Generalized Epilepsy Syndrome

Chaiyos Khongkhatithum, MD
Division of Neurology
Department of Pediatrics
Faculty of Medicine Ramathibodi Hospital

Infancy-Early Childhood

- Myoclonic epilepsy of infancy
- Severe myoclonic epilepsy of infancy (SMEI)
- Lennox Gastaut syndrome

Myoclonic Epilepsy in Infancy

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

Severe Myoclonic Epilepsy of Infancy (SMEI)

Background

- Dravet syndrome (severe myoclonic epilepsy of infancy, SMEI),

- presents in the 1st year of life (typically 6 months) in a normal child with prolonged, febrile and afebrile, focal (usually hemiclonic) and generalized tonic-clonic seizures.

- Tonic seizures and epileptic spasms are not expected

- Other seizure types including myoclonic and atypical absence seizures appear between the age of 1 and 4 years. Seizures are usually intractable and

- from the 2nd year of life- cognitive and behavioral impairments.

- The clinical diagnosis is supported by the presence of abnormalities in the sodium channel gene SCN1A (found in 75% of cases).

-May be considered an 'epileptic encephalopathy'.

Severe Myoclonic Epilepsy of Infancy (SMEI)

Clinical context

- Both sexes are affected.
- Birth and neonatal history is normal. The first seizure is associated with a fever in about 60% of cases. Not all patients start with febrile convulsions.
- Immunization may be a non-specific trigger to the first seizure
- Sensitivity of seizures to fever may persist throughout life.
- Head size and neurological examination are usually normal initially, over time ataxia and pyramidal signs may develop. Development is typically normal in the first year of life, with plateauing or regression in later years.
- Sodium channel blockers may aggravate seizures.

Severe Myoclonic Epilepsy of Infancy (SMEI)

GENETICS

PATTERN OF INHERITANCE

- SCN1A mutations, 95% are de novo and 5% are inherited.
- Carrier relatives are either unaffected or mildly affected with genetic epilepsy with febrile seizures plus phenotypes. Germline and somatic mosaicism have been reported.

KNOWN GENES

- 75% of patients with Dravet syndrome have mutations or copy number variants in SCN1A.
- A small percentage of females have mutations in the PCDH19 gene. These females usually have clusters of seizures with fever as opposed to the prolonged status epilepticus with fever that occurs in SCN1A.

FAMILY HISTORY OF SEIZURES/EPILEPSY

A family history of epilepsy and/or febrile seizures is present in 30-50% of patients.

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.

SMEI: DDx

- Febrile seizures plus (FS+)
- Genetic epilepsy with febrile seizures plus(GEFS+)
- Epilepsy with myoclonic-atonic seizures
- Lennox-Gastaut syndrome

Lennox Gastaut Syndrome (LGS)

OVERVIEW: characterized by the

1. multiple types of intractable seizures (in particular tonic seizures in sleep, but atonic and atypical absence seizures also occur)

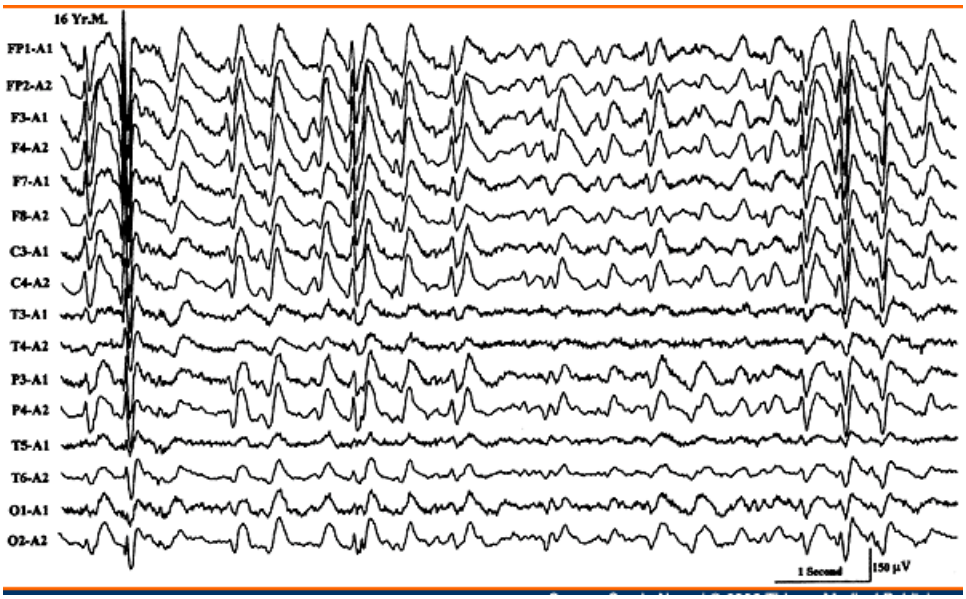
2. cognitive and behavioral impairments and

