Epilepsy

Definitions

- An epileptic disorder is a chronic neurological disorder characterized by recurrent epileptic seizures
- An epileptic syndrome consists of a complex of signs and symptoms that occur together more than by chance and define a unique epilepsy condition
- An epileptic diseases is a pathologic condition with a single specific, well defined etiology

Classification of seizures

- Partial seizures
  - -simple
  - -complex
  - -secondarily generalized seizures

- Generalized seizures
  - -Tonic
  - -Clonic
  - -Tonic clonic
  - -Atonic
  - -Myoclonic
  - -Absence

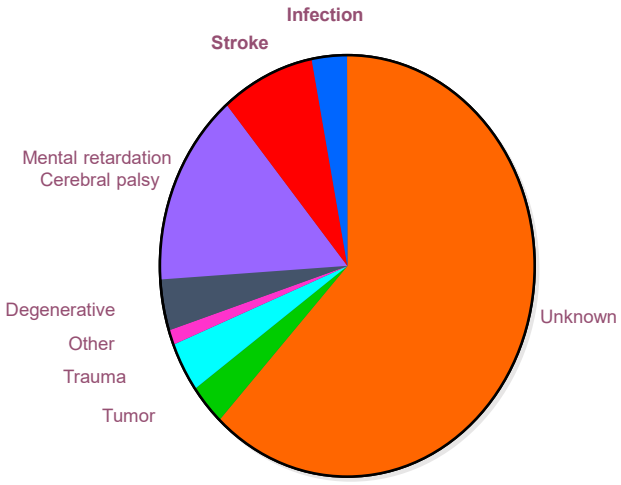
DETERMINATION OF CAUSE
ETIOLOGICAL CLASSIFICATION

- ACUTE SYMPTOMATIC SEIZURE

- ISOLATED CRYPTOGENIC SEIZURE

- EPILEPSIES
  - REMOTE SYMPTOMATIC
  - GENETIC
  - CRYPTOGENIC

Etiology of Epilepsy



Adapted with permission from Olafsson E, et al. *Epilepsia.* 1999;40(11):1529-1534.

Prevalence of generalized and partial seizures children

- Complex partial 23%
- Tonic clonic 19%
- Absence 13%
- other generalized seizures 11%
- Simple partial seizures 11%
- Other partial 7%
- Myoclonic 7%
- Unknown multiple 9%

Prevalence of generalized and partial seizures adults

- Complex partial 49%
- Tonic clonic 27%
- Simple partial seizures 13%
- Other partial 6%
- Myoclonic 2%
- Unknown multiple 3%

Why classify into epilepsy syndromes

- Impacts diagnostic testing
- Impacts treatment
- Conveys prognostic information
- Helpful in delineating genetic defect
- Provides insight into pathophysiology

Future directions and obstacles in childhood epilepsy

Syndrome	Pathophysio understood	Effective therapy
Benign rolandic epilepsy	maybe	yes
Absence epilepsy	yes	yes
Infantile spasms	no	no
Mesial temporal lobe sclerosis	yes	maybe

Syndrome	Patho-physio understood	Effective therapy
Severe myoclonic epilepsy of childhood (Dravet)	no	no
Lennox- Gastaut syndrome	no	no
Landau- kleffner syndrome	no	no
Juvenile myoclonic epilepsy	maybe	yes

Classification of epilepsy syndromes

- Idiopathic focal epilepsies of infancy and childhood
- Familial (autosomal dominant) focal epilepsies
- Symptomatic (probably) focal epilepsies
- Idiopathic generalized epilepsies
- Reflex epilepsies
- Epileptic encephalopathies

Engel-2001

Idiopathic focal epilepsies of infancy and childhood

- Benign familial infantile epilepsies
- BECTS
- BECOS (Panyatopoulos-type) early onset
- Late onset childhood occipital epilepsy (Gastaut type)

Engel 2001

Familial autosomal dominant focal epilepsies

- Benign familial neonatal seizures
- Benign familial infantile seizures
- Autosomal dominant frontal lobe epilepsy
- Familial temporal lobe epilepsy
- Familial focal epilepsy with variable foci

Engel 2001

Symptomatic epilepsies

- **Limbic epilepsies**
  - mesial temporal lobe epilepsies with hippocampal sclerosis

  -mesial temporal lobe epilepsies defined by specific etiologies

- **Neocortical epilepsies**
  -Rasmussen syndrome
  -hemiconvulsion-hemiplegia syndrome
  -migrating partial seizures of early infancy

