PEDIATRIC EPILEPSY

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General Information
Definitions

- "Seizure" - a sudden, unprovoked, unpredictable electrical discharge in the brain.
- "Epilepsy" - recurrent unprovoked seizures.
- "Epilepsy syndrome" – cluster of signs and symptoms with specific seizure types

General Information
Magnitude of the Problem

- Approximately 1% of people develop epilepsy
  - 40 million people worldwide
  - 2.3 million people in the US
- Estimated annual cost of epilepsy: $12.5 billion
- Epilepsy has significant effects on self-image, family and peer relationships

Seizure Classification

- Partial/Focal onset seizures
  - Simple
  - Complex
- Generalized onset seizures
  - Tonic, Clonic, Myoclonic, Absence, Atonic

Epilepsy Syndromes

- Neonatal seizures
- Focal/partial epilepsies
- Generalized epilepsies
- Special syndromes

Neonatal Seizures

- In neonates, seizures occur in 1.8 – 3.5 per 1000 live births
- Premature > full term
- Low-birth weight > normal weight infants
- Most frequent overt manifestation of neurologic disorder in neonate
- May be symptomatic of treatable, dangerous condition (hypoglycemia, meningitis)

Selected Pediatric Epilepsy Syndromes

- Febrile convulsions
- Benign partial epilepsy syndromes of childhood:
  - Benign Rolandic
  - Benign Occipital

Febrile Seizures

- 6 mo.-5 yrs.
- simple vs. complex based on duration, focality, repetition
- EEG: normal
- Prognostic implications of complex febrile seizures and of abnormal neurologic status
- Treatment: Diastat/ Oral valium

Benign Rolandic Epilepsy

- Benign epilepsy with centrotemporal spikes (BECTS, BRE)
- 3-13 yrs, peak 7-8yrs
- oropharyngeal simple partial, focal motor or secondarily generalized seizures
- Nocturnal only:50%, both 15%
- Treatment: Gabapentin, Tegretol, Trileptal

Benign Focal Epilepsy with Occipital Paroxysms

- Onset 15m-17yrs
- Type 1: hemiclonic seizures, ictal emesis, headaches, younger onset
- Type 2: visual symptoms, hallucinations, headaches, older onset
- EEG: Occipital spikes
- Treatment: Tegretol, Trileptal

Selected Pediatric Epilepsy Syndromes: Generalized

- Childhood Absence
- Juvenile Absence
- Juvenile Myoclonic Epilepsy

Childhood Absence Epilepsy

- Triad: absence seizures, normal development, 3HZ spike and slow wave on EEG
- Onset 4-8 yrs, peak 6-7 yrs
- 40-60% have GTCS
- 18% photosensitivity
- 10-15% of all childhood epilepsies

Juvenile Absence Epilepsy

- Triad: absence seizures, normal development, 3HZ spike and slow wave
- Onset 10-15 yrs
- 80-85% have GTCS
- 7-8% photosensitivity

Absence Epilepsy

- Diagnosis: Clinical and EEG
- Hyperventilation high yield, imaging low yield
- Treatment: Zarontin, Depakote first line, Lamictal second line

Juvenile Myoclonic Epilepsy

- Onset: adolescence, early adulthood
- Morning myoclonus, GTC, Absence
- Seizures aggravated by sleep deprivation, alcohol, fatigue
- Photosensitivity common
- EEG: 4-6HZ generalized spike and waves

Juvenile Myoclonic Epilepsy

- Genetic disorder
- Lifelong seizures, greater than 95% risk of seizures if AEDS stopped despite long periods of seizure freedom
- Treatment: Depakote, Keppra, Lamictal, Topamax

Epileptic Encephalopathies

- West Syndrome: Infantile Spasms
- Lennox-Gastaut Syndrome

Infantile Spasms

- Onset 4-6 months
- Can be seen if previously healthy children or children with known neurologic disease such as Tuberous Sclerosis or Hypoxic-Ischemic Encephalopathy
- Admission for evaluation required at diagnosis

Infantile Spasms

- **Clinical**
  - flexor or extensor spasms
  - Brief flexion or "crunching" or extensions usually occurring clusters of more than 20 spasms per cluster
- **EEG**
  - Hypsarrythmia: interictal EEG pattern with high amplitude, disorganized activity

