Medically Intractable Epilepsy

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Outline

- Definition
- Epidemiology
- Taxonomy
- Pathophysiology of intractable seizures
- Pre-operative diagnosis and work-up
- Management options

Definitions

A ***seizure*** is the clinical manifestation of excessive, synchronous, abnormal firing of large populations of neurons

Intractable epilepsy

- A persistent seizure activity that prevents the individual from normal function or development.

- Characterized by two antiepileptic drug (AED) failures, at least one seizure per month for 18 months, and no seizure-free periods longer than three months during that time.

  *no consensus

Epidemiology

Prevalence of epilepsy is 5 to 10 per 1000 in the North American population

Second most common cause of mental health disability

Approximately 20% of individuals with a diagnosis of epilepsy have seizures that are not adequately controlled by AEDs

Why do patients fail to respond?

- Paroxysmal events that are not epileptic
- Psychogenic seizures
- Misdiagnosis of seizure type
- Non-compliance with medication
- Epileptic disorder with different pathophysiologic mechanism than that targeted by the AED
- Unreliable reporting of seizures
- Unknown factors

When should we intervene surgically?

Failed medical management with >2 AEDs

i.e. At least one seizure every 1-2 months

AND

Seizures are associated with any of:

- Impaired LOC
- Injury (e.g. from falls)
- Accompanied by stigmatizing behaviour (e.g. disrobing, uttering obscenities)
- Accompanied by unpleasant or noxious auras (e.g. vomiting, intense fear)
- Unpredictable occurrence

Factors to consider when making the surgical decision

- Patient's social environment
- Expectations
- Level of function
- Quality of life
- Severity and frequency of seizures
- Medical consequences of the epilepsy

Taxonomy of surgically remediable epilepsy syndromes

Temporal Lobe Epilepsy (TLE)	Idiopathic; Mesial Temporal Sclerosis/MTLE; Lesional (Tumor, Vascular Malformation, Developmental, Ischemic, Traumatic)
Extratemporal Epilepsy	Idiopathic; Lesional (Tumor, Vascular Malformation, Developmental, Ischemic; Traumatic)
Catastrophic Epilepsy	Lesional; (Hemimegalencephaly, Diffuse Cortical Dysplasias, Sturge-Weber, Rasmussen's, Porencephalic Cysts)

Secondarily Generalized Epilepsies	Lennox-Gastaut

Pathophysiology of epilepsy

- Alteration in neuronal excitability by changes in voltage-gated and transmitter-gated ion channels
- Focal reduction in inhibitory neurotransmission
- Alterations in gene expression
- Changes in cellular plasticity of neurons with age or in response to injury
- Developmental alterations in cerebral cortex

Goal of resective epilepsy surgery

Complete resection of the **epileptogenic zone** (the area of cortex that is required to generate clinical seizures)

Its location and boundaries are defined by:

- seizure semiology
- electrophysiologic recordings
- functional testing
- neuroimaging techniques

Seizure Semiology

- Clinical features of a seizure may suggest a location for the symptomatogenic zone and have lateralizing value

Seizure Semiology

Ictal speech	Non-dominant temporal lobe
Dystonic limb posturing	Contralateral to side of temporal lobe seizure onset
Post-ictal nose wiping	Ipsilateral to temporal lobe of onset
Post-ictal dysnomia > 2 min	Onset in the dominant temporal lobe
Forceful head version immediately prior to a secondarily generalized tonic-clonic seizure	Contralateral hemisphere
nonforced head turning at ictal onset without a tonic component or hemifacial clonic twitching	Ipsilateral hemisphere
Asymmetric tonic limb posturing, the "figure four sign,"	The extended limb is usually contralateral to the hemisphere of onset

Seizure Semilogy

Localized contralateral clonic activity and aphasia with speech arrest	Broca's area
Assymetrical bilateral proximal limb movement, version of head, facial grimacing with speech arrest or vocalization, and preserved consciousness	Supplementary motor area
Olfactory, psychic, and emotional auras followed by complex automatisms	Orbitofrontal and cingulate seizures
No warning, Bilateral tonic clonic activity with version, forced thinking, falls, autonomic signs	Prefrontal

Cortical zones

Symptomatogenic zone:

The area of cortex that, when activated by an epileptiform discharge, reproduces the initial ictal symptoms. The zone is defined by careful analysis of the ictal symptoms that can be done with a thorough seizure history and analysis of ictal video recordings

Irritative zone:

The area of cortical tissue that generates interictal electrographic spikes

Seizure onset zone:

The area of cortex from which clinical seizures are generated. This may be larger or smaller than the epileptogenic zone. When the epileptogenic zone is smaller than the seizure onset zone, partial resection of the seizure onset zone may lead to seizure freedom because the remaining seizure onset zone has been weakened sufficiently, rendering it incapable of generating further seizures

Area of functional deficit:

Area of cortex that is functionally abnormal in the interictal period

EEG Recordings

- Interictal and ictal Scalp EEG is used to localize the seizure discharges. Detects radially oriented electrical activity that is attenuated in strength and spatially distorted by tissue between brain and scalp

  Limitation: capable of detecting a seizure discharge only after it has extended considerably and has activated a relatively large area of cortex

EEG Recordings

Patients with temporal lobe epilepsy (TLE) have epileptiform activity consisting of spikes and/or sharp waves that are usually maximal at the anterior temporal (F7 and F8 electrodes) and the mid temporal regions (T3 and T4 electrodes).

Indications for Invasive EEG monitoring

- Bilaterally independent temporal lobe seizures
- Extratemporal lobe-onset seizures with rapid propagation to the medial temporal lobe
- Temporal lobe seizures of localized onset, but with normal MRI and FDG-PET findings
- Discordant EEG localization and imaging findings
- To distinguish neocortical from medial TLE
- Lateralization of seizures to a particular lobe though no abnormalities are seen on structural or functional imaging
- Epileptogenic zone located in or near eloquent cortex

Intracranial electrode placement is associated with a 2-3% complication rate

Neuroimaging

The goal is to locate and define anatomic epileptogenic lesions.

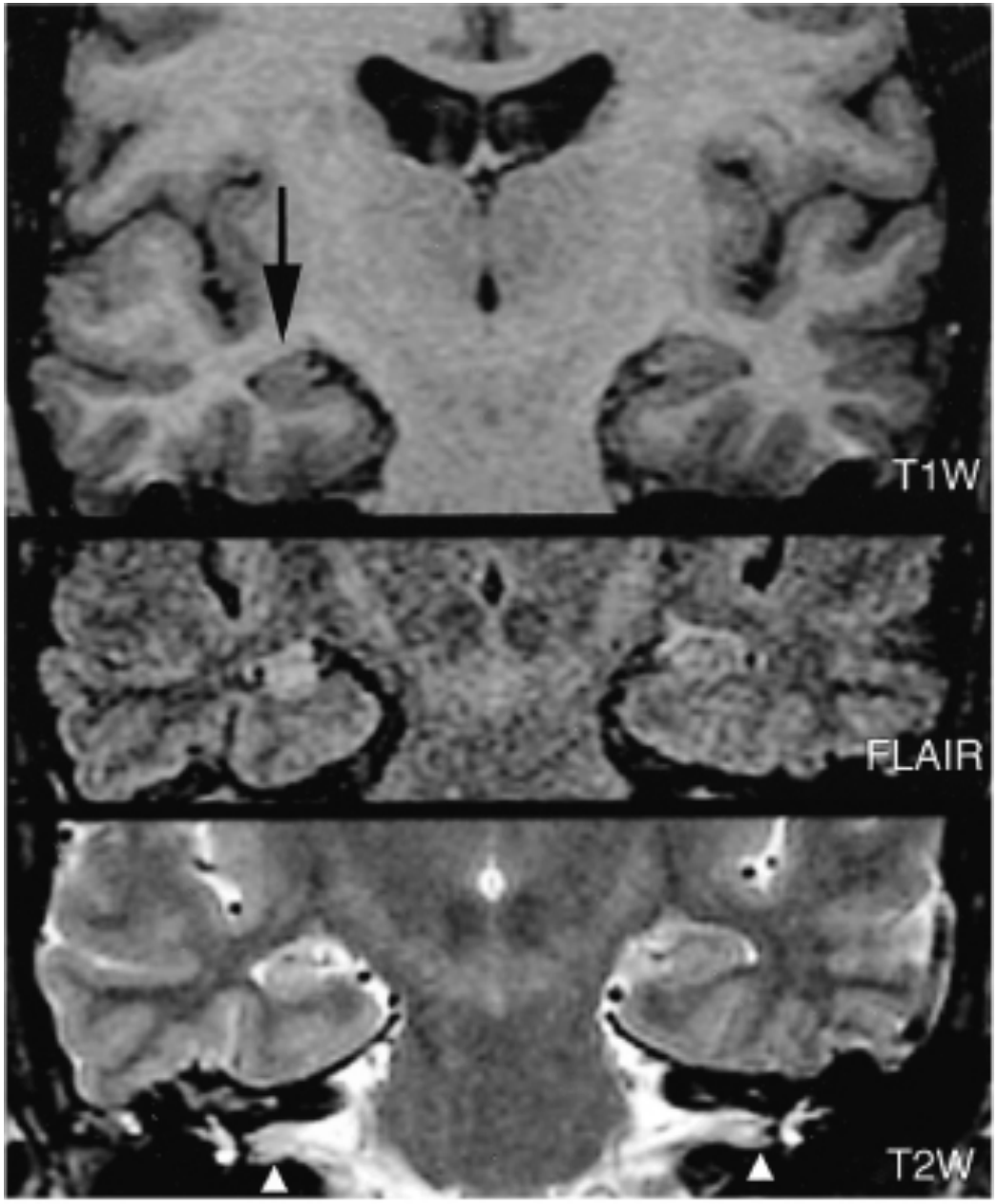
MRI: shown to have better chance of detecting positive pathology than CT scan.