Engel 2001

Idiopathic generalized epilepsies

- Benign myoclonic epilepsies in infancy
- Epilepsy with myoclonic-astatic seizures
- Childhood absence epilepsy
- Epilepsy with myoclonic absences
- Those with variable phenotypes
  -juvenile absence
  -juvenile myoclonic
  -epilepsy with GTC seizures
- Generalized epilepsy with febrile seizures plus(GEFS +)

Engel 2001

Reflex epilepsies

- Idiopathic photosensitive occipital lobe epilepsy
- Primary reading epilepsy
- Startle epilepsy

Engel 2001

Epileptic encephalopathies

- Early myoclonic encephalopathy
- Otohara syndrome
- West syndrome
- Dravet syndrome
- Myoclonic status in nonprogressive encephalopathies
- Lennox-Gastaut syndrome
- Landau-kleffner syndrome
- Epilepsy with continuous spike-waves during slow wave sleep

Engel 2001

Benign familial neonatal convulsions (BFNC)

- Autosomal dominantly inherited epilepsy of the newborn
- Onset day 2-4 of life
- Spontaneous remission of seizures between 2-15 weeks
- Seizures start with a tonic posture, ocular symptoms, and other autonomic features, which often progress to clonic seizures and motor automatisms

Miles and Holmes 1990

Benign familial neonatal convulsions (BFNC

- Between seizures neonates are normal
- Evaluation for etiologies is negative
- Clinical and EEG features suggest generalized onset
- Seizures occur later in life in approximately 16% of cases compared to 2% in the general population

Miles and Holmes 1990

Benign familial neonatal convulsions (BFNC

- Two loci have been identified:
  - -EBN1 to chromosome 20q 13.3
  - -EBN2 to chromosome 8q 24

- Characterization of c - DNA spanning the deleted region identified one coding a novel gated potassium channel (KCNQ2) which belongs to a new KQT like class of potassium channels
- ***Singh et al 1998***

GEFS +

- Family members with multiple febrile seizures in infancy and persistence of afebrile generalized tonic clonic seizures beyond 6 years of life
  - FS + absences
  - FS + myoclonic seizures
  - FS + atonic seizures
- Genetic and phenotypic variability
- ***Scheffer and Berkovic, 1997***

GEFS +

- Linkage to multiple foci
- Mutation in the beta -1 subunit of voltage gated Na channel
- Result of mutation leads to increased excitability

GEFS +

- Seizure phenotype may vary even within the same family
- Other genes or environmental factors are required to determine the sporadic features

Severe myoclonic epilepsy of infancy (SMEI)

- MUTATIONS IN SCN1A have been found in SMEI (Dravet syndrome) and GEFS +
- Mutations in SMEI include missense, nonsense, and frame shift mutations most commonly arising de novo in affected patients
- 50 % of children with SMEI have family history of seizures yet de novo SCN1 mutations occur in 80 % of cases
- Mutations in SMEI could cause more disturbances in Na channel than with other forms of GEFS +

Wallace 2003

Locus heterogeneity and variable expressivity

- SCN1A → severe myoclonic epilepsy of infancy
- SCN1B → GEFS+
- SCN1B → Childhood absence and FS+
- GABRG2 → BFNC

Ottman 2002

Importance of syndrome classification

- Understanding pathophysiology
- Finding genetic basis starts with careful clinical identification
- Novel therapies will require better understanding of aberrant genes

Migrating malignant partial seizures in infancy

- Background : severe developmental delay
- Semiology: varied-hypomotor, versive
- EEG: Ictal migrating bilateral independent ictal discharges
- Outcome: very refractory epilepsy.

Epilepsy syndromes in infancy

- **Epilepsies with prominent myoclonus**

  - Benign myoclonic epilepsy

  - Severe myoclonic epilepsy (Dravet, et al 1986)

  - Early myoclonic encephalopathy (Aicardi and Goutieres)

Epilepsies with prominent myoclonus

-Benign non epileptic infantile spasm (Lombroso and Fejerman 1997)
-true infantile spasms (cryptogenic)
-localization related epilepsies with spasms
-Symptomatic (west, 1841)
-Early infantile epileptogenic encephalopathy(Otohara 1978)
-periodic spasms

West syndrome

- West syndrome is a triad of infantile spasms, developmental retardation or regression, and hypsarrhythmia on EEG. The syndrome presents in infants aged between 6 and 18 months. Presence of a hypsarrhythmic EEG confirms the diagnosis of infantile spasms

- EEG patterns may evolve over a period; they initially appear in the sleep EEG record and subsequently present during the awake state. Hypsarrhythmia is seen in 75% of patients with West syndrome.

