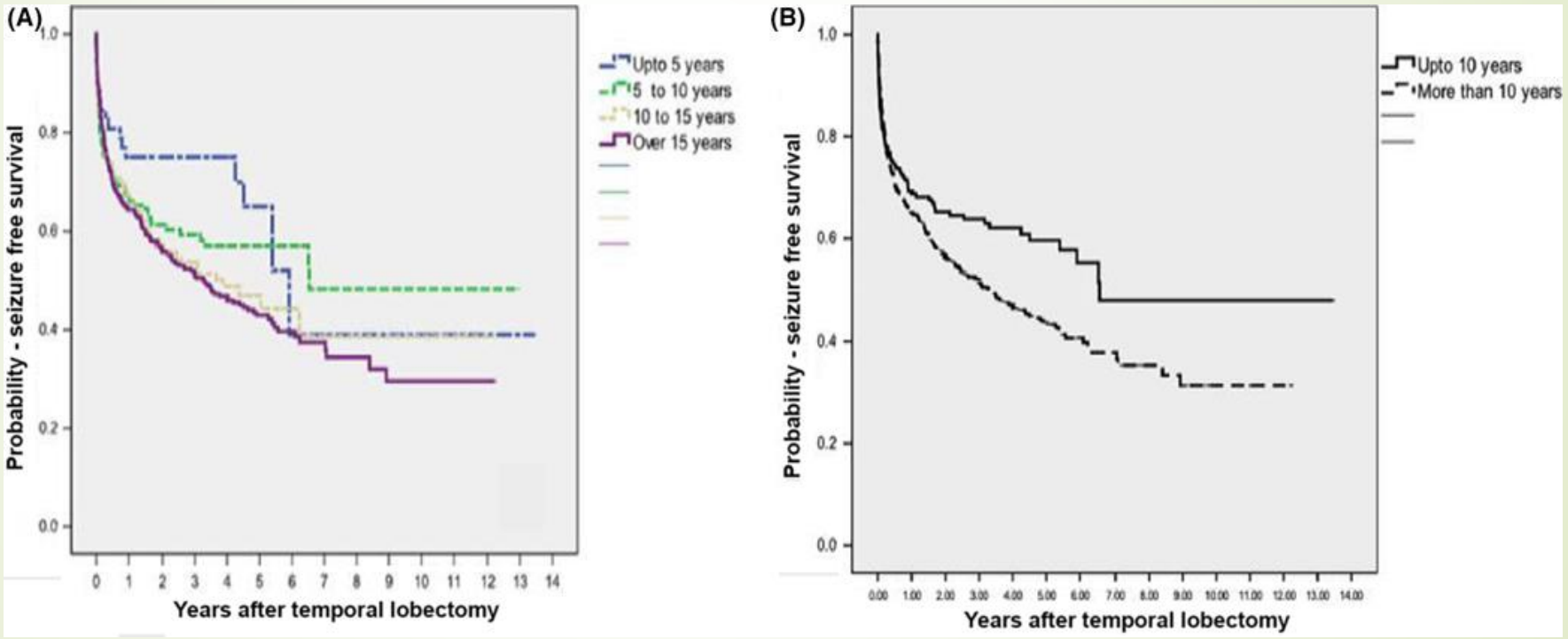
Outcome in Patients According to the Number of Seizures before Treatment.



Kwan P, Brodie MJ. N Engl J Med 2000;342:314-319.

"TIME IS BRAIN"

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



Radhakrishnan A, Menon R, Thomas SV, et al. "Time is Brain"-How early should surgery be done in drug-resistant TLE? Acta Neurol Scand. 2018 Jul 31.

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

AED	Monotherapy focal/mixed (focal + IGE)	Childhood absence epilepsy
Gabapentin	Yes	No
Lamotrigine	Yes	Yes
Topiramate	Yes	No
Tiagabine	No	No
Oxcarbazepine	Yes	No
Levetiracetam	No	No
Zonisamide	No	No

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[3]

AED	Adjunctive focal adult	Focal monotherapy	IGE	LGS	Adjunctive focal pediatric
Gabapentin	Yes	No	No	No	Yes
Lamotrigine	Yes	Yes	Yes (only in CAE)	Yes	Yes
Levetiracetam	Yes	No	No	No	No
Oxcarbazepine	Yes	Yes	No	No	Yes
Tiagabine	Yes	No	No	No	No
Topiramate	Yes	Yes	Yes	Yes	Yes
Zonisamide	Yes	No	No	No	No

Abbreviations: CAE = childhood absence epilepsy; IGE = idiopathic generalized epilepsy; LGS = Lennox-Gastaut syndrome.

