Epilepsy Syndromes in Neonates, Infants & Children

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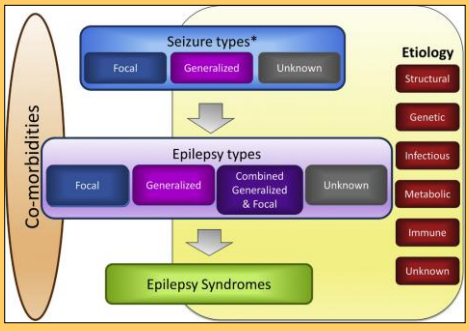
Outline

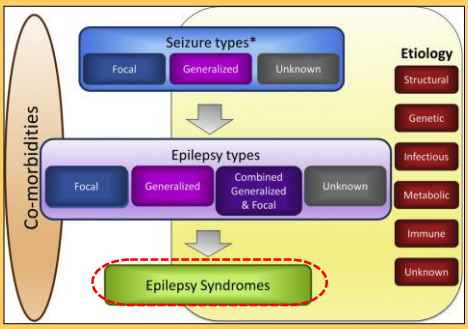
- Classification of Epilepsy Syndromes
- Common epilepsy syndromes
  - Neonates
  - Infants
  - Children



ILAE classification of epilepsies, 2017

Epilepsy Syndrome

- A cluster of features incorporating seizure types, EEG, and imaging features that tend to occur together.
- Age-dependent
- Seizure triggers
- Diurnal variation
- Prognosis
- Etiologies
- Treatment



ILAE classification of epilepsies, 2017

Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005–2009

*†Anne T. Berg, ‡Samuel F. Berkovic, §Martin J. Brodie, ¶Jeffrey Buchhalter, #**J. Helen Cross, ††Walter van Emde Boas, ‡‡Jerome Engel, §§Jacqueline French, ¶¶Tracy A. Glauser, ##Gary W. Mathern, ***Solomon L. Moshé, †Douglas Nordli, †††Perrine Plouin, and ‡Ingrid E. Scheffer

Electroclinical syndromes arranged by age at onset[a]
Neonatal period
Benign familial neonatal epilepsy (BFNE)
Early myoclonic encephalopathy (EME)
Ohtahara syndrome

Conditions with epileptic seizures that are traditionally not diagnosed as a form of epilepsy per se
Benign neonatal seizures (BNS)

Epilepsia. 2010, 51(4):676–685, 2010

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Infancy
- Epilepsy of infancy with migrating focal seizures
- West syndrome
- Myoclonic epilepsy in infancy (MEI)
- Benign infantile epilepsy
- Benign familial infantile epilepsy
- Dravet syndrome
- Myoclonic encephalopathy in nonprogressive disorders

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Childhood
- Febrile seizures plus (FS+) (can start in infancy)
- Panayiotopoulos syndrome
- Epilepsy with myoclonic atonic (previously astatic) seizures
- Benign epilepsy with centrotemporal spikes (BECTS)
- Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE)
- Late onset childhood occipital epilepsy (Gastaut type)
- Epilepsy with myoclonic absences
- Lennox-Gastaut syndrome
- Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)[b]
- Landau-Kleffner syndrome (LKS)
- Childhood absence epilepsy (CAE)

Epilepsia. 2010, 51(4):676–685, 2010

ILAE; Informal Methods of Classification by Age

Neonatal/Infantile Onset	Childhood Onset	Adolescent/Adult Onset	Any Age
Self-limited neonatal seizures and self-limited familial neonatal epilepsy	Epilepsy with myoclonic atonic seizures	Juvenile absence epilepsy	Familial focal epilepsy with variable foci
Self-limited familial and nonfamilial infantile epilepsy	Epilepsy with eyelid myoclonia	Juvenile myoclonic epilepsy	Reflex epilepsies
Early myoclonic encephalopathy	Lennox-Gastaut syndrome	Epilepsy with generalized tonic-clonic seizures alone	Progressive myoclonic epilepsies
Ohtahara syndrome	Childhood absence epilepsy	Autosomal dominant epilepsy with auditory features	
West syndrome	Epilepsy with myoclonic absences	Other familial temporal lobe epilepsies	
Dravet syndrome	Panayiotopoulos syndrome		
Myoclonic epilepsy in infancy	Childhood occipital epilepsy		
Epilepsy of infancy with migrating focal seizures	Photosensitive occipital lobe epilepsy		
Myoclonic encephalopathy in nonprogressive disorders	Childhood epilepsy with centrotemporal spikes		
Febrile seizures plus, genetic epilepsy with febrile seizures plus	Atypical childhood epilepsy with centrotemporal spikes		
	Epileptic encephalopathy with continuous spike and wave during sleep		
	Landau-Kleffner syndrome		
	Autosomal dominant nocturnal frontal lobe epilepsy		

By outcomes

1. Self-limited
   BECTS, CAE
2. Pharmacoresistant
   West syndrome, LGS

Neurologic Clinics. 2021; Vol 39:779-795.
www.epilepsydiagnosis.org.