West syndrome

- Hypsarrhythmia consists of diffuse giant waves (high voltage, >400 microvolts) with a chaotic background of irregular, multifocal spikes and sharp waves and very little synchrony between the cerebral hemispheres. During sleep, the EEG may display bursts of synchronous polyspikes and waves. A pseudoperiodic pattern may be evident. Persistent slowing or epileptiform discharges in the hypsarrhythmic background may be present and may represent an area of focal dysfunction. Several variations to the hypsarrhythmic pattern, which are referred to as hypsarrhythmic variants, may be noted.

West syndrome

- Clinical spasms are associated with a marked suppression of the background that lasts for the duration of the spasm. This characteristic response is called the "electrodecremental response”
- EEG is useful in judging successful treatment of West syndrome. Typically, shortly after treatment with adrenocorticotropic hormone (ACTH) or vigabatrin is initiated, the spasms stop and hypsarrhythmia disappears.
- Hypsarrhythmia rarely persists beyond the age of 24 months. It may evolve into the slow spike and wave discharges seen in LGS.

ILAE epilepsy syndromes

- **Localization related**
  -idiopathic
  -symptomatic
- **Generalized**
  -idiopathic
  -idiopathic or symptomatic
  -symptomatic

ILAE epilepsy syndromes

- **Undetermined**
  1. generalized and focal seizures
  -neonatal seizures
  -severe myoclonic epilepsy in infancy
  -epilepsy with CSWS
  -acquired epileptic aphasias focal or multifocal seizures
  continuous(Coppola et al 1996)
  not continuous

  2. without unequivocal generalized or focal features

Idiopathic partial syndromes

- **BECRS**

- most common partial epilepsy motor syndrome in childhood
-16% of epilepsies begin before the age of 15 years(Cavazzuti 1980)
-up to 67% of partial epilepsies(Roger et al 1992)

Idiopathic partial syndromes

- **Atypical form of rolandic epilepsies**

- Epilepsy with evoked parietal spikes
- Landau Kleffner syndrome
- Atypical benign partial epilepsy of childhood

Idiopathic partial syndromes

- **Benign partial epilepsy with occipital spikes**

- early onset (Panayiotopoulos)
- late onset (Gastaut)

Idiopathic partial syndromes

- **Familial temporal lobe epilepsy**

- CPS similar to lesional epilepsies (Berkovic,1994)
- auditory ictal symptoms (Ottman,1995)

- **AD rolandic epilepsy with speech dyspraxia**

- nocturnal oral facial and brachial features
- centro-temporal spike wave discharges
- oral, speech dyspraxia and cognitive impairment

Idiopathic partial syndromes

- **Benign focal seizures in adolescents** (Loiseau and Orogozo)

- normal exam and EEG
- high rates of remisssion

Simple Mendelian epilepsies

Idiopathic partial epilepsy genes

Disorder	Locus	Citations
AD partial epilepsy with auditory features	10q	Ottman et al 1995
AD rolandic epilepsy with dystonia and writers cramp	16p	Guerrini 1999
Partial epilepsy with pericentral spikes	4p15	Kinton 2002
Familial partial epilepsy with variable foci	2q ,22q	Scheffer 1998, Xiong 1999
Ad nocturnal frontal lobe epilepsy	15q	Philips 1998
BECTS	15q	Neubauer 1998

Lesional epilepsies

- Mesial temporal syndrome

-malformation of CA1 and dentate gyrus render hippocampus more vulnerable to injury

-high incidence of dual pathology (Sloviter 2004)

- HHE syndrome (Gastaut 1960)

Lesional epilepsies

- Syndrome of cystic dilatation of occipital horn with epilepsy (Remillard 1974)
- Rasmussen's syndrome
- Subcortical epilepsies
  - hypothalamic hamartomas with gelastic seizures
  - cerebellar structures

Lesional epilepsies

- **Malformations of cortical development**

- focal cortical dysplasias
- pachygyria
- lissencephaly
- schizencephaly
- developmental tumors

❖Ganglioglioma
❖Gangliocytoma
❖DNET

Partial epilepsy syndromes

- **Clinical manifestations motor**

- secondary generalized seizures
- drop attacks
- focal myoclonic seizures
- focal clonic seizures
- hypermotor seizures

