Epilepsy and Seizures

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Why Do You Need to Know About Seizures and Epilepsy?

- Common pediatric condition
- There are only 800 full time pediatric neurologists in the country
- 50% of these physicians are over 50 years old and are expected to retire in the next 10 years
- There are 4 million consults per year
- Currently, one pediatric neurologist per 100,000
- We are not training enough to replace the loss—32 per year, but half are international medical grads
- Service agreements with primary care providers

Epidemiology of Epilepsy

- Epilepsy is a very common disorder
- Each year, 150,000 children and adolescents in the USA will have a single unprovoked seizure
- 30-45% of these children will go on to develop epilepsy
- 0.5-1.0% prevalence of epilepsy in the general population

Epidemiology of Epilepsy

- Incidence of epilepsy follows a bimodal distribution—highest incidence rates being in children less than 5 years of age and adults over 65 years of age
- Febrile seizures affect 2-5% of children in the USA; 10% in Japan

Single Unprovoked Seizure

- Diagnostic evaluation is an emergency only if there is ongoing status epilepticus
- An outpatient EEG (awake and sleep) and a non-urgent brain MRI scan should be obtained
- Risk of recurrence is less than 50%

Predictors of Seizure Recurrence

- Remote CNS injury or lesions, particularly cortical dysplasia
- Abnormal epileptiform EEG
- Nocturnal seizure
- Prior history of febrile seizures
- Occurrence of Todd’s paralysis

To Treat or Not to Treat—That is the Question!

- The use of AEDs after a single unprovoked seizure is not typically necessary
- Risk of morbidity and mortality is extremely low, even if child has one or two additional seizures
- If a seizure doesn't stop after 5 minutes, it is unlikely to stop spontaneously
- Rectal Diastat (diazepam) is an important safety net

Safety Precautions

- Children require close supervision during bathing
- Showers, not baths, for adolescents and older children
- Risk of drowning is 4 times greater in patients with epilepsy—in bathtubs, not typically swimming pools
- Restriction on swimming and climbing heights for at least 3-6 months
- No babysitting

Definitions

- Seizure: paroxysmal event, resulting from synchronous discharges of a group of neurons
- Epilepsy: unprovoked, recurrent seizures
- Epilepsy Syndrome: cluster of signs and symptoms that have well defined features—this has implications for treatment and prognosis

Classification Issues

- Seizure type classification: determined by consensus from video taped seizures, as well as EEG data
- Epilepsy Syndrome—Classified on the basis of seizure type, age of onset, family history, EEG, neurological exam, developmental status, and neuroimaging

Conditions and Symptoms That May Mimic Epilepsy

- Breath-holding spells
- Syncope
- Tics
- Sleep disturbances
- Gastroesophageal reflux
- Complicated migraine

Conditions and Symptoms That May Mimic Epilepsy

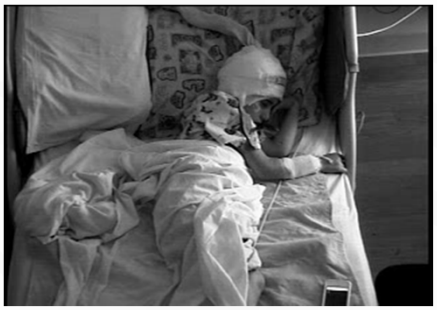
- Shuddering attacks, jitteriness
- Paroxysmal movement disorders
- Startle
- Self-stimulatory behaviors, including masturbation
- Toxic, metabolic states
- Psychiatric disorders

Classification of Seizures

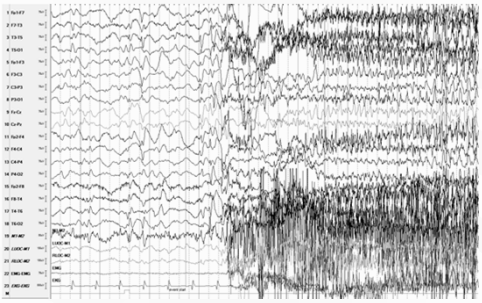
Tonic-Clonic Seizures

- Loss of consciousness
- Tonic phase
- Clonic phase
- May be primarily generalized or secondarily generalized
- Previously called “grand mal”

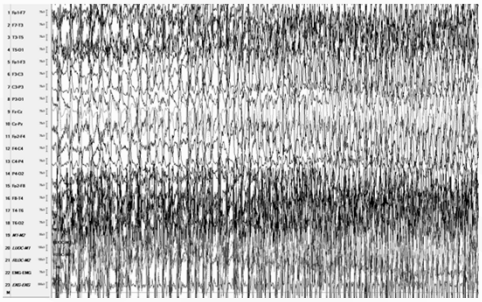
Generalized tonic clonic sz



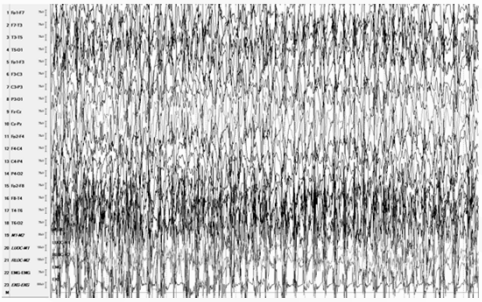
Generalized tonic clonic sz



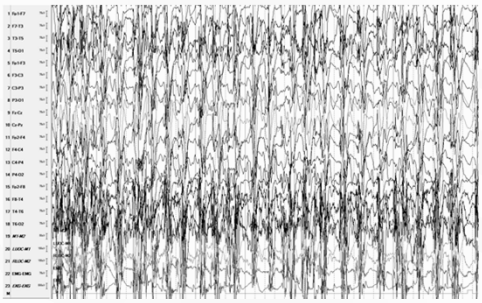
Generalized tonic clonic sz2



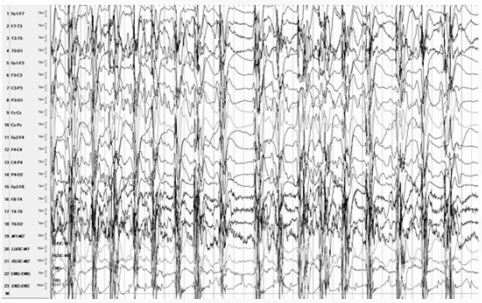
Generalized tonic clonic sz3



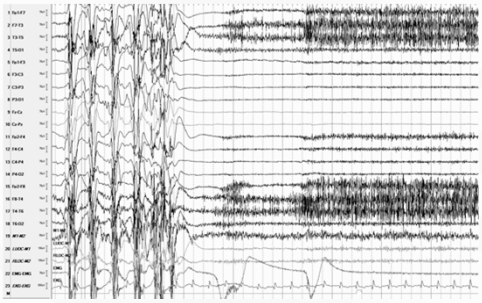
Generalized tonic clonic sz4



Generalized tonic clonic sz5

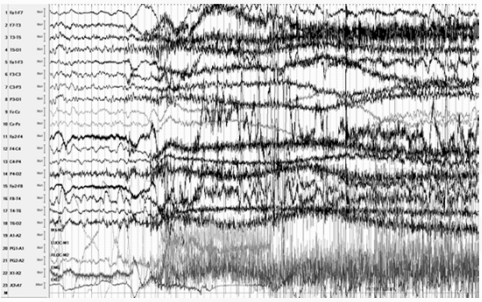


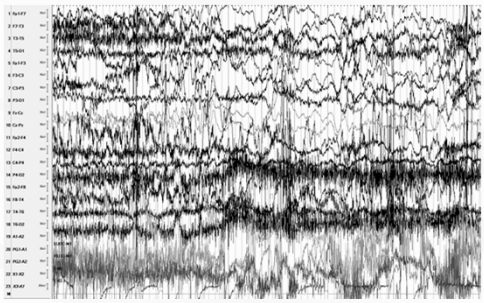
Generalized tonic clonic sz6

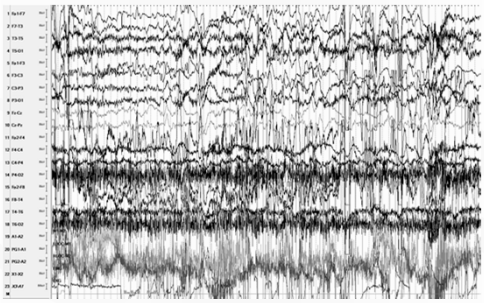


Tonic Seizures

- Sudden, sustained stiffening of the limbs
- May be focal, symmetric or asymmetric
- May fall from the sudden force of the seizure
- Often accompanied by other generalized seizure types
- Protect patient from injury