Neonatal Seizures

- Estimated incidence in US: 80-120/100,000 neonates per year
- Occur within first 4 weeks of life in FT infant and up to 44 weeks PCA for PT infants
- Most frequent during first 10 days of life
- Occur over a few days
- Less than 50% infants develop seizures later in life
- Acute symptomatic rather than “ epilepsy"
- Markedly increases rates of long-term morbidity and neonatal mortality

Neonatal Seizures
Etiology

- History indicates likely etiology
- Positive family history
- Pregnancy history
  - TORCH infections (toxoplasmosis, rubella, cytomegalovirus, herpes)
  - history of fetal distress, pre-eclampsia, or maternal infection
- Delivery history
  - type of delivery and antecedent events
  - Apgar scores

Neonatal Seizures
Etiology

- Hypoxic-ischemic encephalopathy (FT,PT)
  - present within 72 hours of life
- Hemorrhage
  - Subarachnoid (FT)
  - Germinal matrix-intraventricular (PT>FT)
  - Subdural (FT)
- Metabolic (hypoglycemia, hypocalcemia, hypomagnesemia, inborn errors of metabolism)
- Intracranial infections (TORCH, bacterial, herpes)
- Major malformations (lissencephaly, pachygyria, polymicrogyria)
- **Genetics; KCNQ2, SCN2A, KCNT1**

Benign Neonatal Convulsions

SELF-LIMITED NEONATAL SEIZURES
SELF-LIMITED FAMILIAL NEONATAL EPILEPSY

- Onset after birth through day 28 in a healthy infant
- Familial or isolated
- Normal exam and development
- Seizures
  - frequent and brief
  - usually resolve within days but may continue for months
- Status epilepticus
  - common in BNC
  - uncommon in BFNC

SELF-LIMITED FAMILIAL NEONATAL EPILEPSY

- Autosomal dominant
- Voltage-gated potassium channel(KCN) gene defect
- Seizures in the 2nd-3rd day of life
  - tend to persist longer than in BNC
  - disappear by age 2-6 months
  - mainly clonic, sometimes with apneic spells
  - rare tonic seizures
- Normal background
- Favorable outcome but higher risk for subsequent epilepsy

SELF-LIMITED NEONATAL SEIZURES (Fifth-day fits)

- Occur around the fifth day of life (day 1- 7)
- Unknown etiology
- Males > females
- Seizures
  - clonic (partial) and/or apneic
  - resolve within days
- Variable inter-ictal EEG
- Ictal recordings: unilateral or generalized spikes or slow waves
- Diagnosis by exclusion
- Good outcome but increased risk of minor neurological impairment

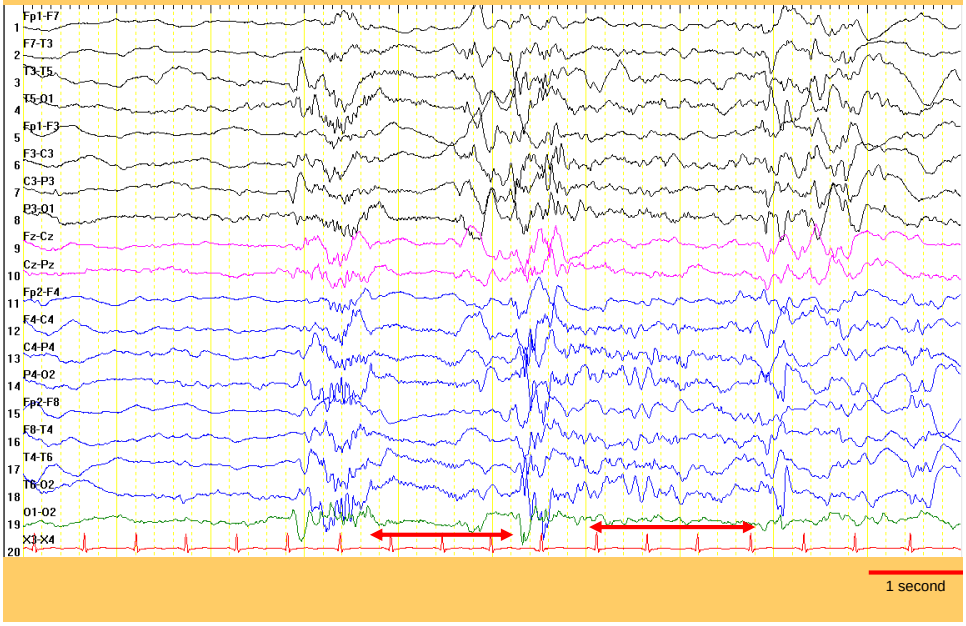
Early Infantile Epileptic Syndromes/Encephalopathies with Suppression-Burst