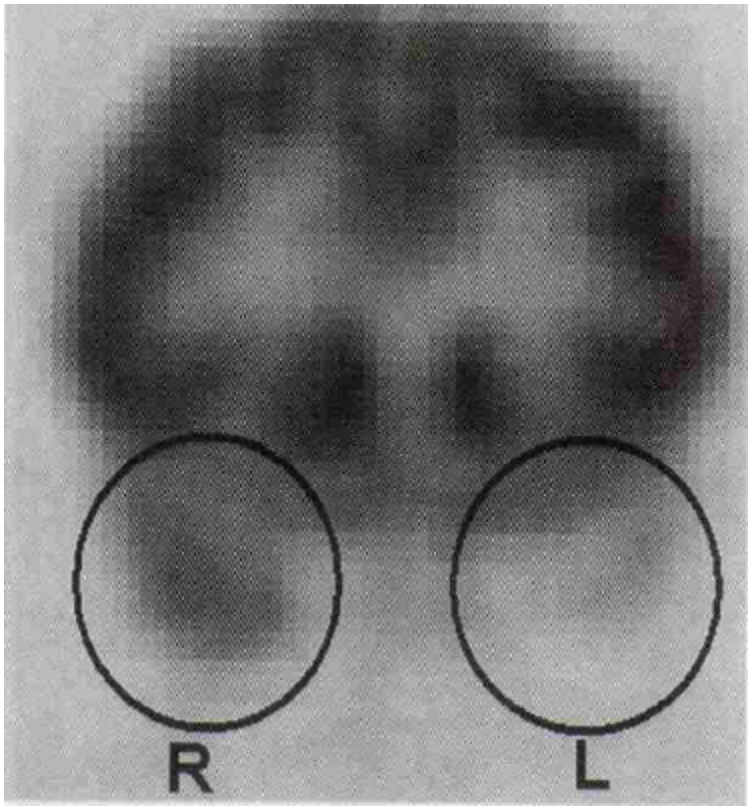
Limitation: cortical dysplasia may be subtle or not visualized on MR imaging

FDG-PET: interictal cortical hypometabolism correlates with the epileptogenic zone in temporal and extratemporal epilepsy

Hippocampal Sclerosis

80-95% of patients with surgically proven hippocampal sclerosis have hippocampal atrophy and hyperintensity on T2-weighted MR





FDG PET in a patient with mesial temporal epilepsy
showing hypometabolism in are aof left mesial temporal lobe

Neuroimaging

Ictal SPECT and functional MRI measure local changes in cerebral blood flow (a relative increase of ictal blood flow with respect to the interictal state). This increase of blood flow is a direct autoregulatory response to the hyperactivity of neurons during epileptogenic activation.

Functional Testing

- **Wada test** is used mainly to lateralize eloquent cortex with regard to language and memory and is used only secondarily as a supplementary method to determine the localization of the epileptogenic zone

What is a Wada Test?

Injection of sodium amobarbital into one carotid artery to temporarily inactivate the ipsilateral cerebral hemisphere, allowing independent testing of memory and language function of the contralateral hemisphere.

IAP is believed to anesthetize ipsilateral carotid artery distribution, which includes the amygdala and the anterior hippocampus.