Partial epilepsy syndromes

- **Clinical manifestations automatisms**
- symptoms predominate and are less purposeful
- older children more complex gestural
- adolescents have full range of complex automatisms
- retrievable auras rare in children

Manifestations of automatisms as a %

characteristic	< 2 years	2-6 years	6-12 years
oroalimentary	72%	43	75
facial	55%	14	50
gestural	45%	71	75
axial	0%	43	75
stereotypy	9%	57	75

Immature brain more vulnerable

- **In absence of cell loss in animals seizures can impair**

- impair spatial learning (Holmes 1999)

- increase late seizure induced damage(Koh 1999)

- alter hippocampal circuits(Sutula 1999)

Consequences of partial seizures in childhood Rolandic epilepsy

- Documented decline in neuropsychological functioning
- Deonna 2000 and Massa 2001
- frequent seizures and ictal discharges
- transient decline in IQ and deficits in sustained attention
- may occur in patients without overt seizures also
- cortical inhibition significant enough to control initiation of ictal activity may also produce temporary cortical disorganization

Important facts

- Causes, clinical presentation and consequences in children vary from adults
- Even benign syndromes may not be so benign
- Recognize wide variety and unique presentations of childhood seizures

BRE

- **Benign rolandic epilepsy**
- Patients with BRE are typically between 3 and 10 years old. They may present with a history of orobuccal numbness on one side of the mouth or with a tingling sensation on one side of the face. These seizures are associated with preserved mentation and are thus simple partial seizures. During sleep, patients may have generalized tonic-clonic convulsions.

BRE

- EEG features of BRE include frequent spike and wave discharges in the centrotemporal region . The electrical field of epileptiform discharges is not distributed widely. Frequently, the dipole is located tangentially, with positivity in the frontal regions. The negative pole is 150-300 microvolts, and the entire spike and wave complex lasts for 80-120 milliseconds. Characteristically, the spike is triphasic and blends into the after-coming slow wave.

BRE

- Commonly, epileptiform discharges occur in runs. Discharges may be bilateral in 30% of patients; when they occur bilaterally, the discharges are independent and asynchronous. Unilateral discharges are more common. Activating movements or eye opening does not block the discharges.
- Sleep, however, has a prominent activation on the epileptiform discharges Non-REM sleep, in particular, may show a 400-500% increase in the spike-wave index. Over time, the epileptiform discharges decrease, and they finally disappear at around age 15 years.

BRE

- BRE appears to be a dominantly inherited condition with variable penetrance. The reader should keep in mind that BRE is a syndromic diagnosis with the EEG forming an important component of the diagnosis. Epileptiform discharges in the rolandic region do not necessarily mean that the patient has BRE.

Generalized seizure

"A seizure whose initial semiology indicates, or is consistent with more than minimal involvement of both hemispheres''

ILAE DEFINITION

Generalized seizure types

- Myoclonic-sudden < 100ms contraction of muscle
- clonic-repetitive rythmic myoclonus at 2-3 Hz
- Tonic-sustained muscle contraction secs to mins
- Generalized tonic clonic
- Atonic-sudden brief 1-2 sec decrease in tone without preceeding myoclonic or tonic event
- Astatic- loss of posture due to atonic, myoclonic or tonic event

Generalized epilepsies and syndromes -1989

- Idiopathic

-BFNC

-benign myoclonic epilepsy in infancy

LGS

- LGS is a childhood (onset age 3-5 years) epileptic encephalopathy that manifests with atonic seizures, tonic seizures, and atypical absence seizures associated with mental retardation and a characteristic EEG pattern. Infantile spasms and West syndrome frequently transform into LGS. Unlike West syndrome, LGS tends to be a lifelong epileptic encephalopathy.

LGS

- EEG shows an abnormally slow background and diffuse slow spike and slow wave (<2.5 Hz) activity . The slow spike and wave activity serves to differentiate (poor-prognosis) LGS from benign absence epilepsy, in which diffuse 3-Hz spike and wave activity is seen, and from some of the more benign myoclonic types of epilepsy characterized by fast spike and wave (>2.5 Hz) activity, which carries a dramatically better prognosis than LGS. Many other epilepsy syndromes overlap with LGS, however, including myoclonic astatic epilepsy of Doose and other severe myoclonic epilepsies.

  EEG features of LGS may be divided into interictal and ictal.