- Early-Infantile Epileptic Encephalopathy (EIEE: Ohtahara syndrome)
- Early Myoclonic Encephalopathy (EME)

EIEE (Ohtahara Syndrome)

- Newborn or first 3 months of life
- Tonic spasms (isolated or clusters)
- Partial seizures (30-50%)
- Myoclonic seizures (rare)
- EEG: BS pattern (awake/sleep)
- Abnormal neuroimaging
- Resistant to AEDs
- Poor neurodevelopmental outcome

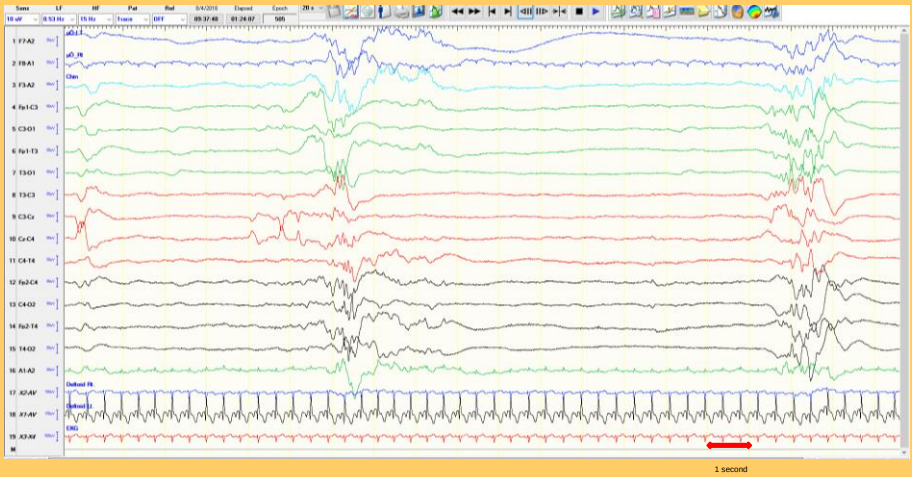
Burst-Suppression



EME

- Mostly within 1 month of birth
- Fragmentary myoclonic seizures
- Partial seizures (frequent)
- Tonic spasms (occasional/transient)
- EEG: BS pattern (enhanced by sleep)
- Inborn error of metabolism
- Intractable to AEDs
- Very poor outcome & high mortality rate

EEG: Suppression-Burst



Different Characteristics

Features	EIEE	EME
Etiology	Brain malformation	Metabolic disorders
Clinical sz	Tonic spasms	Myoclonic/partial
EEG (BS) - Interburst - Circadian cycle - Evolution	 Regular, shorter Sleep⇔Awake →Hypsarrhythmia	 Irregular, longer Predom. Sleep Persist after 1 Y

Different Characteristics

Features	EIEE	EME
Treatment	ACTH, ZNS, etc	Intractable
Sz. evolution	To WS, LGS	Persistent regression
Prognosis	Poor	Extremely poor