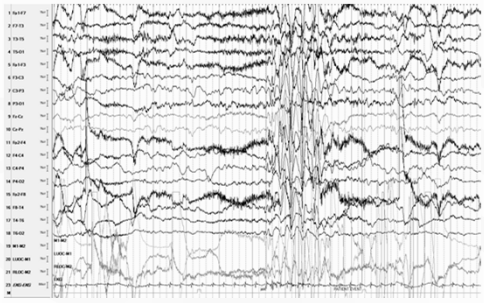




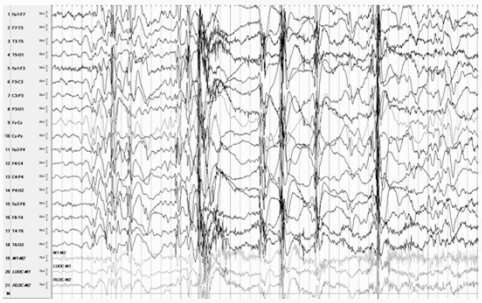


Myoclonic Seizures

- Sudden single jerk of one part of the body
- May fall from the suddenness of the myoclonic seizure
- Accompanied by loss of consciousness, although usually undetectable
- Often occur in clusters

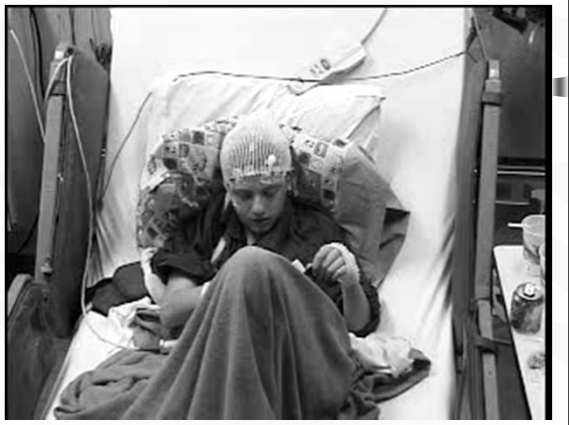


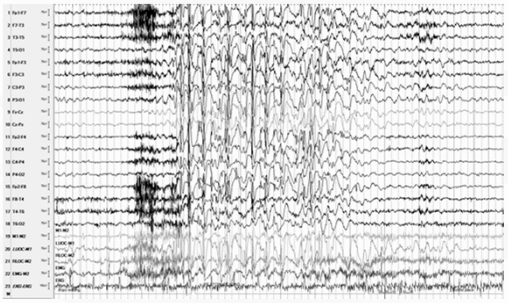
Myoclonic astatic seizure



Typical Absence Seizures

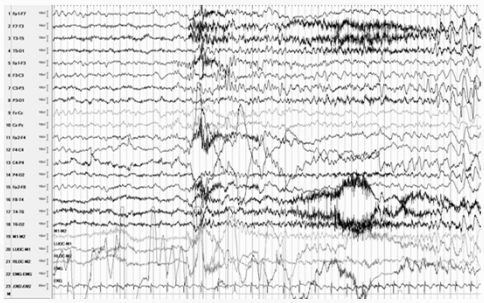
- Previously called “petit mal”
- Brief loss of consciousness
- May have facial (e.g. eye, mouth) movements
- Triggered by hyperventilation
- May also have tonic-clonic seizures
- Student with absence seizures may miss information presented throughout the school day

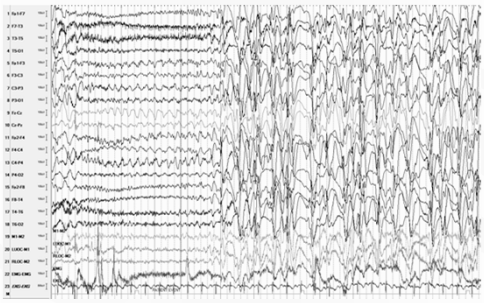


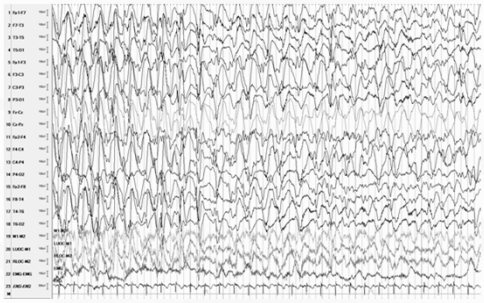


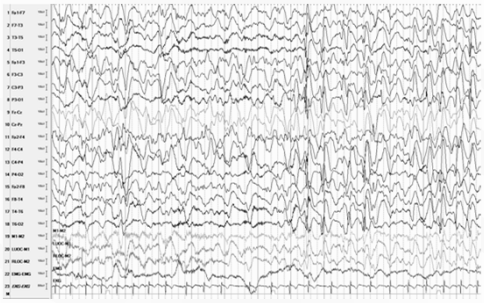
Atonic/Astatic Seizures

- Sudden loss of postural tone
- Often results in a head drop, although may suddenly drop to the ground
- Often accompanied by other generalized seizure types
- Frequently requires the wearing of a helmet to prevent injury









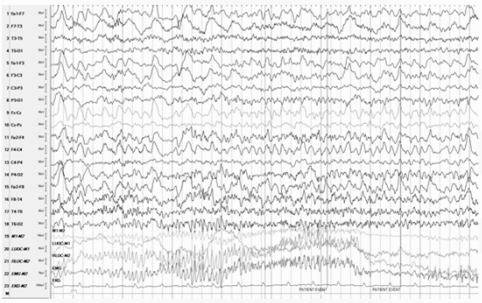
Simple Partial Seizures

- ❖Consciousness is preserved
- ❖May be sensory or motor
- ❖Previously called an “aura”
- ❖Simple partial seizures are localized to one focal area of the brain
- ❖May spread to larger brain area, resulting in complex partial or secondarily generalized seizures

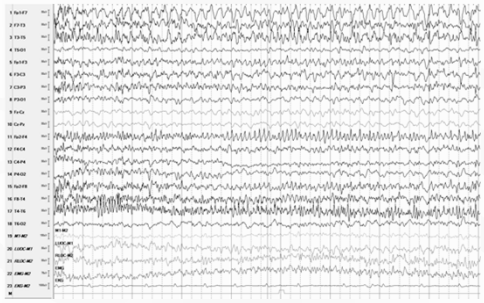
Complex partial seizures

- Consciousness impaired
- Focal features in seizure semiology
- May progress to a generalized tonic clonic seizures
- Associated with postictal phase