Injection ipsilateral to the epileptogenic zone assesses the functional adequacy of the contralateral hippocampus to sustain memory

Contralateral hemiparesis and ipsilateral EEG slowing confirm the adequacy of injection

Epilepsy syndromes amenable to surgery

Mesial Temporal Lobe Epilepsy

- History of early insult in infancy or childhood
- Hippocampal sclerosis and atrophy on MRI
- Abnormal Creatine/NAA on MRS
- Temporal hypometabolism on interictal PET
- Characteristic pattern of hypoperfusion and hyperperfusion on SPECT
- Anteromedial epileptogenic zone on EEG
- Memory deficits on Wada testing
- Histology: loss of principal hippocampal neurons, synaptic re-organization, sprouting of mossy fibers, enhanced expression of glutamate receptors

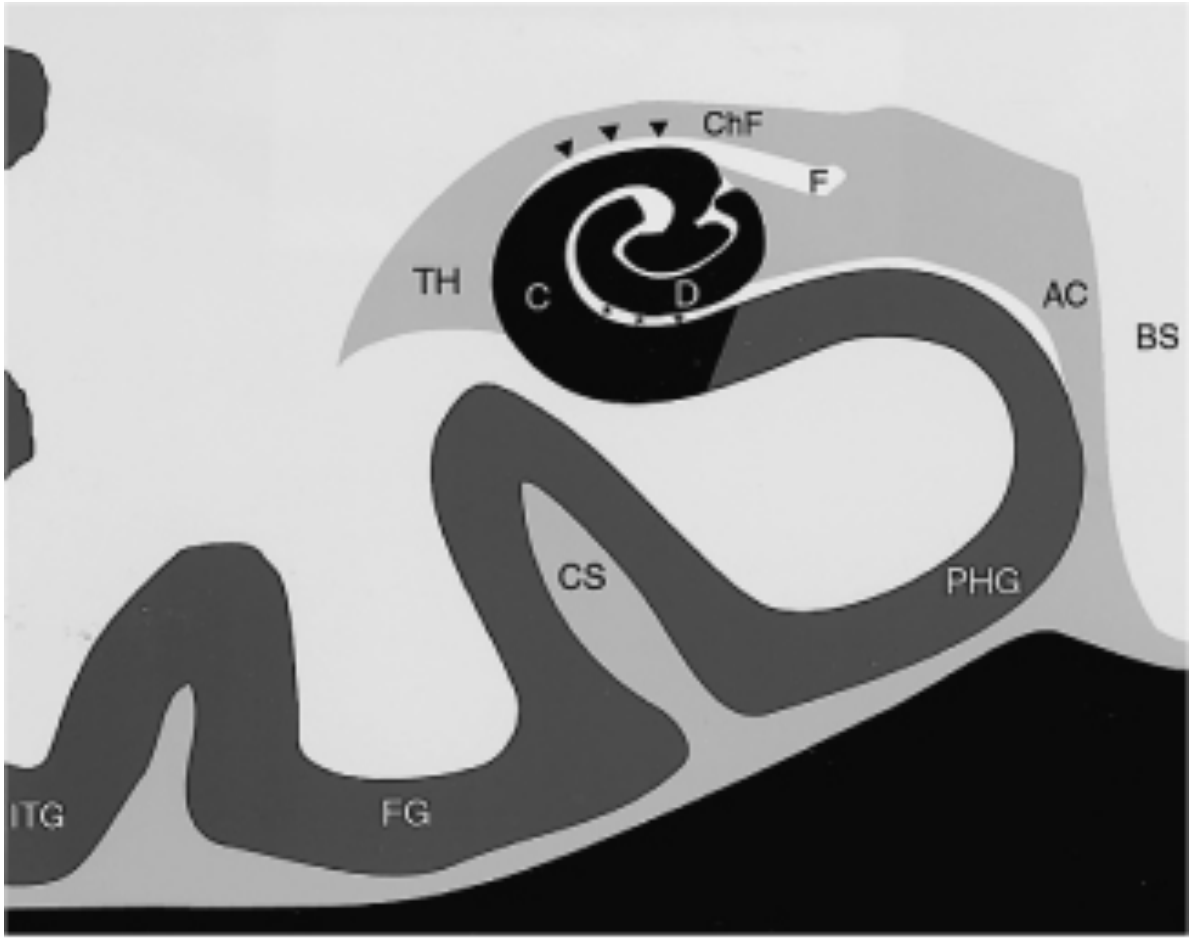


Figure 149-7 Diagram of a coronal slice through the medial temporal lobe. The hippocampus is composed of 2 <ss>U</ss>-shaped lamina of gray matter, the cornu ammonis (C) and dentate gyrus (D). Between them is the white matter of the molecular layer (*). The hippocampus is bordered by the alveus *(arrowheads),* choroid fissure (ChF), and temporal horn (TH) superiorly. The alveus converges medially to form the fimbria (F), which in turn is a component of the fornix. The ambient cistern (AC) and brainstem (BS) are situated medially. Inferior to the hippocampus is the parahippocampal white matter and gyrus (PHG). The temporal horn (TH) borders the hippocampus on its lateral aspect. CS, collateral sulcus; FG, fusiform gyrus or lateral occipital-temporal gyrus; ITG, inferior temporal gyrus. (From Bronen RA: Epilepsy: The role of MR imaging. AJR Am J Roentgenol 159:1165-1174, 1992.)

Frontal Lobe Epilepsy

- Second most common epilepsy syndrome referred for surgery
- Wide variety of seizure types depending on origin and spread
- Often prominent motor manifestations
- Interictal EEG spikes in one or both frontal lobes, temporal spikes may be seen
- Neuroimaging is usually negative

Lesional partial epilepsy

- 30% of patients undergoing epilepsy surgery have a structural lesion as underlying pathology

e.g. Focal encephalomalacia, tumor, vascular malformation, congenital developmental anomaly

- Anatomical location is primary determinant of seizure presentation

Neocortical cryptogenic epilepsy

Clinical history and electrical data suggest seizure of cortical origin but no structural lesion is identified

Surgical treatment based on EEG delineation of the epileptogenic zone.

Surgical Approaches for Epilepsy

Resective Surgery	Temporal lobe resections (anteromedial selective amygdalohippocampectomy); Extratemporal resections; Lesional resections; Anatomic or functional hemispherectomy
Disconnection surgery	Corpus callasotomy; Multiple subpial transections; Keyhole hemispherotomies
Radiosurgery	Mesial temporal lobe epilepsy; hypothalamic hamartomas