Infantile Spasms: Evaluation

- **EEG**
- **LP**
- **MRI**
- **Metabolic/Genetic testing**

Infantile Spasms: Treatment

- **If no underlying cause is determined: ACTH or Vigabatrin**
- **If diagnosis of Tuberous Sclerosis is made: Vigabatrin**
- **If diagnosis of other neurologic disease (HIE, metabolic, genetic): Vigabatrin, Topamax, Depakote**
- **Ketogenic diet**

Infantile Spasms: Outcome

- **Prognosis in general is poor, most patients have uncontrolled seizures and mental retardation long term.**
- **Some do well with normal development with seizure resolution**
- **If TSC is the diagnosis, IS usually resolve but other seizure types may occur**

Lennox-Gastaut Syndrome

- **Triad of medically intractable epilepsy usually with drop seizures and tonic seizures**
- **Mental retardation**
- **Abnormal EEG pattern with bifrontal slow spike and wave**

Lennox-Gastaut Syndrome

- **Many underlying causes or diseases result in LGS**
- **Treatment: Depakote, Banzel, Lamictal, VNS, ketogenic diet, any broad spectrum medications**
- **In general poor outcome with significant delays and frequent seizures**

Treatment of Epilepsy

- Anticonvulsant Medications
- Ketogenic Diet
- Vagus Nerve Stimulator
- Epilepsy Surgery

Anticonvulsant Drugs Marketed in the U.S.

1912	**phenobarbital (Luminal)**	**Winthrop**
1935	mephobarbital (Mebaral)	Winthrop
1938	**phenytoin (Dilantin)**	**Parke-Davis**
1947	Mephenytoin (Mesantoin)	Sandoz
1954	primidone (Mysoline)	Ayerst
1957	methsuximide (Celontin)	Parke-Davis
1957	ethotoin (Peganone)	Abbott
1960	**ethosuximide (Zarontin)**	**Parke-Davis**
1968	diazepam (Valium)	Roche
1974	**carbamazepine (Tegretol)**	**Ciba-Geigy**
1975	clonazepam (Klonopin)	Roche
1978	**valproate acid (Depakene)**	**Abbott**
1981	chlorazepate (Tranxene)	Abbott
1993	felbamate (Felbatol)	Carter-Wallace
1993	gabapentin (Neurontin)	Parke-Davis
1994	lamotrigine (Lamictal)	Glaxo-Smith-Kline
1996	topiramate (Topamax)	Ortho-McNeil
1997	tiagabine (Gabitril)	Abbott
2000	zonisamide (Zonegran)	Elan Pharma
2000	levetiracetam (Keppra)	UCB Pharma
2000	oxcarbazepine (Trileptal)	Novartis
2009	Rufinamide (Banzel)	Eisai
2009	Lacosimide (Vimpat)	UCB Pharma

Choosing Antiepileptic Drugs

- **Partial onset seizures**

***carbamazepine(CBZ)**	***oxcarbazepine(OXC)**
valproate(VPA)	**lamotrigine(LTG)**
zonisamide(ZNS)	**topiramate(TPM)**
tiagabine(TGB)	**levetiracetam(LEV)**
phenytoin(PHT)	**gabapentin(GBP)**

*** First line**

Choosing Antiepileptic Drugs

- **Generalized onset seizures**

Absence:	**valproate*, ethosuximide(ESM)**
Myoclonic:	**valproate, levetiracetam, benzo's**
Tonic-clonic:	**valproate, lamotrigine, topiramate,**
Alternatives:	**zonisamide, levetiracetam**
Avoid:	**carbamazepine, oxcarbazepine**

* the risk of valproate-induced hepatic failure must be carefully weighed in young children

Continuation of treatment

- **Start at low dose and slowly escalate.**
- **Look for side effects and seizure control.**
- **Goal is to have no seizures and no side effects.**

Monitoring blood work

- **LFTs**
- **Electrolytes**
- **CBC**
- **Drug levels**

Drug levels

- Toxicity.
- Compliance issues.
- Adjusting the medication dose.
- No good seizure control.

How long?

- If no seizures for 2 years.
- EEG / V.EEG at that time is normal.
- Will consider to wean the medication.
- If the EEG comes abnormal but no seizures, will continue the medicine.
- Keep repeating the EEGs every 6 to 12 months.

Seizure precautions

- No unsupervised swimming.
- No unsupervised baths.
- No sleep deprivation.
- No heights and speed.
- No alcohol.
- No flash lights if there is photo paroxysmal response during EEG
- No driving for 6 months from last seizure.