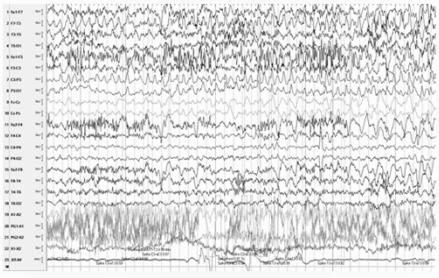
Complex Partial Seizure



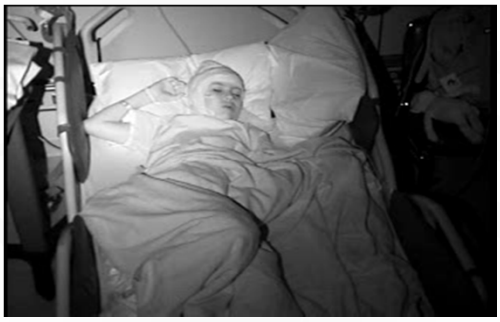
Complex Partial Seizure



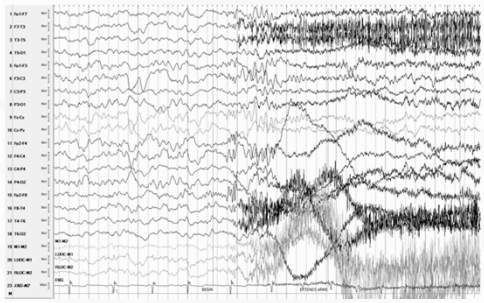
Complex partial seizure



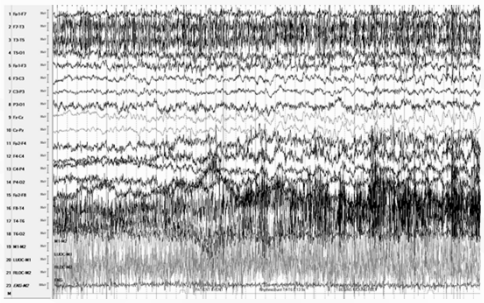
Complex partial sz, frontal



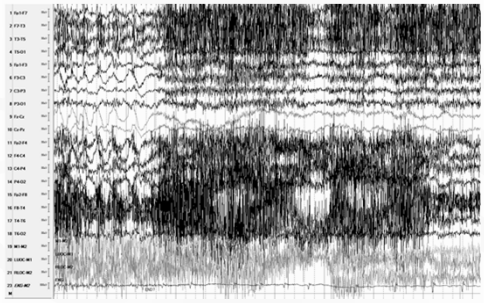
Complex partial sz, frontal



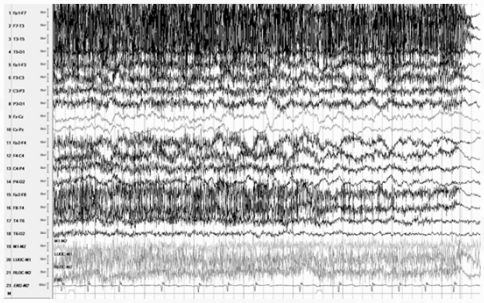
Complex partial sz, frontal2



Complex partial sz, frontal3



Complex partial sz, frontal4



Epilepsy Syndromes

- Single biggest predictor of prognosis
- Single biggest determinant of AED treatment options
- Single biggest predictor of AED success and chance of remission

Epilepsy in Children Differs from Epilepsy in Adults

- Epilepsy syndromes are different
- Differential diagnosis of paroxysmal spells and seizures is broader—vasovagal syncope, breath-holding spells, sleep disturbances, movement d/o
- Etiologies are different
- Decision to treat may differ
- Children may receive treatments not used in adults

Etiology of Epilepsy

- Idiopathic=Genetic
- Symptomatic=Underlying lesion or other CNS pathology
  - Malformation of Cortical Development/Cortical Dysplasia
  - Cerebrovascular accident
  - Trauma/Asphyxia
  - Meningitis/encephalitis
  - Chromosomal abnormality
  - Inborn Error of Metabolism

The Good, the Bad, and the Ugly

- Seizure control follows a 60:40 rule
- If AED is not effective in seizure control, the chance of a second AED working is 10%
- If the AED is not tolerated due to side effects, the chance of a second AED working is 40%
- After the failure of 2-3 AEDs, there should be an evaluation at a tertiary care center for correct diagnosis and consideration for epilepsy surgery

The Good, the Bad and the Ugly

- An infant with intractable epilepsy and a lesion on MRI scan of the brain should be evaluated for epilepsy surgery as the first AED is being started.
- The developing brain is much more vulnerable to the catastrophic effects of epilepsy

The Genetics of Epilepsy

- Many childhood epilepsies are genetic—complex genetic interactions
- The earlier the age of onset, the greater the chance of remission
- The genetic epilepsies are predominantly channelopathies—T type Ca channels; Na or K channels

Epilepsy Syndromes—Generalized, Idiopathic

- Benign neonatal convulsions
- Febrile seizures
- Febrile seizure “plus” syndrome
- Childhood absence epilepsy
- Juvenile absence epilepsy
- Juvenile myoclonic epilepsy
- Severe myoclonic epilepsy of infancy
- Myoclonic-astatic epilepsy of Doose

Patient J.K.

- 2 year old female
- Previous history of 2 simple febrile seizures
- Presents now with afebrile generalized tonic-clonic seizure
- Family history of febrile seizures in father; cousin with epilepsy
- EEG shows sleep activated rare generalized tonic-clonic seizures
- Mild speech delays; otherwise, normal exam
- What is the epilepsy syndrome?

Febrile Seizure "Plus" Syndrome

- Febrile seizures=Generalized tonic-clonic seizure associated with fever, not a CNS process, occurring in children <5 yrs of age
- Nonfebrile seizures, usually GTCS, but can be myoclonic, absence, complex partial
- Positive family history of epilepsy/febrile sz
- SCNa channelopathy

Clinical Pearls

- This child most likely has febrile seizure "plus" syndrome
- Carbamazepine and oxcarbazepine can exacerbate generalized epilepsy syndromes
- AED options include valproate, topiramate, zonisamide, levetiracetam, and lamotrigine
- Topiramate may produce cognitive slowing and word finding difficulties
- Good chance of remission

Differentiation between the epilepsy syndromes

- The idiopathic generalized epilepsy syndromes are probably channelopathies, some of which involve the T-type calcium channels or GABA channels/networks
  - Childhood absence epilepsy
  - Juvenile absence epilepsy
  - Juvenile myoclonic epilepsy

Case One

- 8 year old young girl with poorly controlled epilepsy
- Probable onset at 4-5 years of age
- Four recent hospitalizations for seizures, one for nonconvulsive status epilepticus

Case One

- History of prematurity at 34 weeks
- Mild cognitive delays; IEP in place
- Seizure semiology: Staring spells with eyelid fluttering, TNTC.
- No history of generalized tonic-clonic seizures
- EEG demonstrates generalized spike and slow wave discharges

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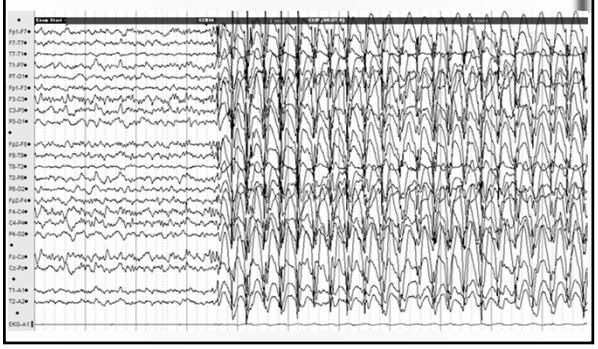

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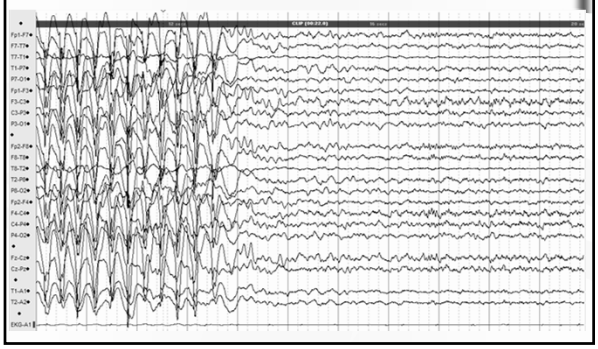