West Syndrome

- Epileptic(infantile) spasms
- Delayed development
- EEG- Hypsarrhythmia

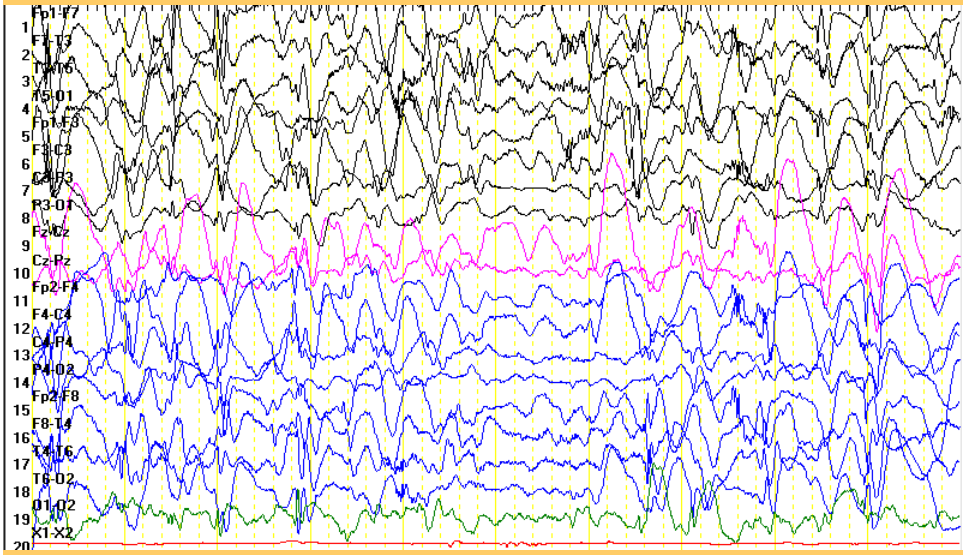
West Syndrome

- Onset 3-7 months of age
- 1.6-4.3 of each 10,000 live birth
- Spasms- flexor, extensor or mixed
- In clusters, frequently during drowsiness/arousal
- EEG: Hypsarrhythmia(chaotic, irregular, diffuse asymmetric, high-voltage, interspersed with sharp waves and spikes)

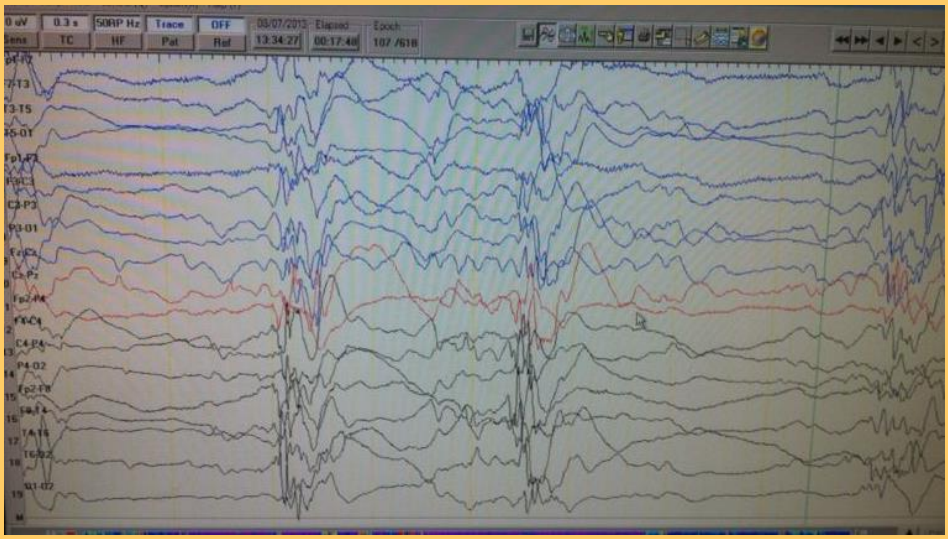
Epileptic(Infantile) Spasms

- Sustained contraction of axial muscles
- Flexion of neck & trunk with abduction and elevation of both arms
- **"Salaam position"**
- Initial movement relatively fast (myoclonic-like)
- Remain in the Salaam position for few seconds before relaxation
- Duration of each spasm: milliseconds to 5-10 seconds
- In **CLUSTER**
- Ictal EEG: Diffuse high-voltage slow followed by background attenuation