3. diffuse slow spike-and-wave and paroxysms of fast activity on EEG

- LGS is considered an 'epileptic encephalopathy'
- onset of seizures from age 1 to 7 years (peak 3 to 5 years). Both sexes are affected.
- Antecedent, birth and neonatal history may be normal or a history related to a structural brain abnormality (developmental or acquired).
- 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.
- Around 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 in all cases from onset of seizures, with generalized or focal slowing.

(prominent bi-parietal rhythmic theta- consider epilepsy with myoclonic-atonic seizures)

Interictal

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

Activation

Hyperventilation (if adequate co-operation) may facilitate spike-and-wave and atypical absences.

Slow (<2.5Hz) spike-and-wave and paroxysmal fast activity are prominent in slow sleep.

Focal and multifocal abnormalities seen in the awake state become bisynchronous in sleep.

(If activation with intermittent photic stimulation right arrow consider epilepsy with myoclonic-atonic seizures.)

Ictal

For ictal EEG patterns, refer to individual seizure types.

LGS: DDx

- Dravet syndrome
- Epilepsy with myoclonic-atonic seizures
- Atypical childhood epilepsy with centrotemporal spikes
- Epileptic encephalopathy with continuous spike-and-wave during sleep
- Landau Kleffner syndrome

Lennox-Gastaut Syndrome

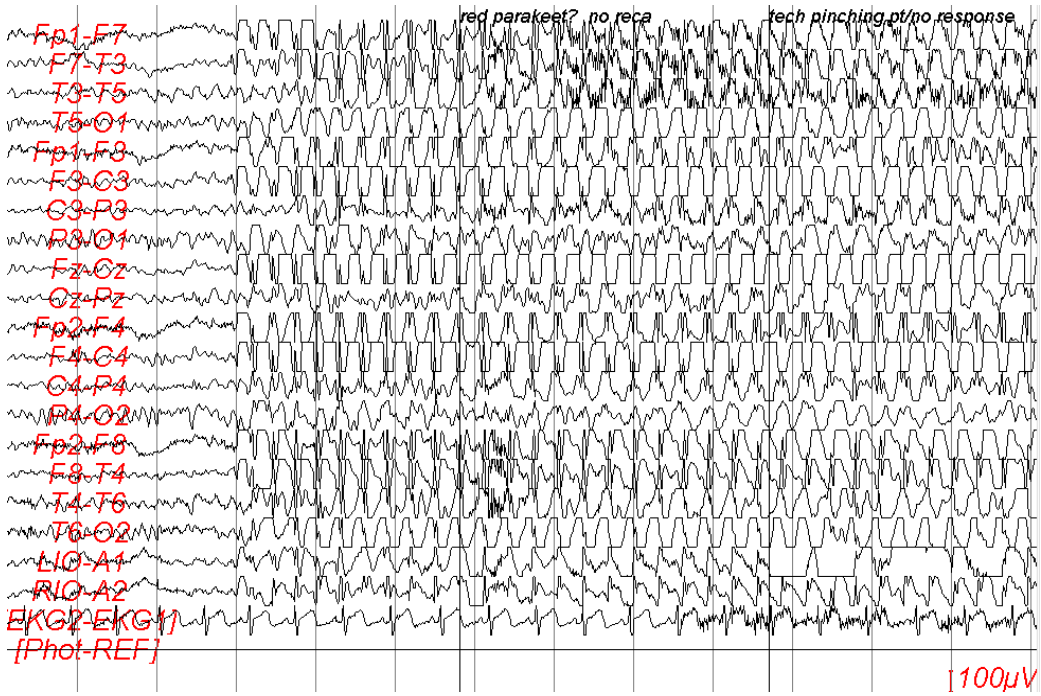
- Treatment
  - Usually intractable, not respond to AED
  - AEDs
    - Valproate, benzodiazepines, lamotrigine
    - Topiramate, levetiracetam, zonisamide
    - Rufinamide, CBD oil
  - Surgical treatment
    - VNS, Corpus callosotomy, lobectomy
  - Ketogenic diet