New AED

Table 2 Mechanism of action of the 8 newly approved antiepileptic drugs (AEDs)

AED	Mechanism of action
Clobazam	Binding to benzodiazepine at the $GABA_A$ ligand–gated chloride channel complex
Eslicarbazepine	Use-dependent blockage of voltage-sensitive sodium channels
Ezogabine	Positive allosteric modulator of KCNQ2-5; positive allosteric modulator of $GABA_A$ receptors
Lacosamide	Slow inactivation of voltage-gated sodium channels; binds to CRMP-2
Perampanel	AMPA receptor antagonist
Pregabalin	Binding to the α2-δ protein subunit of voltage-gated calcium channels
Rufinamide	Use-dependent blockage of voltage-sensitive sodium channels
Vigabatrin	Inactivation of GABA transaminase

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).

Kanner AM, Ashman E, Gloss D, Harden C, Bourgeois B, Bautista JF,et al. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs II: Treatment-resistant epilepsy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2018 Jul 10;91(2):82-90.

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

Kanner AM, Ashman E, Gloss D, Harden C, Bourgeois B, Bautista JF,et al. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs II: Treatment-resistant epilepsy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2018 Jul 10;91(2):82-90.

Level B

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

Kanner AM, Ashman E, Gloss D, Harden C, Bourgeois B, Bautista JF,et al. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs II: Treatment-resistant epilepsy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2018 Jul 10;91(2):82-90.

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

Luder H. Textbook of Epilepsy Surgery. Informa UK

Epilepsy surgery: indication

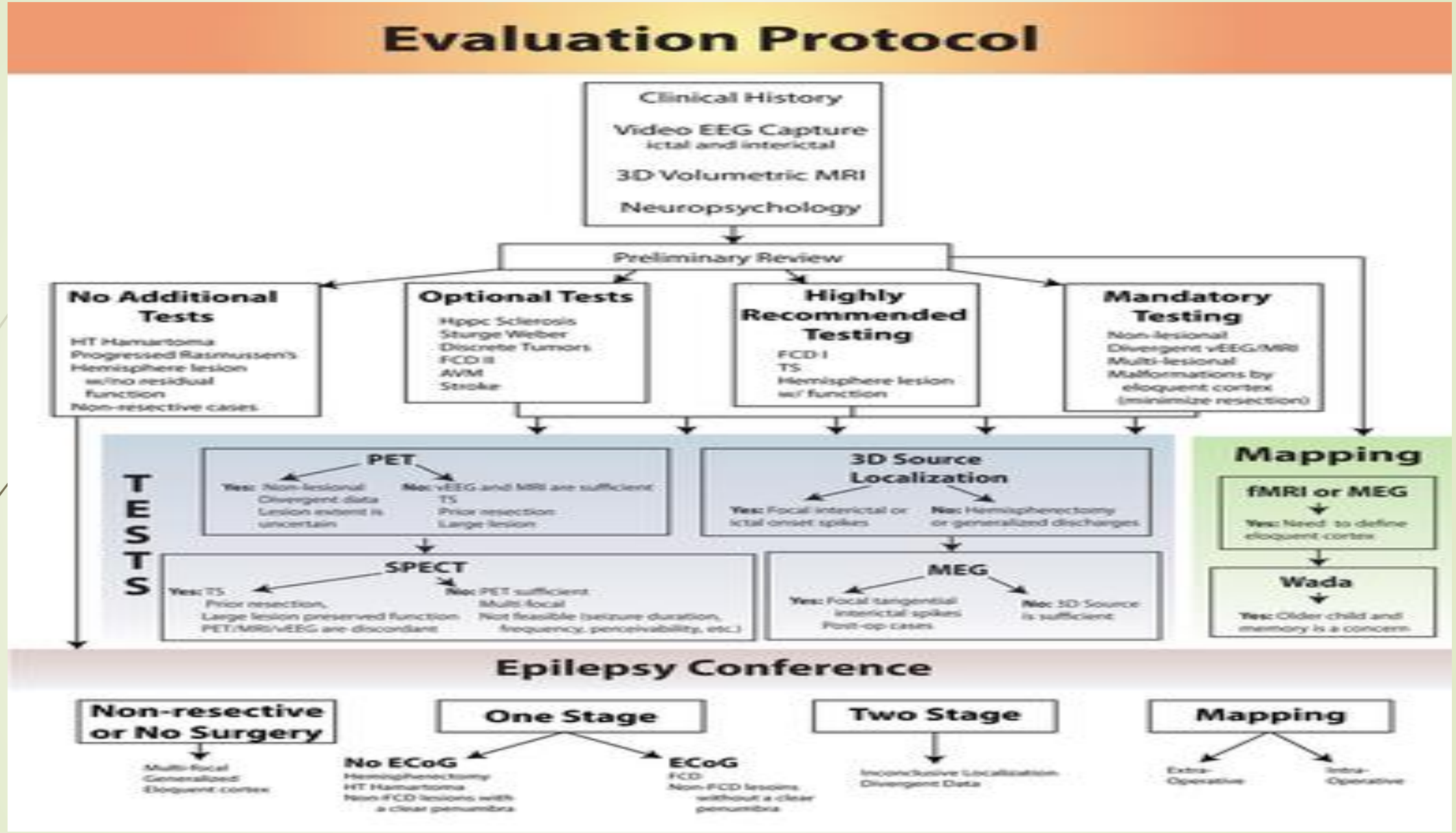
- Drug resistance epilepsy
- Failure to achieve sustained seizure freedom with adequate trials of at least 2 appropriately chosen and used AED regimens (whether administered as monotherapies or in combination)
- Issue: inappropriate, inadequate, poor tolerability, seizure freedom—free from all seizure types