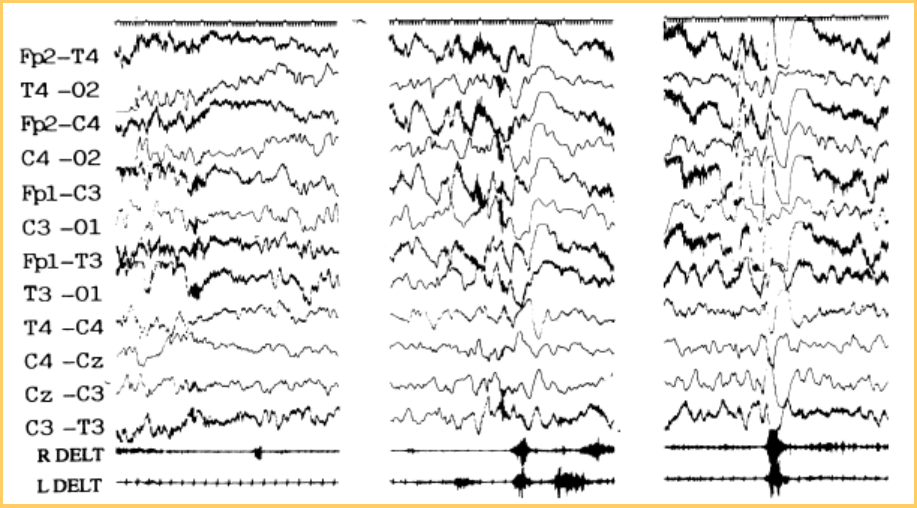
Hypsarrhythmia



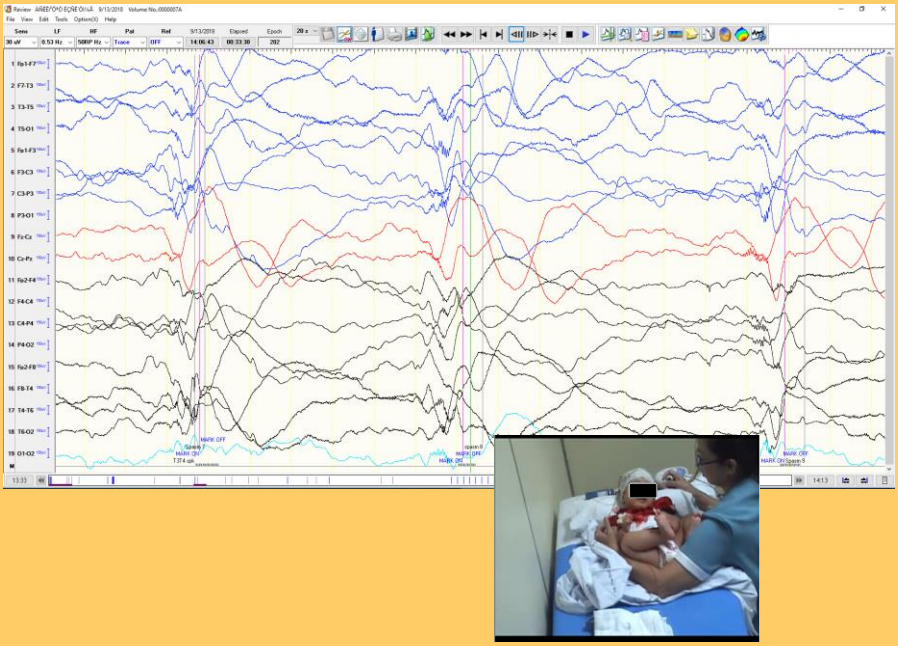
Interictal EEG: Sleep



Ictal EEG and EMG during Spasms



Federico Vigevano, Brain & Development 23 (2001) 467–472



Etiologies in West Syndrome

Causes	Percentage
Brain malformation/ Tuberous sclerosis	35
Perinatal insults	9
Undetermined pre/perinatal factors	19
Infections	2
Hypoglycemia	8
Metabolic causes	9
Idiopathic	18

West Syndrome

- Treatment: ACTH, vigabatrin
- Alternatives: valproic acid, nitrazepam, pyridoxine, lamotrigine, topiramate, zonisamide
- Prognosis α etiologies
  - 1/3 died (30% before 3 years)
  - 2/3 survived
    - 25% normal/slightly impaired
    - 25% need special education
    - 50% uneducable

Myoclonic Epilepsy in Infancy

- 2% of children<3 years with epilepsy
- Neurologically normal
- Onset: 6 months- 2 years
- Family history of epilepsy in 20-25%
- Preceding febrile seizures in 20%
- EEG: gen. SAW or polyspike-waves (drowsiness/early sleep stages) w/photosensitivity
- AEDs: VPA
- Educational difficulties (20-40%)

Severe Myoclonic Epilepsy of Infancy (SMEI)

- "Dravet syndrome", M=F
- 1st year of life (typically 6 months) in a normal child with prolonged, febrile and afebrile, focal (usually hemiclonic) and GTC. (60% with fever)
- Vaccination may be a non-specific trigger to the first seizure.
- Myoclonic and atypical absence seizures: age of 1-4 years.
- Sensitivity of seizures to fever may persist throughout life.
- After the 2nd year of life-cognitive and behavioral impairments.
- Ataxia and pyramidal signs may develop.
- Diagnosis is supported by the mutation in the sodium channel gene SCN1A (found in 75% of cases).
- Sodium channel blockers may aggravate seizures.
- "Developmental & epileptic encephalopathy"

www.epilepsydiagnosis.org.