Childhood-Adolescent

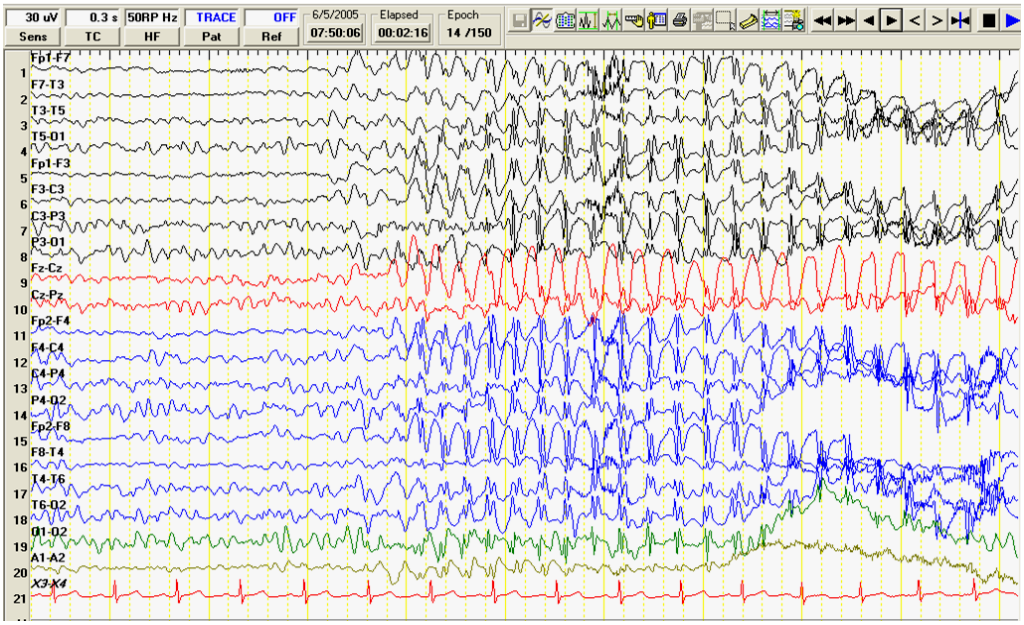
- Childhood/Juvenile Absence epilepsy
- Juvenile Absence epilepsy
- Juvenile Myoclonic epilepsy
- Epilepsy with generalized tonic-clonic seizures alone

Childhood Absence Epilepsy: CAE

- **OVERVIEW**
  - genetic/idiopathic generalized epilepsy
  - normal child with multiple daily absence seizures associated with 2.5 - 3.5 Hz generalized spike-and-wave.
  - Absence seizures are provoked by hyperventilation. Between 8 and 12 years of age the distinction between the clinical syndromes of JAE and CAE depends on the frequency of absence seizures.
- **Clinical context**
  - onset between the ages of 2 to 12 years (peak 5-6 years).
  - Both sexes are equally affected.
  - Antecedent and birth history is normal. A previous history of febrile seizures may occur (seen in 15-20% of cases).
  - Neurological examination, development and cognition are typically normal.
  - Attention deficit hyperactivity disorder and learning difficulty may occur.
  - Seizures are typically self-limiting.
- Onset of absence seizures <4 years → consider glucose transporter disorders (GLUT).