LGS

- Interictal EEG features: Background slowing and diffuse slow spike and wave activity lasting from several minutes to a near continuous state are characteristic.
- Duration of epileptiform discharges tends to correlate with epilepsy control, with shorter durations occurring in patients with better control of seizures. Spikes, or more commonly sharp waves, are typically 200 milliseconds in duration and are followed by slow waves.
- Polyspike discharges are seen in those epilepsy variants with prominent myoclonic seizures or during non-rapid eye movement (REM) sleep.

- Ictal EEG features: Electrographic accompaniment varies with the seizure type

CAE

- Childhood absence epilepsy (CAE) presents between ages 3 and 5 years and usually remits by ages 10-12 years. Unlike juvenile absence epilepsy, CAE usually is not associated with tonic-clonic seizures.
- EEG shows a normal background for age and 3-Hz generalized spike and wave discharges frequency of the spike-wave complexes is usually 4 Hz at the onset of the absence seizures and may slow to 2.5 Hz at the end of a seizure. Typically, an initial positive component is followed by one or more negative components and then a negative slow wave. They are frontally dominant . Duration of discharges is typically 3-25 seconds.

CAE

- Discharges are not truly bisynchronous; usually a millisecond difference is noted between left and right cerebral hemispheres. Eye opening does not alter the discharges. However, discharges are state dependent. Their frequency increases with non-REM sleep, although the duration of the discharges is reduced. During REM sleep, the frequency of discharges resembles that seen in wakefulness. Some patients display occipital intermittent rhythmic delta discharges (OIRDA), which is thought to be a favorable prognostic indicator.

- Generalized discharges are ictal in nature. They may be so brief that no obvious clinical movements are seen, although typically minor eyelid fluttering or subtle rhythmic contractions of the mouth are seen. These minor motor accompaniments occur in 85% of patients with absence epilepsy.

CAE

- Absence status epilepticus occurs in about 10% of patients with CAE. Typically, a child with staring spells is misdiagnosed as having partial complex seizures and treated with carbamazepine. In fact, carbamazepine can precipitate absence status, which is a nonconvulsive status epilepticus in which patients appear to be in a "twilight state." They are able to answer questions intermittently, although at times they are confused. EEG is crucial in the diagnosis. It shows near-continuous generalized spike and wave discharges.

- Absence should be differentiated from atypical absence seizures, which usually are seen in patients with LGS. EEG in atypical absence seizures shows a less abrupt onset and offset than in typical absence seizures. Furthermore, EEG background is slow, and duration of discharges is shorter.

EEG

- Hyperventilation and sleep deprivation are provocateurs.
- Sleep deprivation is always a good idea.
- Upto 3 EEG's are needed sometimes to increase the yield to about 95% of finding an abnormality-this is used more often in adult neurology.
- Mild paroxysmal abnormalities or sometimes even epileptiform discharges in patients with explosive outbursts or behavior problems does not necessarily imply a diagnosis of epilepsy.

EEG

- Helps make a diagnosis of a partial or generalized epilepsy.
- Define an epilepsy syndrome.
- Helps in predicting recurrence of seizure after a new onset seizure.

  Generalized abnormailty-50%

  Focal/partial abnormality-75%
- Guides in discontinuation of therapy.
- Helps asses control of seizures-Absence epilepsy

CT head

- Post traumatic seizure.
- Generalized seizure new onset ?
- New seizure with altered mental status in ER/PICU setting.
- New onset partial seizure brief-abnormal examination MRI not available.
- New onset partial seizure brief, normal exam but anxious parents.
- New onset partial seizure prolonged cannot wait on MRI.

CT head limitation

- Poor visualization of abnormalities such as
  - ❖ Cortical dysplasias
  - ❖ Mesial temporal sclerosis
  - ❖ Migrational abnormalities
  - ❖ Mild acute demyelination
  - ❖ Low grade tumors
  - ❖ Metabolic disorders

MRI head

- Partial or focal seizures.
- Focal EEG abnormalities in setting of generalized seizure.
- Refractory generalized epilepsies.
- Patient with a history of generalized epilepsy starts having partial seizures.
- Questionable abnormality on CT head.
- Gadolinium usually not necessary