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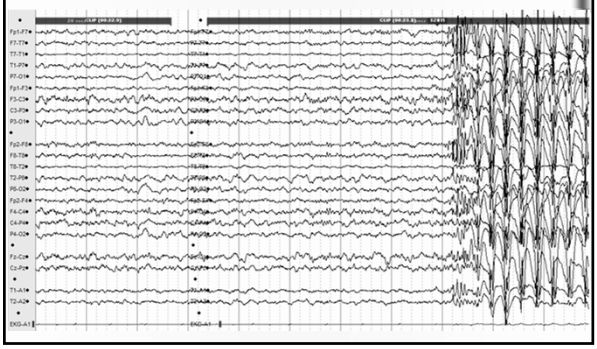

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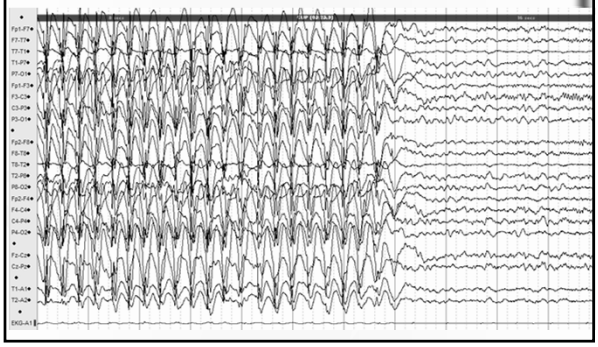


Absence Epilepsy

- Probable Ca channelopathy
- Complex genetic interaction
- Childhood absence epilepsy (< 9 yrs of age) associated with GTCS in <17%
- Juvenile absence epilepsy (>9 yrs of age) associated with GTCS in 85%

Treatment Options

- Ethosuximide
- Valproate
- Lamotrigine
- NIH study recently completed to determine efficacy of the AEDs listed above
- Levetiracetam and topiramate-- unproven therapy

Ethosuximide

- FDA approved for treatment of absence epilepsy
- Can cause aplastic anemia and liver dysfunction
- Main side effects include gastric upset, nausea hiccups, and sleep disturbance
- Dosing: 20-40 mg/kg/day

Valproate (Depakote)

- FDA approved for the treatment of both partial and generalized seizures
- Risk of hepatotoxicity in children less than two years of age, with an underlying neurological deficit, and on other AEDs is estimated at 1:500
- Carnitine supplementation is recommended

Valproate (Depakote)

As monotherapy, risk of hepatotoxicity is very low.

As polytherapy, risk will vary from 1:500 in children less than 2 yrs old to 1:8,300 in children between 3-10 yrs of age

POLG1 mutation associated with hepatotoxicity

Valproate

- Weight gain is seen in close to 60% of patients, sometimes as much as 10-15% of body weight
- Tremor
- Alopecia
- Thrombocytopenia
- Risk of pancreatitis—new black box warning

Lamotrigine

- FDA approved as monotherapy for partial seizures and generalized tonic clonic sz
- Mechanism of action: Prolongs inactivation of voltage sensitive Na channels; inhibits glutamate release
- 55% protein bound
- Metabolized by the UDP system in the liver

Lamotrigine

- Numerous drug interactions
- EIAEDs result in half-life of 15 hours
- Valproate inhibits metabolism, resulting in t ½ of 72 hours
- Risk of allergic rash; reports of Stevens Johnson syndrome

Lamotrigine

- Risk of severe, life-threatening allergic rashes, including STJ and TEN
- Risk of rash is greater in pediatric population and with rapid titration
- New German registry data indicates if the dosage is titrated up slowly, esp with valproate, risk of allergic rash is no greater than with PB, PHT, and CBZ (.8%)

Lamotrigine: Serious Rash Summary

- Incidence of serious rash leading to hospitalization and discontinuation
  - Pediatric 0.8%
  - Adult 0.3%
- Risk of rash may be increased by:
  - Coadministration with valproate
  - Exceeding the recommended initial dose or dose escalation of lamotrigine
- Almost all rashes occurred within 2-8 weeks of treatment initiation

Product Information for Lamotrigine Tablets.

Lamotrigine Dosage

- Valproate inhibits the metabolism of lamotrigine; the half-life is extended to 72 hours
- The initial dosage of lamotrigine when combined with valproate should be .15 mg/kg for the first two weeks; then increased by .3 mg/kg increments per week
- Usual maintenance dose: 1-5 mg/kg/day

Lamotrigine Dosage

- The enzyme-inducing AEDs (EIAEDs) increase the metabolism of lamotrigine
- The initial dosage of lamotrigine when combined with EIAEDs is .6 mg/kg for the first two weeks; then it is increased by 1.2 mg/kg increments each week
- Usual maintenance dosage: 5-15 mg/kg/day

Patient B.S.

- Onset of seizures at 10 years of age
- Generalized tonic-clonic seizures
- Jerkiness and clumsiness in the AM
- Occasional staring episodes

Patient B.S.

- Normal growth and development; excellent student; athlete
- Positive family history for febrile seizures and generalized tonic-clonic seizures
- Normal physical exam
- EEG demonstrates generalized 4-5 Hz polyspike, spike, and slow wave discharges
- MRI scan normal

Juvenile Myoclonic Epilepsy

- Generalized epilepsy syndrome
- Onset at the time of puberty
- Probable channelopathy—Probably Ca
- Genetic predisposition
- Myoclonic seizures in the morning
- Generalized tonic-clonic seizures >95%
- Unlikely to go into remission

AED Treatment Options

- Valproate
- Primidone
- Lamotrigine
- Topiramate*
- Levetiracetam
- Zonisamide*
- * Not FDA approved for JME

Valproate

- In adolescent girls, there may be an increased risk of polycystic ovarian syndrome with concomitant valproate use, based on data from Isojarvi and Morrell
- Preliminary studies from Columbia indicate higher rate of PCOS and anovulatory cycles in women with epilepsy who use valproate

Valproate-Endocrine disorders

- Centripetal obesity based on hyperinsulinemia (60%)
- Polycystic ovarian-like syndrome
- Increased androgen hormones
- Higher incidence of anovulatory cycles
- Possible decreased bone mineralization

Polycystic Ovary Syndrome

- Enlargement of ovaries with thickened stroma and >8 subcapsular follicular cysts 2-8 mm in diameter
- Hirsutism and acne
- Obesity
- Elevated androgens
- Increased LH levels and changes in FSH/LH ratio
- Irregular anovulatory cycles and infertility
- Insulin resistance with compensatory hyperinsulinemia
- Increased risk of diabetes, cardiovascular disease, and endometrial cancer

FSH = follicle-stimulating hormone.

Hypothalamic Pituitary Axis

- Women with epilepsy have increased risk of polycystic ovary syndrome:
  - In general population, PCOS risk is estimated at 7%-15%
  - In women with epilepsy, PCOS risk is 25%
  - In women with primary generalized epilepsy with exposure to valproate within last 3 years, risk of polycystic ovaries is approximately 56%

Hypothalamic Pituitary Axis

- Women with epilepsy have an increased risk of anovulatory cycles
  - Women with localization-related epilepsy: 14%
  - Women with primary generalized epilepsy: 27%
  - Women with epilepsy and who have had valproate exposure within the last 3 years: 43%
  - Women with primary generalized epilepsy with valproate exposure within the last 3 years; not correlated with obesity: 56%

Mechanisms of Action

- Disruption of hypothalamic-pituitary-gonadal axis, possibly correlated with density and distribution of interictal and ictal epileptiform discharges
- Abnormalities in metabolism of gonadal steroids due to AEDs, such as valproate
- Direct effect of valproate on the ovary
- Effect of valproate on androgen production
- Weight gain not predictive of PCOS/anovulatory cycles

Valproate

- Teratogenic effects, especially neural tube defects (meningomyelocele)
- There are other concerns:
  - Fetal valproate syndrome
  - Increased risk of neurocognitive effects on the fetus (NEAD study)

Levetiracetam (Keppra)

- Recently FDA approved as adjunctive therapy for myoclonic seizures, as well as partial seizures
- Mechanism of Action: Binds to stereoselective site on ionic synaptic membrane, inhibiting bursting
- Low side effect profile—irritability and behavioral disinhibition can occur