Medically refractory epilepsy

- In spite of 2 AEDs at their full doses, if the child continues to have seizures, it is called medically refractory epilepsy.
- After failing two AEDs appropriate for seizure type, 10% chance another AED will be effective
- 20%-30% of patients become medically refractory
- Alternative treatments: Ketogenic Diet, Vagus Nerve Stimulation, Surgery

Ketogenic Diet

- Anti-seizure effect of ketosis
- Low carbohydrate, low protein, high fat
- Fasting no longer used to initiate ketosis
- Patients no longer kept in acidosis
- Main experience with children, especially with multiple seizure types
- Efficacy usually within 2 weeks-2months

Ketogenic Diet

Results from a prospective, multicenter study, show the diet appears to be equally effective for all seizure types:

- 54% of patients experience ≥50% seizure reduction at 3 months
- 10% have seizure freedom at 1 year

- 47% continuation rate at 1 year

Vining EP, et al. *Arch Neurol.* 1998;55:1433-1437.

Ketogenic Diet

- **Side effects may include[1]**
  - Hyperlipidemia
  - Vitamin Deficiencies
  - Constipation/diarrhea
  - Kidney stones
  - Acidosis during illness
- **Other information[2]**
  - Initiation of diet usually requires hospitalization
  - Food must be carefully weighed and measured

[1]Wheless JW. *J Child Neurol.* 2001;16:633-635.
[2]Vining EP, et al. *Arch Neurol.* 1998;55:1433-1437.

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Modified Atkins Diet

- **Easier to maintain than ketogenic diet**
- **Food does not need to be weighed/measured**
- **No admission required for initiation**
- **Patients have a goal carbohydrate amount per day, fats are encouraged**

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Ketogenic Diet Summary

- **Effective in treating all seizure types**
- **Difficult to maintain especially in older children**
- **Modified Atkins offers a better tolerated, effective option**
- **Overall 1/3 are seizure free, 1/3 have significant improvements and 1/3 do not respond**
- **Best candidates: young children, dedicated teenagers, tube fed patients**

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Ketogenic diet at CHP

- **We have 50+ patients on ketogenic diet.**
- **We have our ketogenic diet clinic every second Tuesday of the month.**
- **We are a team of 2 epileptologists, one nurse practitioner and a dietician.**
- **On average we get 2 -3 new patients admitted for the initiation of the diet.**

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Vagus Nerve Stimulator (VNS)

- **Implantable pacemaker-like device with electrodes placed around the vagus nerve**
- **Intermittent stimulation is applied to the vagus nerve 24 hours a day, turning on and off at preset parameters**
- **Stimulation of the vagus nerve changes the way the brain works and decreases seizures**

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Pulse Generators

Pulse Model 102

Demipulse Model 103

Pacemaker-like pulse generator

Turns on and off at pre-programmed intervals

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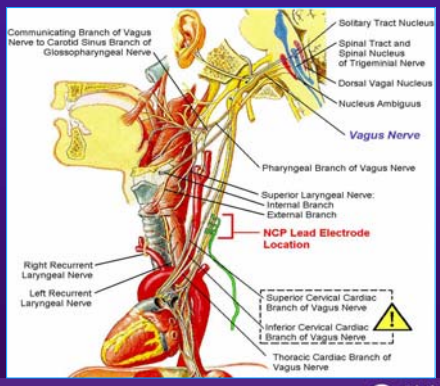


VNS: Summary

- **No serious adverse effects reported, low incidence of mild adverse effects**
- **Improvements seen in various aspects of quality of life including increase in level of alertness and a decrease in post-ictal periods, these improvements were not always related to seizure control.**

VNS: Summary

- **Overall median seizure reduction:**
  - Children <18 yrs: 3m-49%, 12m-58%
  - Cognitively challenged: 3m-47%, 12m-57%
- **VNS appears to be an effective adjunctive therapy for patients with refractory epilepsy**

Epilepsy Surgery

- **Best option for qualified candidates to achieve a "cure"**
- **Patients need to have:**
  - focal onset seizures
  - seizures focus in a region of cortex safe to remove
  - medically refractory (failed 2-3 AEDs)

Epilepsy Surgery

- **Extensive pre-surgical evaluation (Phase 1)**
  - Video/EEG monitoring to record 4-6 seizures and localize seizure onset to one region
  - MRI/MRS/MEG
  - SPECT scans: evaluate blood flow
  - PET scans: evaluate glucose metabolism
  - Neuropsychologic testing: baseline evaluation and localization