Luder H. Textbook of Epilepsy Surgery. Informa UK

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

Diagnostic test utilization in evaluation for resective epilepsy surgery in children



Diagnostic test utilization in evaluation for resective epilepsy surgery in children, Volume: 55, Issue: 4, Pages: 507-518, First published: 11 February 2014, DOI: (10.1111/epi.12544)

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

Jayakar P, Gaillard WD, Tripathi M, et al. Diagnostic test utilization in evaluation for resective epilepsy surgery in children. Epilepsia. 2014 Apr;55(4):507-18. doi: 10.

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

Jayakar P, Gaillard WD, Tripathi M, et al. Diagnostic test utilization in evaluation for resective epilepsy surgery in children. Epilepsia. 2014 Apr;55(4):507-18. doi: 10.

NPT

- 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

Jayakar P, Gaillard WD, Tripathi M, et al. Diagnostic test utilization in evaluation for resective epilepsy surgery in children. Epilepsia. 2014 Apr;55(4):507-18. doi: 10.

PET and SPECT

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

Jayakar P, Gaillard WD, Tripathi M, et al. Diagnostic test utilization in evaluation for resective epilepsy surgery in children. Epilepsia. 2014 Apr;55(4):507-18. doi: 10.

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

Jayakar P, Gaillard WD, Tripathi M, et al. Diagnostic test utilization in evaluation for resective epilepsy surgery in children. Epilepsia. 2014 Apr;55(4):507-18. doi: 10.

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

Jayakar P, Gaillard WD, Tripathi M, et al. Diagnostic test utilization in evaluation for resective epilepsy surgery in children. Epilepsia. 2014 Apr;55(4):507-18. doi: 10.

Magnetoencephalgraphy (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

Jayakar P, Gaillard WD, Tripathi M, et al. Diagnostic test utilization in evaluation for resective epilepsy surgery in children. Epilepsia. 2014 Apr;55(4):507-18. doi: 10.

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 filed 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

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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

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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

Jayakar P, Gaillard WD, Tripathi M, et al. Diagnostic test utilization in evaluation for resective epilepsy surgery in children. Epilepsia. 2014 Apr;55(4):507-18. doi: 10.