SMEI: EEG

Background

The background EEG activity is typically normal in the first year of life. Post-ictal slowing may be seen initially, diffuse slowing may appear over time.

Interictal

By the second to fifth year of age, generalized spike-and-wave and multifocal discharges are seen.

Activation

Photic stimulation precipitate generalized spike-and-wave, with or without associated clinical events (atypical absence seizures and/or myoclonic seizures). Photosensitivity can be present in infancy and is seen at all ages. EEG abnormality is enhanced by sleep deprivation and by sleep.

Ictal

The ictal EEG varies according to the type of seizure.

www.epilepsydiagnosis.org.

Severe Myoclonic Epilepsy of Infancy(SMEI)

- Highly intractable to AEDs
  - Useful AEDs: VPA, Benzodiazepines(CNZ, Clobazam, Lorazepam), Stiripentol
  - Alternative: ZNS, VGB, Ketogenic diet
  - CBD oil, Fenfuramine
  - Avoid: LTG, PHT, CBZ
- Prognosis is very poor

Childhood Epilepsy with Centro-temporal Spikes

- Benign Rolandic epilepsy, BECTS
- Most common childhood epilepsy syndrome, 15% to 20% of all epilepsies in children.
- Age of onset 6-9 years
- Nocturnal focal aware seizures
  - Hemifacial sensorimotor seizures with associated gurgling and hypersalivation and speech arrest.
  - Focal to bilateral tonic-clonic seizures (50%)
- ADHD, LD, ID 30%
- Atypical evolutions (9-50%) →LKS, ESES, CSWS

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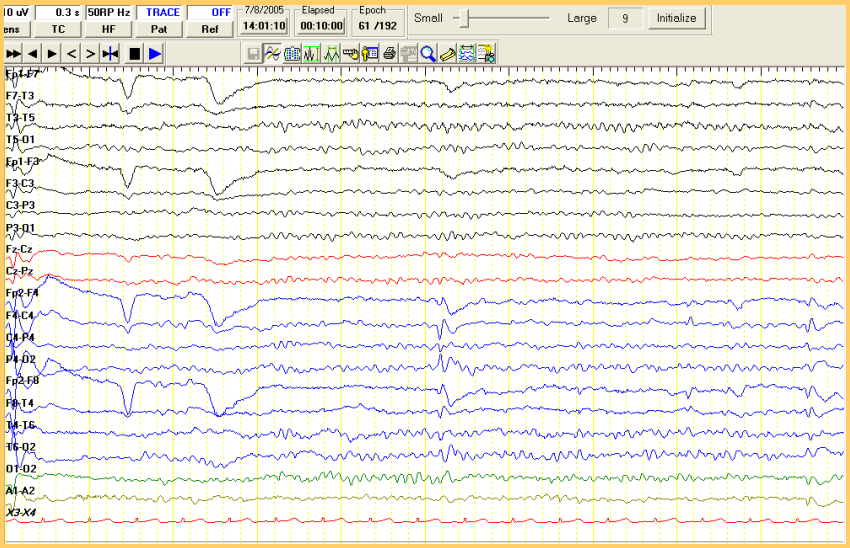
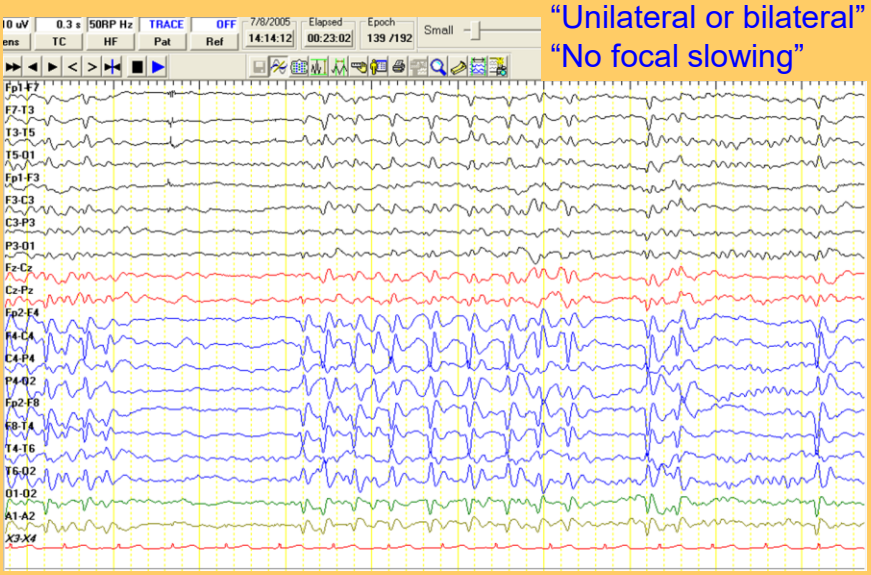
Awake



Sleep

- "Tangential dipole"
- "Unilateral or bilateral"
- "No focal slowing"



Childhood Epilepsy with Centro-temporal Spikes

- Self-limited epilepsy.
- No need ASMs except frequent sz or multiple convulsive sz.
- ASMs: carbamazepine, levetiracetam, and oxcarbazepine, valproate.
- Remission within 2 to 4 years of onset, almost always after puberty.