Levetiracetam

- No drug interactions
- Does not induce hepatic enzymes
- No significant protein binding
- Excreted by the kidneys
- Ease of administration
- Dosage range in children is 30-60 mg/kg/day

Topiramate

- FDA approved for children 2 years and older for adjunctive therapy in the treatment of partial seizures
- Mechanisms of action:
  - Inhibition of voltage sensitive Na channels
  - Agonist at the GABA receptor
  - Antagonist at the non-NMDA glutamate receptor

Topiramate

- Major side effects include somnolence, cognitive impairment, and word finding difficulties
- It can cause renal stones, due to its weak carbonic anhydrase inhibition
- Metabolic acidosis
- Oligohydrosis
- Partially metabolized in the liver

Topiramate

- Half-life is 24 hrs if given as monotherapy
- Half-life is 15 hrs if given with EIAEDs
- Infants require higher dosages, averaging 20-40 mg/kg/day
- Usual childhood and adolescent dosage is 5-7 mg/kg/day

Zonisamide (Zonegran)

- Newly approved by the FDA for control of partial seizures
- Sulfonamide containing drug
- Japanese experience would indicate that zonisamide is effective in the treatment of progressive myoclonic epilepsies

Zonisamide

- Mechanism of Action: Blocks voltage sensitive Na channels and reduces T-Type Ca channel currents
- Side effects include somnolence, anorexia, nausea, headaches, and dizziness
- Oligohydrosis has also been reported in children

Zonisamide

- Dosing range varies from 200-400 mg /day
- In children, the initial dosage should be 2 mg/kg/day, maximum 10 mg/kg/day
- Available in 100 mg capsule, as well as 25 mg and 50 mg capsules.
- Capsule contents can be mixed with liquid

What AED was chosen?

- Valproate is relatively contraindicated in young adolescent girls and adult women
- Lamotrigine is promising, but in rare individuals, has resulted in aggravation of myoclonus
- Levetiracetam and topiramate appear promising
- Topiramate may produce significant cognitive issues
- Levetiracetam has no drug interactions and is not a P450 enzyme inducer

Patient B. S.

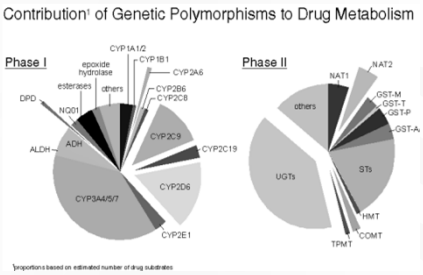
- Started on lamotrigine
- She is sexually active; mother unaware
- She contacts our office and tells my nurse that she has started on oral contraceptives
- What advice would you give this patient, especially knowing the possible drug interactions?
- Another scenario: BS has seizures only at the time of menses. What are her therapeutic options?

BIOTRANSFORMATION

3 CYP families (1,2,3)

7 primary isozymes

CYP1A2,
CYP2A6
CYP2C8/9
CYP2C19
CYP2D6
CYP2E1
CYP3A4



Evans WE, Relling MV. *Science* 1999.

AEDs and P450 Enzymes

- AED inducers
  - Phenobarbital
  - Phenytoin
  - Carbamazepine
  - Oxcarbazepine
  - Topiramate
- Neutral AEDs or inhibitors
  - Valproate
  - Felbamate
  - Gabapentin
  - Lamotrigine
  - Vigabatrin
  - Levetiracetam
  - Tiagabine
  - Zonisamide

AED Effects on Sex Hormones

- P450-inducing AEDs increase sex hormone binding globulin
- P450-inducing AEDs increase metabolism of sex hormones
- Elevation in androgens with P450-inhibiting AEDs

Contraception

- P450-inducing AEDs increase metabolism and binding of hormones
- 6% failure rate of OCP with enzyme-inducing AEDs
- P450-inducing AEDs increase failure rate of oral, subdermal, and intramuscularly administered contraceptives
- Use of barrier techniques advocated in conjunction with P450-inducing AEDs
- If using P450-inducing AEDs and OCPs, 50 μg estrogen is required in the OCP

OCP = oral contraceptive pill.

Lamotrigine and Hormonal Contraception

- Lamotrigine does not affect the metabolism of ethinyl estradiol, but does decrease the levonorgestrel plasma concentration
- OCPs will mildly induce the metabolism of lamotrigine, causing a modest decline in serum level
- During the placebo week of OCPs, some women can experience a rise in lamotrigine levels and signs and symptoms of toxicity

Effect of Lamotrigine on a Combination Oral Contraceptive

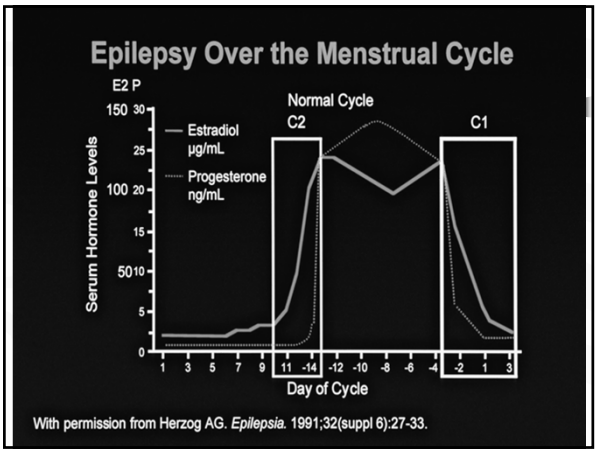
- Minimal effect on ethinylestradiol concentrations
- Modest effect on levonorgestrel plasma concentrations
- No hormonal evidence of ovulation, but increases in FSH and LH concentrations
- Therefore, in some patients, efficacy of OCPs cannot be guaranteed

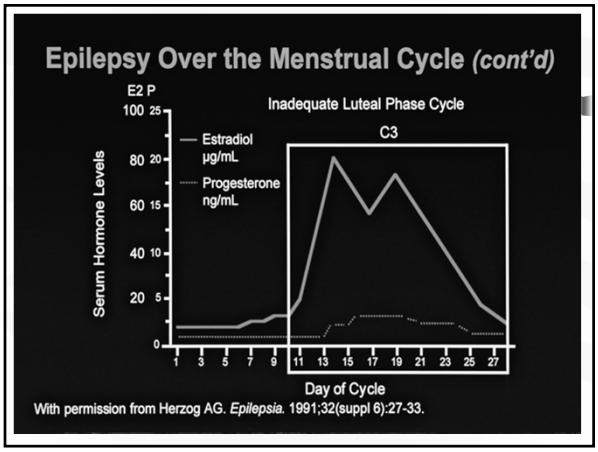
FSH=follicle stimulating hormone; LH=luteinizing hormone.

Catamenial Seizures

- Seizure onset at menarche common
- 10%-75% of women with epilepsy
- 25%-75% during ovulation or early menses
- Related to estrogen/progesterone ratio and possibly the decline of AED levels prior to menses
- Treatment considerations: OCPs, progesterone suppositories, neuroactive steroids, LHRH agonists

LHRH = luteininzing hormone-releasing hormone.