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

Alomar S, Jones J, Maldonado A, Gonzalez-Martinez J. The Stereo- Electroencephalography Methodology. Neurosurg Clin N Am.2016;27 (1):83-96

SEEG

Advantage

- Access to recording from deep cortical structures
  - depths of sulci, mesial temporal lobe, cingulate gyrus, posterior orbitofrontal region, insula
- Ability to localize epileptogenic zone when subdural grids have failed to do
- Possible multifocal seizure onsets, need for bihemispheric explorations
- Capability in mapping 3D aspect of epileptic networks (limbic system, F/T, F/P) in non-leisonal MRI

Limitation

- More challenging to map plane continuously over an eloquent region of interest by using spaced SEEG electrodes
- Need for sophisticated equipment, including a stereotactic frame or robotic system
- Costly disposable electrodes and skull anchor bolts
- Neurosurgeon's experience
- Steep learning curve associated with learning the technique

Alomar S, Jones J, Maldonado A, Gonzalez-Martinez J. The Stereo- Electroencephalography Methodology. Neurosurg Clin N Am.2016;27 (1):83-96

Method of choice for invasive monitoring

Table 1
Selection criteria for different methods of invasive monitoring in medically refractory focal epilepsy

Clinical Scenario	Method of Choice	Second Option
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.	SDG	SEEG
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.	SEEG	SDG with depths
Need for bilateral explorations and or reoperations.	SEEG	SDG with depths
After subdural grids failure	SEEG	SDG with depths
When the AEC hypothesis suggest the involvement of a more extensive, multilobar epileptic network.	SEEG	SDG with depths
Suspected frontal lobe epilepsy in nonlesional MRI scenario	SEEG	SEEG

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

Alomar S, Jones J, Maldonado A, Gonzalez-Martinez J. The Stereo- Electroencephalography Methodology. Neurosurg Clin N Am.2016;27 (1):83-96

Outcome and Complication

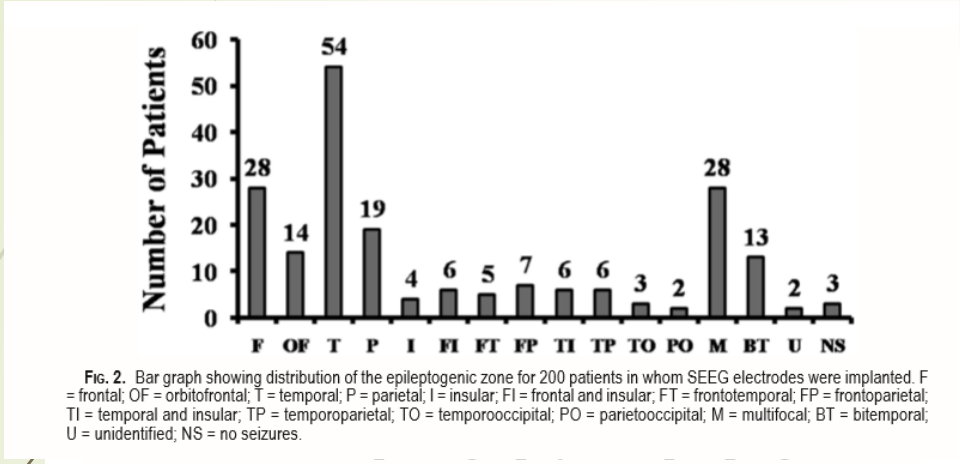


FIG. 2. Bar graph showing distribution of the epileptogenic zone for 200 patients in whom SEEG electrodes were implanted. F = frontal; OF = orbitofrontal; T = temporal; P = parietal; I = insular; FI = frontal and insular; FT = frontotemporal; FP = frontoparietal; TI = temporal and insular; TP = temporoparietal; TO = temporooccipital; PO = parietooccipital; M = multifocal; BT = bitemporal; U = unidentified; NS = no seizures.