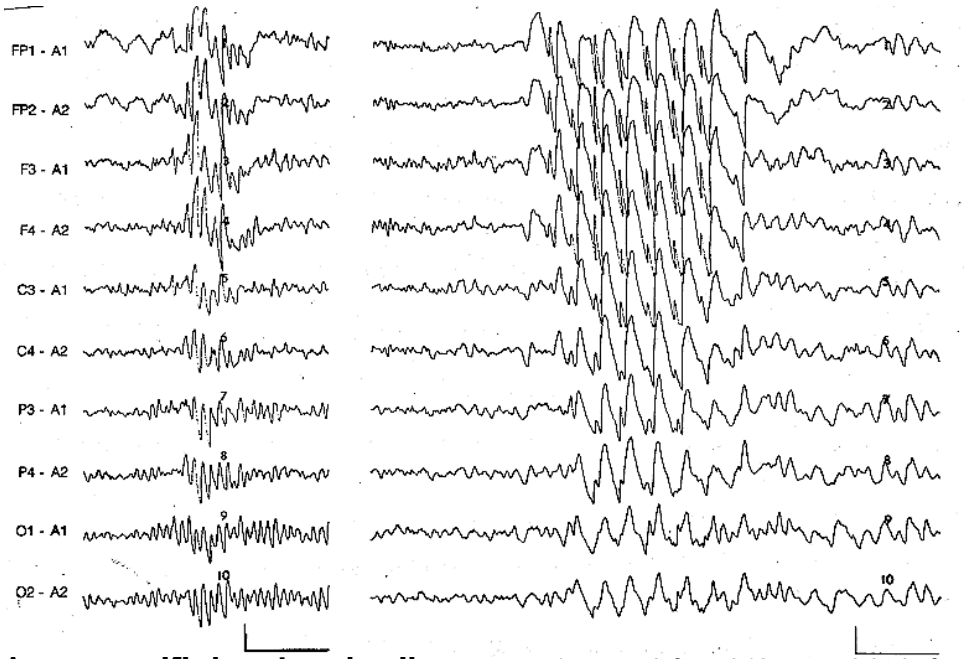


3 Hz-Generalized Spike-and-wave complexes



Generalized Spike-and-Waves Complexes/Discharges

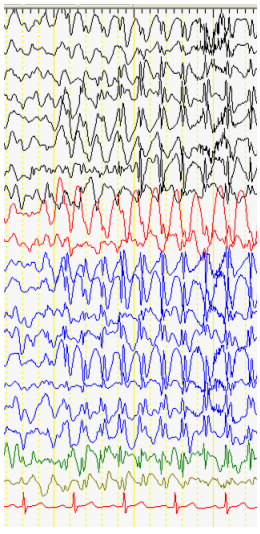
- Bilaterally synchronous spike-wave complexes with repetition rate of 2.5 - 4 Hz.
- Repetition rates slows during long paroxysms.
- Maximum amplitude usually at F3, F4; occasionally posterior.
- Variable anterior-posterior extension.
- May be maximally or exclusively expressed in one hemisphere; such asymmetric shifts.
- Incomplete forms are common.



A **non-specific burst and spike-waves**. 17 years *(left)*, and 18 years *(right)*. Left calibration signal 1 sec, 150uV. Right calibration signal 1 sec, 200uV.

Childhood Absence epilepsy

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



Childhood Absence Epilepsy: Available Evidence

- A total of 8 RCTs examined initial monotherapy of children with Childhood Absence Epilepsy
- Division of trials
  - Class I (n=1)
  - Class II (n=0)
  - Class III (n=7) - 3 Double Blinded

    ESM, LTG, VPA

Childhood Absence Epilepsy: Recommendations

Level A: ESM, VPA

Level B: None

Level C: LTG

Level D: None

Level E: Others

Level F: CBZ, GBP, OXC, PB, PHT,TGB,VGB

Juvenile Absence Epilepsy (JAE)

- Absence seizures are not as frequent as seen in childhood absence epilepsy.
- Loss of awareness may not be complete.
- Occasionally can respond to commands
- Absence status can occur
- GTCs are common (80% of cases), usually in 30 minutes after waking
- If myoclonic seizure presents→ myoclonic absence epilepsy or JME

JAE: EEG

Background

- The background is normal. Occipital intermittent rhythmic delta activity (OIRDA) may be seen.

Interictal

- Generalized spike-and-wave, fragments of generalized spike-and-wave or polyspike-and-wave.

Activation

- Generalized spike-and-wave or polyspike-and-wave and clinical absences are provoked by hyperventilation.

- If hyperventilation is performed well for three minutes and no generalized spike-and-wave is seen, absence seizures are unlikely.

- EEG abnormality is enhanced by sleep deprivation, by sleep and on wakening. Generalized spike-and-wave often becomes fragmented with sleep deprivation or in sleep.

Ictal

- Regular 3-6 Hz generalized spike-and-wave or polyspike-and-wave occurs with absence seizures.

- With generalized tonic-clonic seizures the ictal EEG is often obscured by artifact. Generalized fast rhythmic spikes are seen in the tonic stage, in the clonic phase bursts of spikes and after-coming slow waves are synchronous with clonic jerks. A postictal period of irregular slow activity follows generalized convulsions.