Safety/Independence

- Compliance is enhanced when a routine is established and pill box is used
- Showers, not baths
- Restrictions should apply initially
  - No babysitting
  - No climbing of heights
  - Restriction of bicycle riding to nonbusy streets
  - No swimming

Safety/Independence

- Driving a motor vehicle in Wisconsin is allowed if three months seizure free —depends on which state adolescent resides in.
- Obtaining a driver's license is a potent inducer of compliance
- Athletics and sports should be encouraged
- Swimming may be only exception—if seizures poorly controlled

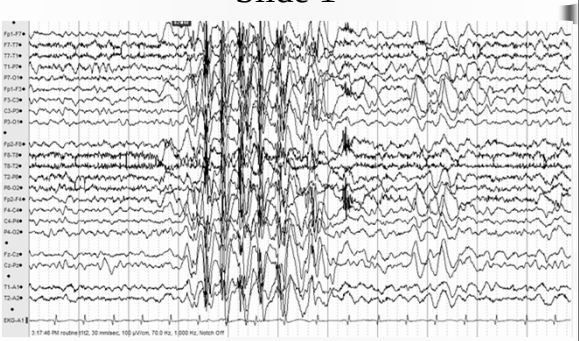
Case Three

- 5 year old young boy with onset of epilepsy at 3 years of age and cognitive decline
- Seizures characterized by generalized tonic clonic seizures and "absence seizures", with myoclonic features
- EEG demonstrates generalized spike and slow wave discharges, per report

Case Three

- "Absence Seizures" TNTC
- Standard MRI scan of the brain is normal
- Has failed lamotrigine and topiramate
- Allergic to valproate, ethosuximide, and zonisamide
- Currently on phenytoin and topiramate
- During examination, had >10 brief seizures characterized by eyes rolling up, quick breath expulsion, and eye fluttering

Slide 1



Myoclonic-Astatic Epilepsy of Doose--?idiopathic epilepsy

- Seizures present between 1-5 years of age
- Boys > Girls by 3:1 ratio
- Seizures characterized by generalized tonic-clonic, myoclonic, atonic, and absence sz
- EEGs demonstrate generalized irregular ps, spike and slow wave D/Cs at 2-3 Hz

Myoclonic-Astatic Epilepsy of Doose

- Normal growth and development initially
- Prognosis can be variable with at least one third developing Lennox-Gastaut syndrome
- Can be difficult to distinguish this syndrome from LGS
- Nocturnal tonic seizures predict a poorer prognosis

Myoclonic-Astatic Epilepsy of Doose--Treatment

- Valproate
- Lamotrigine--not particularly effective
- Felbamate
- 10 boys, felbamate as monotherapy or in combination with valproate, all seizure free
- Ketogenic diet and levetiracetam
- ?Clues to mechanism of epilepsy?

Severe Myoclonic Epilepsy of Infancy

- First described by Dravet in 1978
- There are now close to 500 published cases in the world's literature
- Rare disorder with an incidence of probably less than 1 per 40,000
- Strong family history of epilepsy or febrile seizures; girls may have the more severe phenotype

Severe Myoclonic Epilepsy of Infancy

- Normal growth and development as infants
- Seizures present in the first year of life
- Initially, generalized tonic-clonic seizures, often prolonged and unilateral, associated with fever
- EEGs normal during awake and sleep state

Severe Myoclonic Epilepsy of Infancy

- From 1-4 years of age, there is evolution to myoclonic seizures, atypical absence seizures, afebrile generalized tonic-clonic seizures, and complex partial seizures, usually with secondary generalization
- Episodes of nonconvulsive status epilepticus
- Concomitant psychomotor decline
- EEGs demonstrate irregular generalized and multifocal ps, spike and slow wave D/Cs

Severe myoclonic epilepsy of infancy—variations on the theme

- Febrile seizures, but more typically presenting at a slightly later age, i.e. 7 months
- Generalized tonic clonic seizures associated with fever, not necessarily focal
- Positive family history of febrile seizures in 56%
- Mild to moderate cognitive impairments
- Evolution to afebrile seizures, including multiple types

Severe Myoclonic Epilepsy of Infancy

- Genetic studies implicate mutations in the SCN1A gene, resulting in abnormalities in the sodium channel
- The mutations are typically truncating mutations in the SCN1A gene
- SMEB mutations are more commonly associated with missense mutations in the SCN1A gene

Berten PGM, Ceulemans, MD, Liever RF, et al. Clinical correlations of mutations in the SCN1A gene: From febrile seizures to severe myoclonic epilepsy in infancy. Pediatr Neurol 2004; 30:236-243.

SMEI/SMEB—High correlation with SCN1A mutations

- Classical SMEI had more truncating, splice site, or genomic alterations in SCN1A gene (64.5%)
- SMEB were more likely to have missense mutations (62.5%), particularly in the S5-S6 part of the channel
- Truncating mutations were associated with earliest onset of FS (5 months)
- Missense mutations were associated with later onset of FS (7 months)

Marini C, Mei D, et al. Idiopathic epilepsies with seizures precipitated by fever and SCN1A abnormalities. Epilepsia 2007; 48(9):1678-1685.

Vaccine encephalopathy

- Vaccines have been implicated as a direct cause of an encephalopathy with refractory seizures and intellectual impairment
- In a retrospective study, SCN1A mutations were identified in 11/14 patients with alleged vaccine encephalopathy, a diagnosis of a specific epilepsy syndrome was made in all 14 cases

Berkovic S, Harkin L, et al. De-novo mutations of the sodium channel gene SCN1A in alleged vaccine encephalopathy: a retrospective study. Lancet Neurol 2006; S488-492.

Vaccine encephalopathy

- Cases of alleged vaccine encephalopathy could, in fact, be genetically determined epileptic encephalopathies associated with SCN1A mutations.
- The findings in this study could have important clinical implications for diagnosis and management, as well as major societal implications

Severe Myoclonic Epilepsy of Infancy--Treatment

- Topiramate
- Stiripentol
- Valproate
- Clobazam
- Felbamate
- Ketogenic diet
- Lamotrigine and carbamazepine appear to aggravate the seizures

Severe Myoclonic Epilepsy of Infancy

- In one study, topiramate, as an add-on therapy, 75-100% reduction in convulsive and partial seizures for several months
- Stiripentol, in association with valproate and clobazam, 15/21 children (71%) were responders, defined as having more than 50% reduction in seizure frequency; nine were seizure free (43%)

Epilepsy Syndromes—Localization Related; Idiopathic

- Benign rolandic epilepsy
- Benign occipital epilepsy
- Autosomal dominant frontal lobe epilepsy
- Familial temporal lobe epilepsy

Patient M. M.

- 6 year old young boy
- Presents to ED after having had GTCS at 5:30 AM, lasting minutes, began with drooling and unilateral facial twitching
- Normal growth and development
- Normal exam
- EEG documents normal background activities, but drowsy and sleep activated central-temporal spike and slow wave discharges, maximum left

Benign Rolandic Epilepsy

- Most common childhood epilepsy syndrome—accounts for 15-25% of childhood epilepsy
- Nocturnal partial and generalized seizures—often occurring in the early morning hours prior to awakening
- Infrequent seizures
- Abnormal EEG with drowsy and sleep activated centrotemporal spike and slow wave discharges
- Prognosis for remission excellent

Patient K. K.

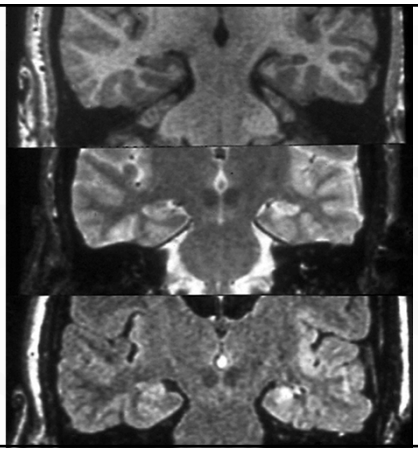
- Two prolonged febrile seizures at 12 and 14 months of age
- Then at 20 months, developed afebrile seizures characterized by aura of fear, staring, decreased responsiveness, and lip smacking automatism
- Having two seizures per month
- Has had episodes of status epilepticus
- Normal growth and development until recently
- Normal neurological examination

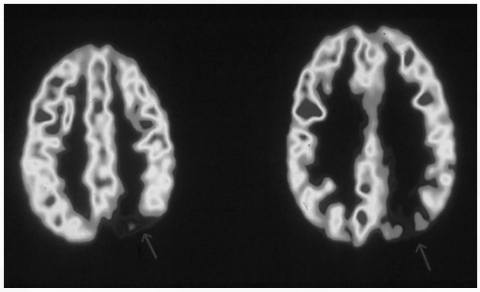
Patient K.K.