Neuroaugmentative surgery	Vagal nerve stimulators; Deep brain stimulation
Diagnostic surgery	Depth electrodes; subdural strip electrodes; subdural grids

Summary of Surgical Procedures for Epilepsy

- **Anteromedial temporal resection (AMTL):** The superior temporal gyrus is spared, and the middle and inferior temporal gyrus is resected 4-5 cm from the tip of the nondominant side and 3-4 cm of the dominant side. The amygdala is resected totally; the hippocampus and the parahippocampal gyrus are resected to the level of the colliculus.

- **Standard en bloc anterior temporal lobectomy:** This resection is similar to the AMTL except that the superior temporal gyrus, 2 cm from the temporal tip, also is resected.

- **Amygdalo-hippocampectomy:** In this procedure, the amygdala, hippocampus, and parahippocampal gyrus are resected, with sparing of the lateral and basal temporal neocortex.

- **Lesionectomy:** The lesion as delineated by MRI is resected, with a margin. In some cases, electrocorticography may be recommended to guide the margins of the resection.

Summary of Surgical Procedures for Epilepsy

- **Tailored neocortical resection:** This resection is based on imaging and EEG data and is tailored on the basis of functional mapping data such that eloquent cortical regions are spared. In some cases multiple subpial transections (MST) are recommended when the epileptogenic zone involves eloquent cortex. With MST, the horizontal fibers that are important for seizure propagation are interrupted at 5-mm intervals. The vertically oriented fibers that are important for function remain intact.

- **Functional hemispherectomy:** It consists of removal of sensorimotor cortex and the temporal lobe. The frontal lobe and the parieto-occipital lobes are left intact but are disconnected from cortical and subcortical structures.

- **Corpus callosotomy:** The anterior two thirds of the corpus callosum is resected. Sometimes, a complete callosotomy is performed; however, the risk of developing disconnection syndrome is greater with this procedure. May be employed in the setting of non-localized tonic, clonic, or atonic seizures that cause falls and injury.

- **Multilobar resection:** This usually involves the frontoparietal, parieto-occipito-temporal, or parieto-occipital lobes. The technique includes corticectomy (resection of grey matter), lobe excision (resection of grey and white matter), lobe disconnection, or a combination of these.

Is surgery for epilepsy effective?

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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*

At 1 year 58% of patients who underwent surgery were free of seizures impairing awareness versus 8% of patients who received medical treatment. Patients who underwent surgery also had significantly better HRQOL.

References

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