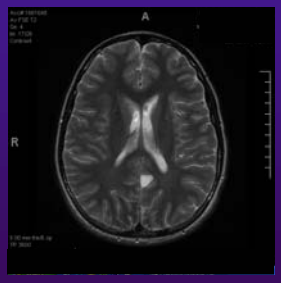
Case 1

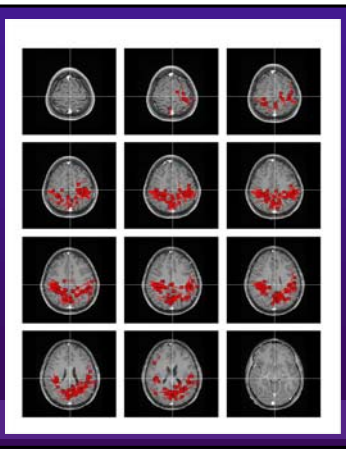
- **14 yr old male with one year since seizure onset**
- **Complex partial seizures numerous every day, brief but grades have dropped from honor roll to failing**
- **Failed 5 AED's**
- **MRI with cystic lesion felt to be extra axial demoid or epidermoid right parasagittal**

Case 1

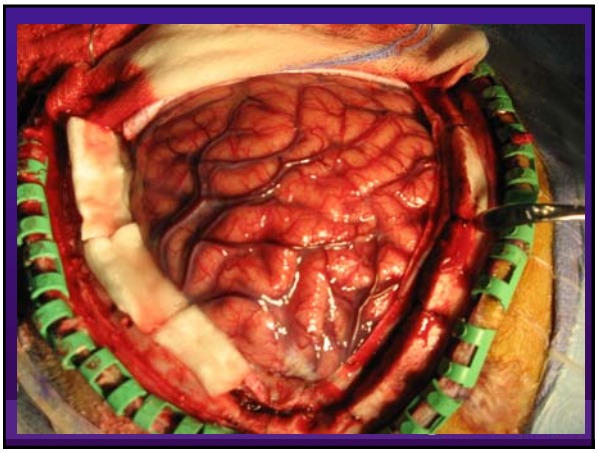
- EEG: interictal left frontal spikes, ictal generalized sharp wave followed by left frontal spike and slow wave
- SPECT: ictal increased uptake left temporal
- MEG: bilateral posterior

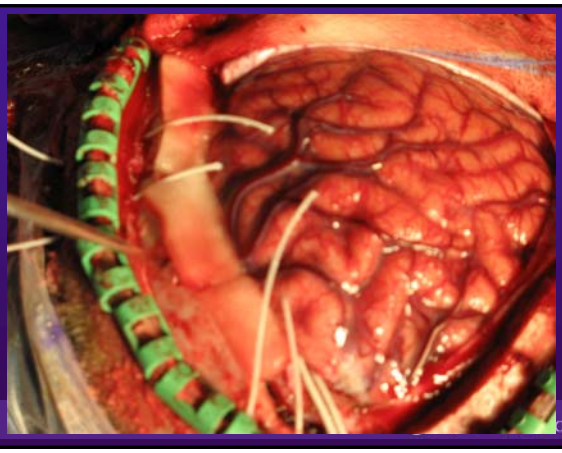
MRI

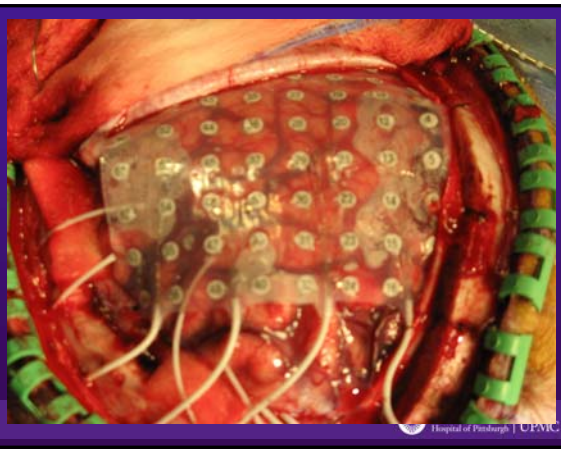




- Based on MEG results and MRI abnormality patient had inter-hemispheric grid and left posterior grids placed