JAE: Genetics

GENETICS

PATTERN OF INHERITANCE

Complex/polygenic inheritance.

KNOWN GENES

Genes linked to this syndrome include GABRG2, CACNA1A and others.

FAMILY HISTORY OF SEIZURES/EPILEPSY

A family history is occasionally present, typically family members having a related genetic/idiopathic generalized epilepsy

JAE: DDx

- Juvenile myoclonic epilepsy - the presence of myoclonic seizures distinguishes juvenile absence epilepsy from this syndrome
- Childhood absence epilepsy - frequent (multiple daily) absence seizures in a child < 12 years of age
- Epilepsy with eyelid myoclonias - repetitive, rhythmic, fast >4 Hz jerks of the eyelids, with upward deviation of the eyeballs and with head extension; seizures are very frequent
- Epilepsy with myoclonic absences - 3 Hz myoclonic jerks of upper limbs with tonic abduction

JME

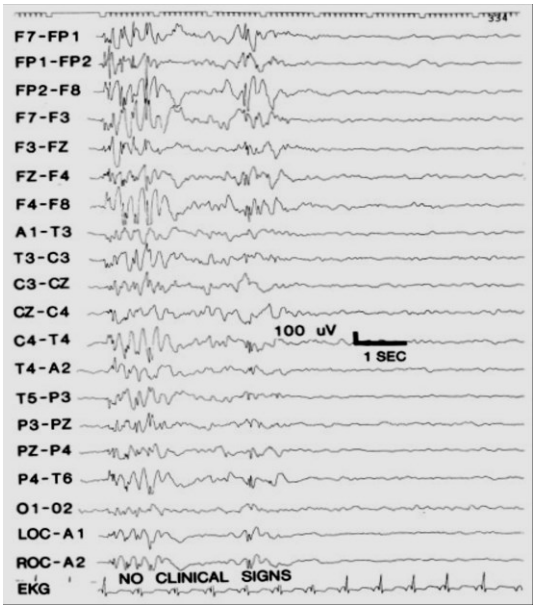
OVERVIEW

- One of the most common genetic/idiopathic generalized epilepsies
- Myoclonic and generalized tonic-clonic seizures in an otherwise normal adolescent or adult.
- EEG shows generalized spike-and-wave and polyspike-and-wave.
- Photosensitivity is common.