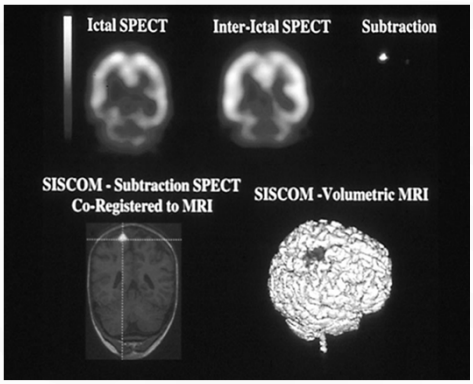
- EEG is normal interictally while awake; rare left temporal spikes during sleep.
- Abnormal MRI scan of the brain –increased signal on T2 weighted imaging in the hippocampus, with probable hippocampal atrophy
- What is the epilepsy syndrome?

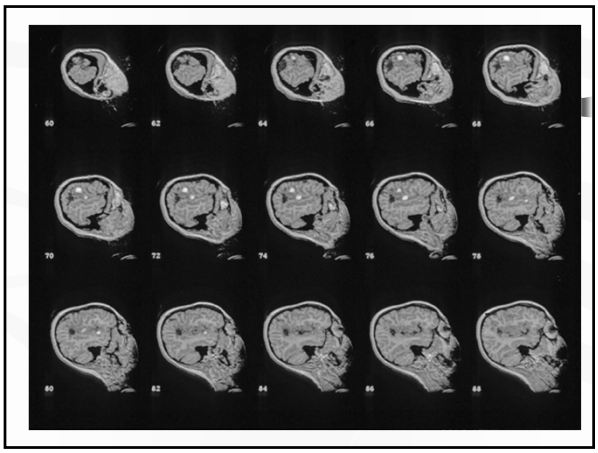
Patient K. K.

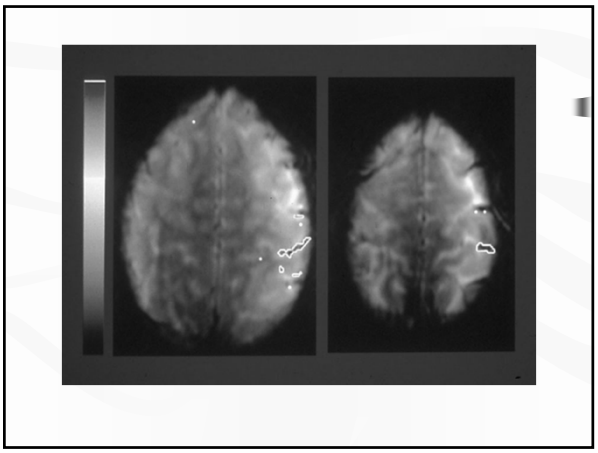
- Patient has symptomatic localization related epilepsy with complex partial seizures with and without secondary generalization
- Has failed two AEDs
- Prognosis for remission--poor
- MRI scan is an indicator for continued intractability
- Candidate for epilepsy surgery



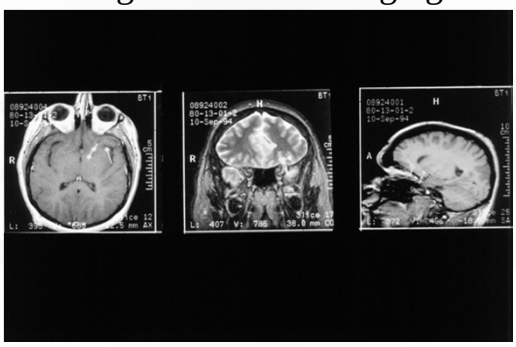


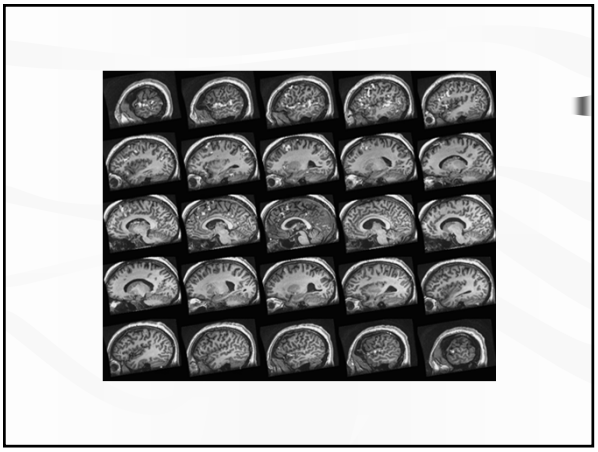


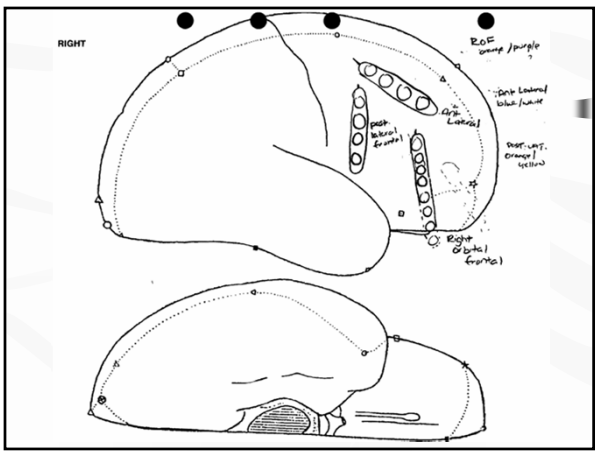


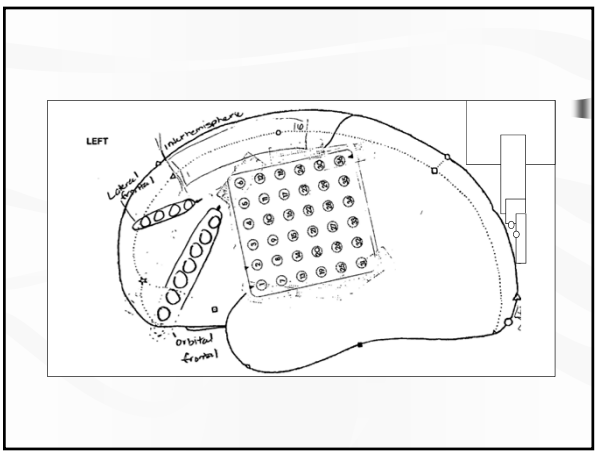


Magnetic Source Imaging

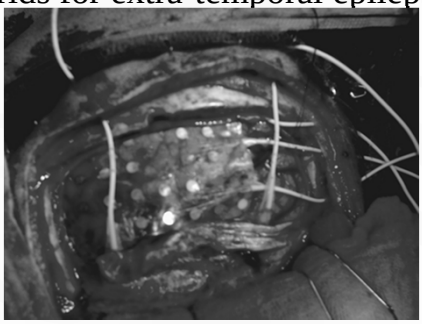


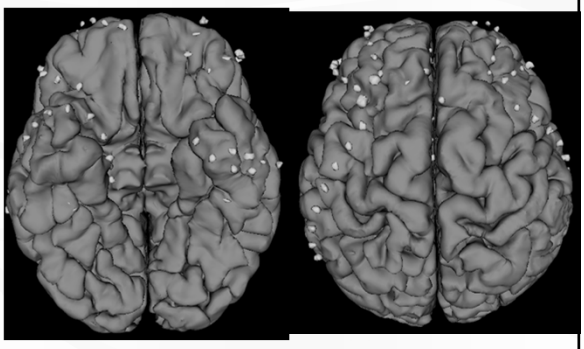






Grids for extra-temporal epilepsy





Epilepsies Syndromes --Generalized

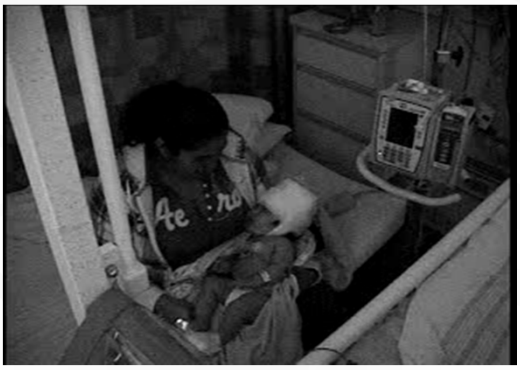
- Symptomatic
  - Early myoclonic epileptic encephalopathy
  - Ohtahara's syndrome
  - Infantile spasms
  - Lennox Gastaut syndrome