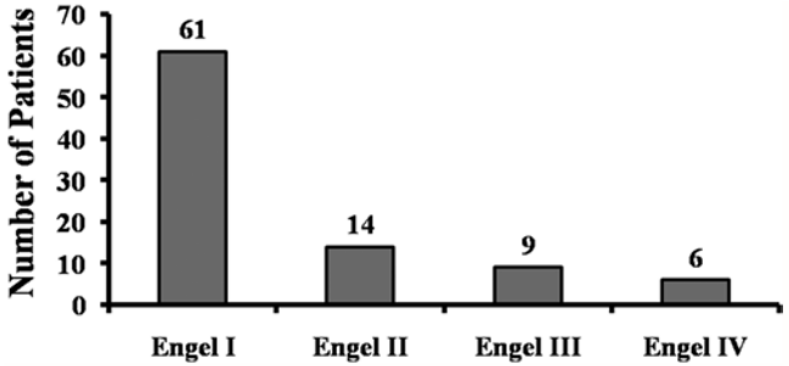


FIG. 5. Bar graph showing postoperative seizure control outcomes for a cohort of 90 patients undergoing SEEG implantation for invasive monitoring and subsequent resective surgery. Length of follow-up was a minimum of 12 months (average follow-up of 2.4 years).

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

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

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

Serletis D, Bulacio J, Bingaman W, Najm I, González-Martínez J. The stereotactic approach for mapping epileptic networks: a prospective study of 200 patients. J Neurosurg. 2014 Nov;121(5):1239-46.

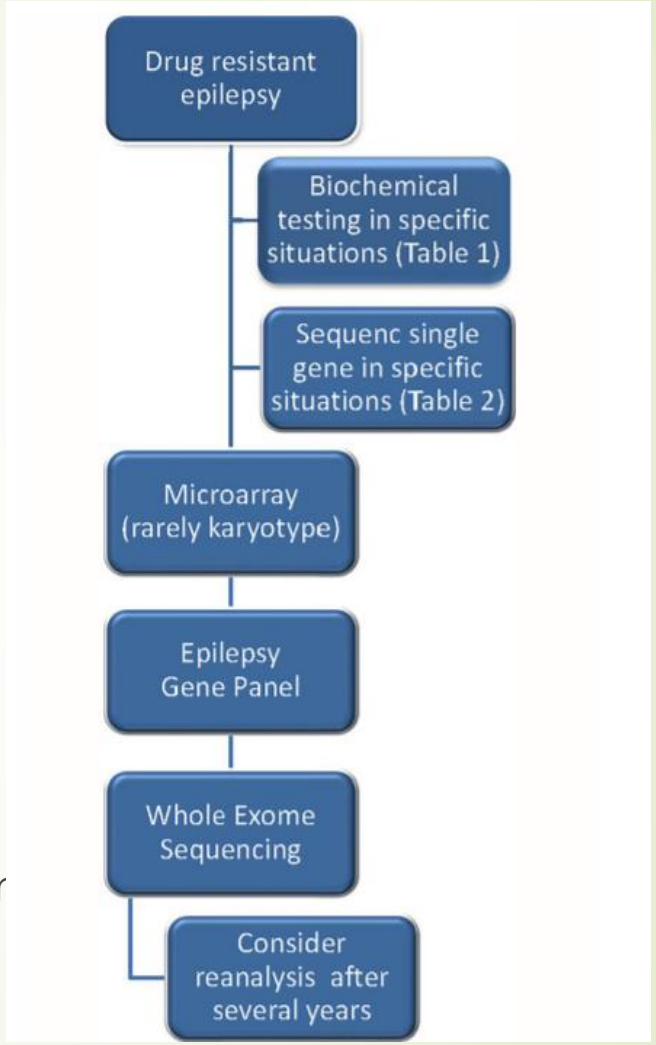
Genetic test

- 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

Ream MA, Patel AD. Obtaining genetic testing in pediatric epilepsy. Epilepsia. 2015;56(10):1505-14.

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, som large insertion, deletion and duplication
  - High cost
- Whole genome sequencing



Ream MA, Patel AD. Obtaining genetic testing in pediatric epilepsy. Epilepsia. 2015;56(10):1505-14.

Syndromes and some of the more commonly associated genes

Syndrome	Gene
Benign familial neonatal convulsions	*KCNQ2* *KCNQ3*
X-linked infantile spasms	CDKL5 ARX
Dravet syndrome	SCN1A SCN2A GABRG2 GABRA1 PCDH19 STXBP1 HCN1

Ream MA, Patel AD. Obtaining genetic testing in pediatric epilepsy. Epilepsia. 2015;56(10):1505-14.

Thank you