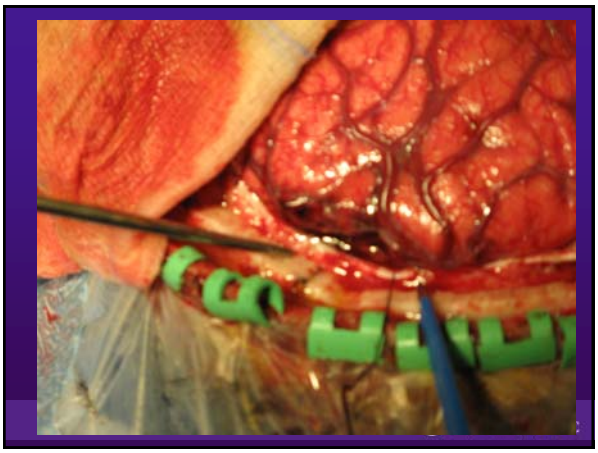




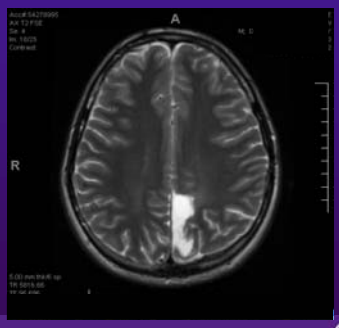


Case 1

- Seizure onset in area of lesion
- Seizure focus and lesion removed pathology consistent with tumor not dermoid cyst
- Patient seizure free post-op and grades improved



MRI



Case 2

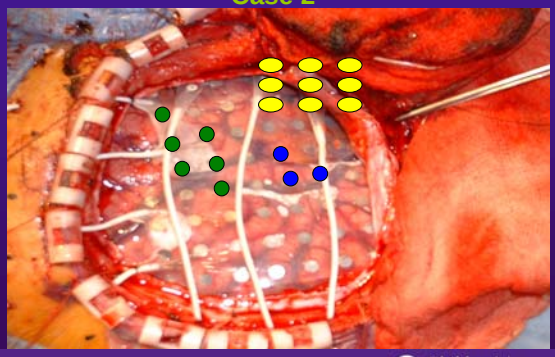
- S/P traumatic brain injury at age 15
- Seizure onset after accident with feelings of déjà vu and inattentiveness
- MRI: gliosis and encephalomalacia left temporal lobe (anterior, middle and superior gyri), left medial frontal lobe extending 3 cm, right mesial frontal

Case 2

- Video/EEG monitoring showed interictal left anterior temporal spikes and slowing, generalized spike and slow wave discharges during sleep
- Ictal: 3 electro-clinical seizures widespread onset left fronto-temporal, 2 electrographic seizures onset left anterior temporal

Case 2

Case 2



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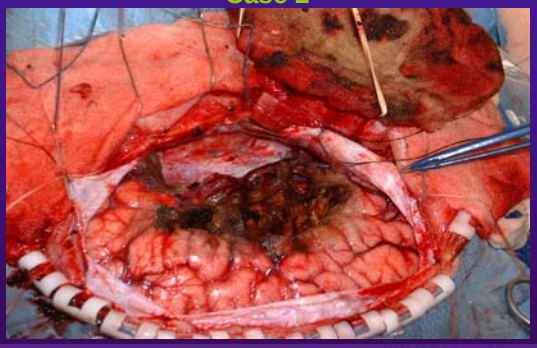

Case 2

CHP Results

- Results reported out of 46 patients remaining with follow-up data available.
- Follow-up ranges from 6 months-2.5yrs
- 30 patients underwent grid/strip/depth electrode placement

Epilepsy Surgery Results

- Engel Grading Scale
  - Class I: Free of disabling seizures
  - Class II: Rare disabling seizures
  - Class III: Worthwhile improvement
  - Class IV: No worthwhile improvement

CHP Results

- Overall results (46 patient)
  - Class I: 82.6%
  - Class II: 6.5%
  - Class III: 4.3%
  - Class IV: 2.8%

CHP Results

- Overall 41/46 patients (89%) either seizure free or with only rare non-debilitating seizures.
- Complications low with only two infections and one patient with improving word finding difficulties

SUMMARY

- Epilepsy is common in pediatric patients
- Accurate diagnosis is crucial to determining the best treatment options and predicting outcomes (EEG/MRI/Video)
- Medications should be chosen based on epilepsy syndrome, seizure type, side effect profile and patient age

SUMMARY

- Most children with epilepsy have a benign syndrome and do well long term
- For those patients who become medically refractory, new treatment options are now available to improve both seizure control and quality of life.