Age-Dependent Epileptic Encephalopathies

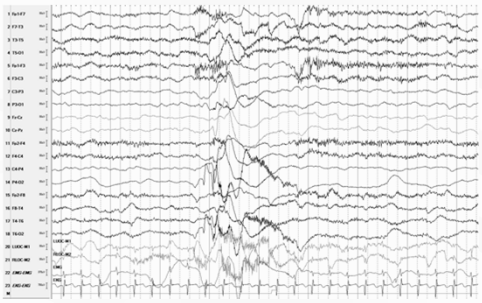
- Evolution of seizure semiology
- Evolution of EEG characteristics
- Directly correlated with the increasing, programmed synaptogenesis and reorganization of the developing brain
- Results in increased synchronization of EEG and changing seizure phenotype

Infantile Spasms

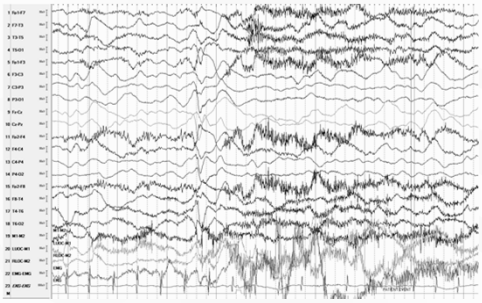
- Onset at 4-8 months of life
- Characterized by clusters of flexor, extensor, or mixed myoclonic jerks
- May have associated autonomic or focal features
- Various etiologies
- Resistant to standard AEDs



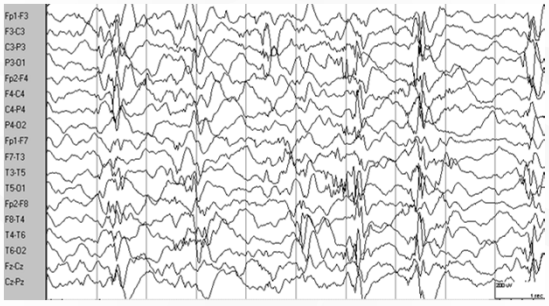
Infantile Spasms



Infantile Spasms2



Infantile spasms--Hypsarrhythmia



What causes infantile spasms?

- Brain development requires excitatory pathways for active neurogenesis, synaptogenesis, and programmed apoptosis
- Subcortical pathways are initially better developed than the cortical pathways, resulting in subcortically mediated volleys of epileptogenic discharges

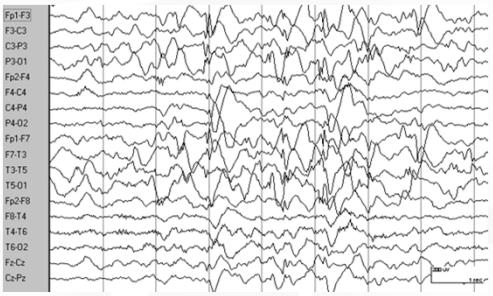
Infantile Spasms

- Malformations of cortical development create an imbalance between excitatory and inhibitory pathways--?inefficiency of GABA
  - ?Decreased production
  - ?Decrease in receptor density
  - ?Abnormal receptor binding
  - ?Destruction of GABA in synaptic cleft

Treatment of Infantile Spasms

- ACTH—Treatment of choice
- Vigabatrin—Treatment of choice for patients with tuberous sclerosis
- Prednisone—Not as effective
- None of the other AEDs has proven efficacy
- A small subset of patients with infantile spasms are candidates for epilepsy surgery

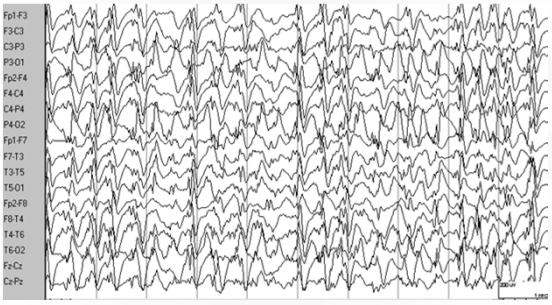
Infantile spasms, intractable, malformation of cortical development, left post quadrant



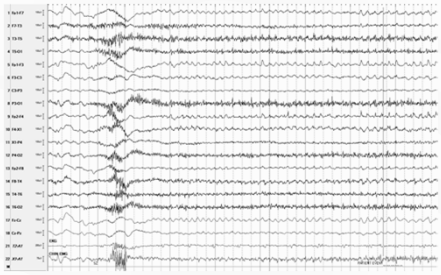
Lennox-Gastaut Syndrome

- Generalized 1 ½ -2 hertz polyspike, spike and slow wave discharges, often irregular in distribution and frequency
- Multiple seizure types, including tonic, atonic, generalized tonic-clonic, atypical absence, and myoclonic seizures
- Cognitive impairments (variable)

Lennox-Gastaut Syndrome



Lennox-Gastaut Syndrome—Ictal Event



AED Options with Lennox-Gastaut Syndrome

- Valproate—obesity; thrombocytopenia; pancreatitis; liver failure rare in older patient
- Topiramate—cognitive slowing; renal stones; oligohydrosis; metabolic acidosis
- Lamotrigine—allergic rash; requires slow titration; can exacerbate myoclonic seizures; can produce motor and vocal tics
- Felbamate—risk of aplastic anemia and liver failure; there has never been a pediatric patient < 13 years of age with aplastic anemia; cognitive enhancer; anorexia and insomnia

Rufinamide

- FDA approved for medically refractory seizures associated with Lennox-Gastaut syndrome, especially tonic and atonic seizures
- Mechanism of action: Slow sodium channels
- Side effects: Nausea, vomiting, somnolence

Clobazam

- 1, 5 benzodiazepine
- Recently FDA approved for treatment of tonic/atonic/myoclonic seizures associated with Lennox-Gastaut syndrome
- Mechanism of action: GABA receptor
- Side effects: Sedation, somnolence, increased salivation, pyrexia/resp infections

Other Therapeutic Options

- Vagal nerve stimulator
- Ketogenic diet
- Epilepsy surgery
  - Cortical resection
  - Corpus callosotomy
  - Corpus callosotomy and resection

Epilepsy Surgery for LGS

- Generalized epilepsy syndromes with focal features may be remediable to epilepsy surgery
  - Focal seizure semiology
  - Focal EEG or MEG characteristics
  - Focal neuroimaging, using MRI, SPECT, PET, or MR Spectroscopy

Conclusions

- The ability to name the specific epilepsy syndrome is the biggest factor in determination of prognosis and treatment
- Epilepsy syndromes are be divided into two categories:
  - Idiopathic (genetic)
  - Symptomatic (lesional or underlying known etiology)

Conclusions—AED Therapy

- Valproate is relatively contraindicated in women in the reproductive age
- Carbamazepine and oxcarbazepine can exacerbate the generalized epilepsy syndromes
- Lamotrigine and levetiracetam have no known cognitive side effects
- Felbamate is an excellent drug for refractory epilepsy, especially Lennox-Gastaut syndrome

Conclusions

- Once there has been failure of a single AED, patient should be referred to pediatric neurologist/epileptologist
- Failure of two or more AEDs should prompt evaluation for epilepsy surgery
- Epilepsy surgery should NOT be avenue of last resort