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Lennox Gastaut Syndrome (LGS)

- Characterized by the
    1. multiple types of intractable seizures (*tonic seizures in sleep)
    2. cognitive and behavioral impairments
    3. diffuse slow SWC and paroxysmal fast activity on EEG
- An 'epileptic encephalopathy'
- Onset of seizures from age 1 to 7 years (peak 3 to 5 years).
- M=F.
- Birth and neonatal history may be normal or a history related to a structural brain abnormality.

Lennox Gastaut Syndrome (LGS)

- Neurological exam and head circumference may be normal or may reflect underlying structural brain abnormality.
- Development and cognition prior to presentation is usually abnormal, but occasionally onset may occur in an otherwise normally developing child.
- Subsequent developmental stagnation or regression is typical after the onset of seizures.
- 10-30% of cases of LGS evolve from earlier onset epilepsy syndromes, including West and Ohtahara syndromes.
- Occasionally there is a history of previous febrile seizures, focal seizures or generalized seizures.

Causes:

- Structural brain abnormalities (most common cause, 70% of cases) e.g. brain anomalies, HIE.
- Genetic etiologies (de novo mutations)

LGS: EEG

Background

- The EEG background is abnormal.
- Generalized or focal slowing.

Interictal

- Focal or multifocal spike-and-wave or sharp-slow waves, with an anterior predominance.
- Slow (<2.5 Hz) SWC and paroxysmal fast activity (10 Hz or greater) in slow sleep are mandatory requirements.
- Periods of suppression of the EEG may occur.

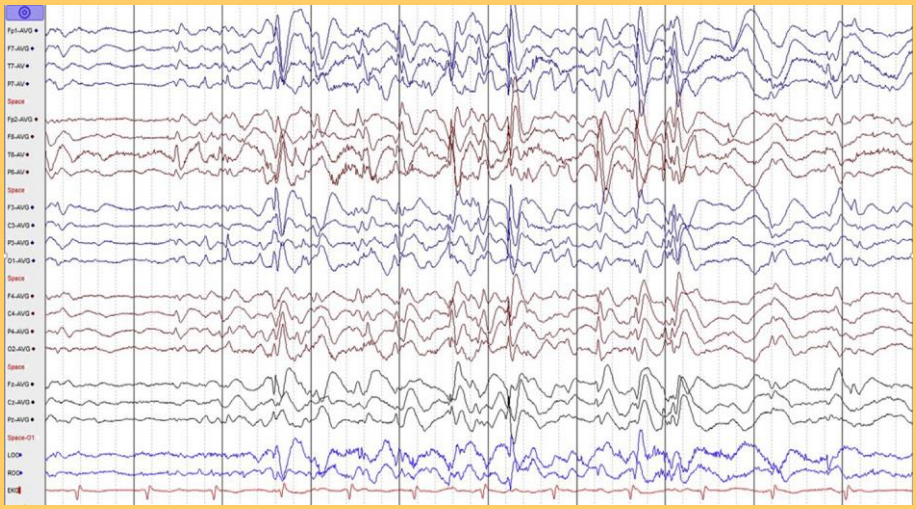
Activation

- Hyperventilation may facilitate SWC and induce atypical absences.
- Focal and multifocal abnormalities seen in the awake state become bisynchronous in sleep.

Ictal

- Along with individual seizure types.