MEDICAL MANAGEMENT

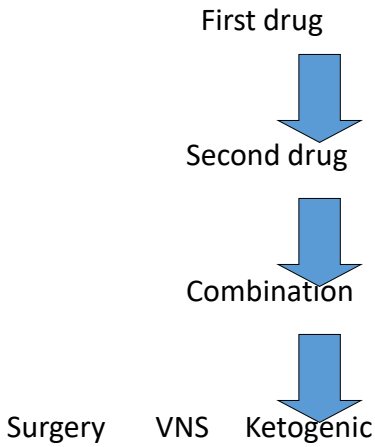
- CORRECT DIAGNOSIS OF SEIZURE AND EPILEPSY TYPE.
- IS TREATMENT NECESSARY.
- WHICH DRUG.
- COUNSELLING-FIRST AID AND SEIZURE PRECAUTONS
  -AIM,DURATION AND PROGNOSIS
  -IMPORTANCE OF COMPLIANCE
  -SIDE EFFECTS

Principles of treatment.

- Confirm it is a seizure.
- What type of seizure.
- What is the cause for the seizure.
- Is it an epilepsy syndrome.
- Are you sure it is not a non epileptic event.
- What are the co morbid conditions-obesity,depression,ADHD,migraine bipolar affective disorder.

Treatment algorithm

Confirm seizure diagnosis



DRUG CHOICES BY SEIZURE TYPES
AND EPILEPSY SYNDROMES

A. Partial seizures (with or without secondary generalization)

- **First choice: Carbamazepine/oxcarbazepine,**
- **Second choice: Gabapentin, lamotrigine, topiramate, valproate**
- **Third choice: Levetiracetam, tiagabine,zonisamide, phenytoin, phenobarbital, primidone**
- **Consider: Benzodiazepine, acetazolamide, vigabatrin, felbamate**

DRUG CHOICES BY SEIZURE TYPES AND EPILEPSY SYNDROMES

B. Generalized tonic-clonic seizures

- First choice: Valproate, carbamazepine, phenytoin
  - Second choice: Topiramate, lamotrigine
  - Third choice: Phenobarbital, primidone
- Consider: Zonisamide

DRUG CHOICES BY SEIZURE TYPES AND EPILEPSY SYNDROMES

C. Childhood absence epilepsy

Before age 10 years:

- **First choice: Ethosuximide (if no convulsions), valproate**
- **Second choice: Lamotrigine**
- **Consider: Methsuximide, acetazolamide, benzodiazepine, topiramate, zonisamide**

DRUG CHOICES BY SEIZURE TYPES AND EPILEPSY SYNDROMES

C. Juvenile absence epilepsy

After age 10 years:

- **First choice: Valproate**
- **Second choice: Lamotrigine**
- **Third choice: Ethosuximide, methsuximide, acetazolamide, topiramate, zonisamide, benzodiazepine**

DRUG CHOICES BY SEIZURE TYPES AND EPILEPSY SYNDROMES

D. Juvenile myoclonic epilepsy

- **First choice: Valproate**
- **Second choice: Lamotrigine, topiramate, clonazepam**
- **Third choice: Phenobarbital, primidone, zonisamide**
- **Consider: Felbamate**

DRUG CHOICES BY SEIZURE TYPES AND EPILEPSY SYNDROMES

E. The Lennox-Gastaut and related syndromes

- **First choice: Valproate**
- **Second choice: Topiramate, lamotrigine**
- **Third choice: ketogenic diet, VNS, felbamate, zonisamide, benzodiazepine, phenobarbital**
- **Consider: Ethosuximide, methsuximide, ACTH or steroids, pyridoxine, vigabatrin**

DRUG CHOICES BY SEIZURE TYPES AND EPILEPSY SYNDROMES

F. Infantile spasms

- First choice: ACTH, vigabatrin, valproate
- Second choice: Topiramate
- Third choice: lamotrigine, tiagabine, benzodiazepine
- Consider: Pyridoxine, zonisamide, felbamate

DRUG CHOICES BY SEIZURE TYPES AND EPILEPSY SYNDROMES

F. Infantile spasms

- First choice: ACTH, vigabatrin, valproate
- Second choice: Topiramate
- Third choice: lamotrigine, tiagabine, benzodiazepine
- Consider: Pyridoxine, zonisamide, felbamate

DRUG CHOICES BY SEIZURE TYPES AND EPILEPTIC SYNDROMES

G. Benign epilepsy of childhood with centrotemporal spikes

- **First choice: Sulthiame, gabapentin, valproate**
- **Second choice: Carbamazepine, phenytoin**
- **Third choice: Phenobarbital, primidone, benzodiazepine**
- **Consider: Lamotrigine, topiramate**