Interictal EEG



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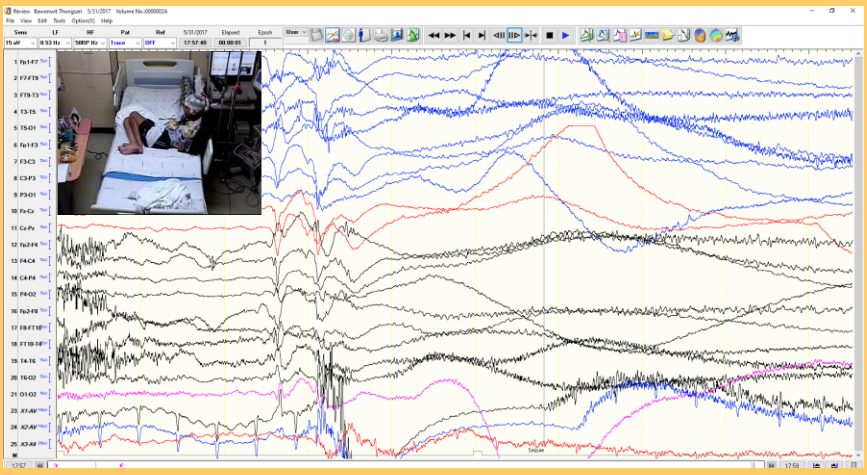
Tonic sz & Ictal EEG



Lennox-Gastaut Syndrome

- **Treatment**
  - Usually intractable, not respond to AED
  - AEDs
    - Valproate, benzodiazepines, lamotrigine
    - Topiramate, levetiracetam, zonisamide
    - Rufinamide, CBD oil
  - Surgery
    - VNS, corpus callosotomy, lobectomy
  - Ketogenic diet

Childhood Absence Epilepsy

- Clinical criteria
  - Inclusion
    - Frequent (many per day), brief (around 10 s, more than 4 s) typical absences with abrupt and severe consciousness impairment
    - Age of onset between 2-8 years (peak 5 years)
    - Remission occurs before age of 12 years
  - Exclusion
    - Absences with marked eyelid or perioral myoclonus, single or rhythmic limb and trunk myoclonic jerks
    - Absence with mild or not clinically detectable consciousness impairment
    - Other types of epileptic seizures in early stages (infrequent GTCS in adult life may occur in no more than 3% of patients)
    - Stimulus-sensitive absences (photic, pattern, fixation-off sensitive, etc.)

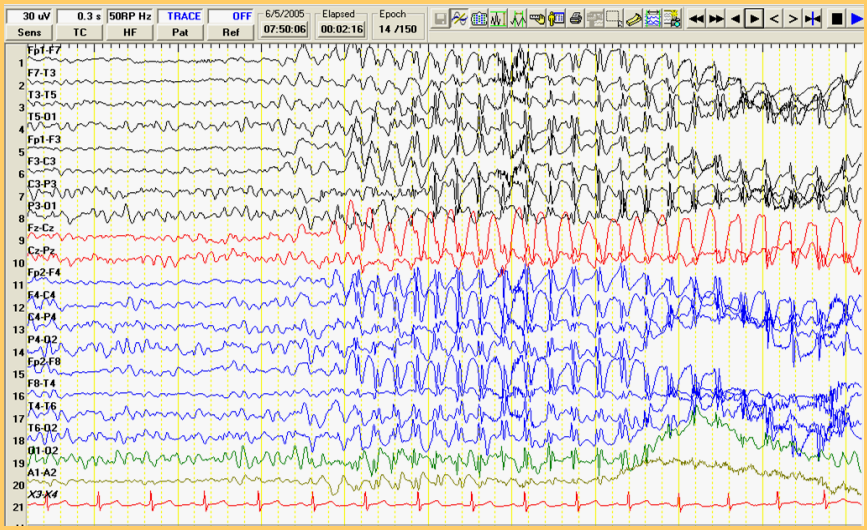
Seizure. 2017;44:53-57.

Childhood Absence Epilepsy

- EEG criteria
  - Inclusion
    - Generalized, spike or double-spike and slow wave regular complexes at 3 Hz (2.7–4 Hz)
  - Exclusion
    - Discharge fragmentation (within one second) and multiple spikes
    - Irregular, arrhythmic spike and multiple spike and slow wave discharges with marked variations of the intradischarge frequency or of the spike and multiple
    - Predominantly brief discharges of less than four second
    - Posterior rhythmic slow activity is accepted and probably favors diagnosis

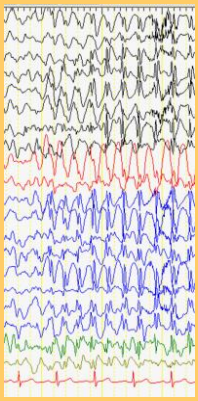
Seizure. 2017;44:53-57.

3 Hz-Generalized Spike-and-wave complexes



Childhood Absence Epilepsy

- Good response to treatment
  - Ethosuximide or valproate
- Favorable prognosis (by age 20)



Thank You for Your Attention

http://www.epilepsydiagnosis.org/