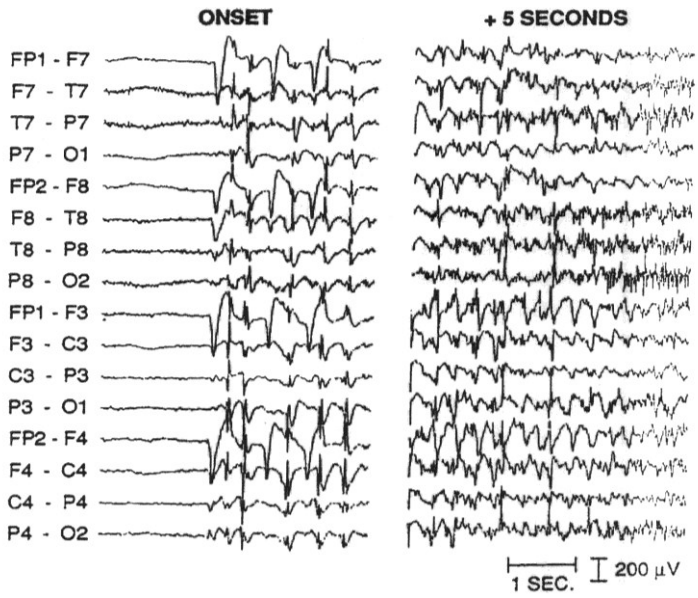
Clinical context

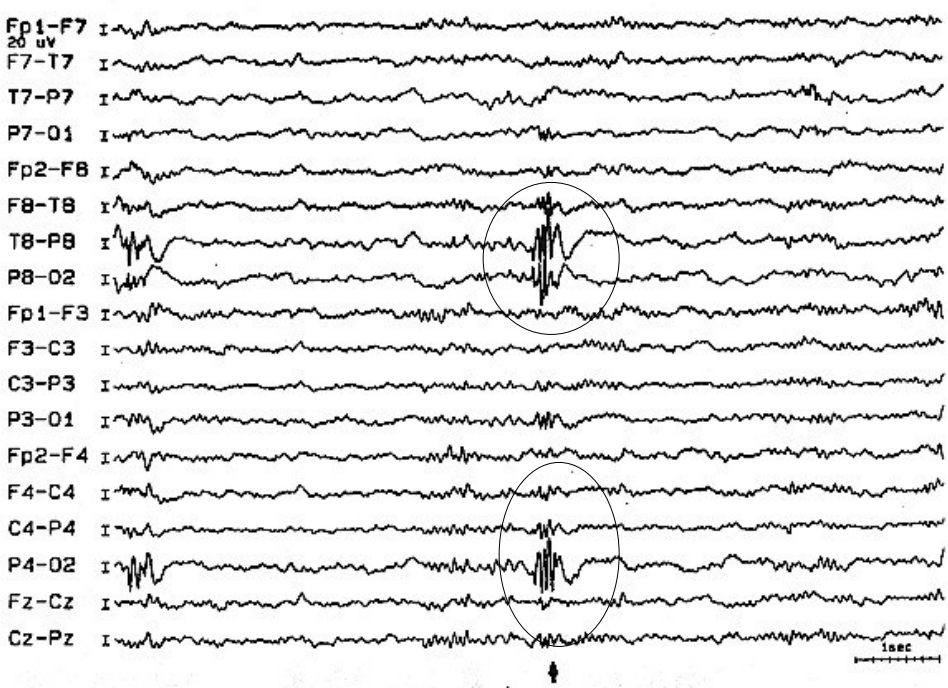
- Onset between 8 to 25 years of age.
- 5% of cases evolving from childhood absence epilepsy.
- Both males and females are equally affected.
- Antecedent and birth history is normal.
- Development and cognition are typically normal.
- Neurological examination and head size are normal.
- Febrile seizures is seen in 5-10%.
- Good prognosis with treatment, usually life-long

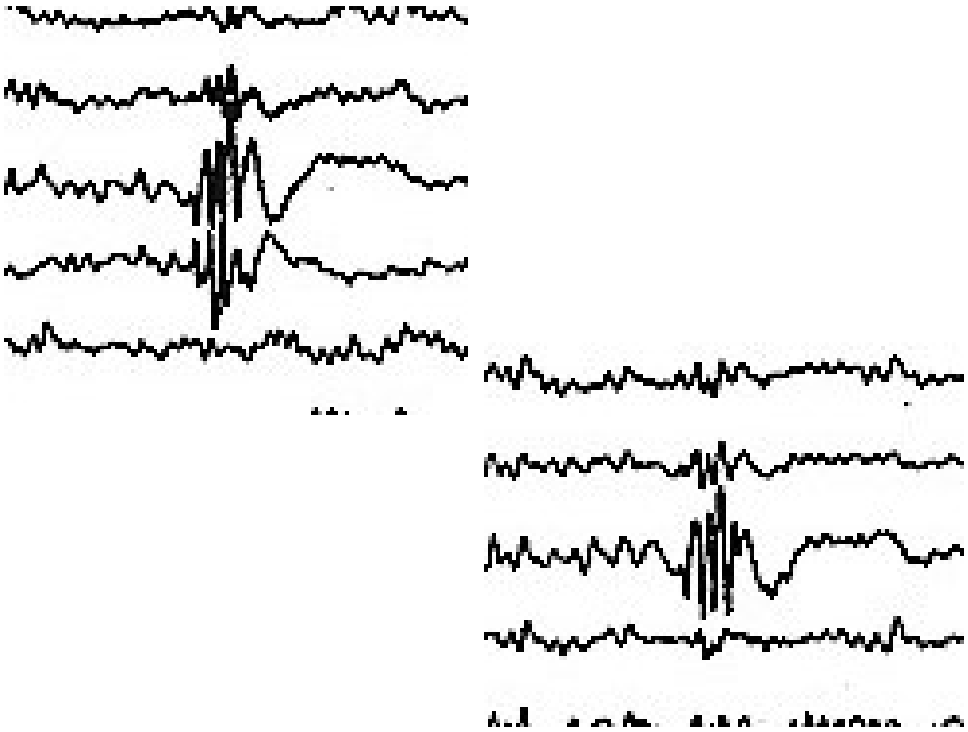
Polyspike-and slow wave discharges



Cluster of myoclonic jerks







JME

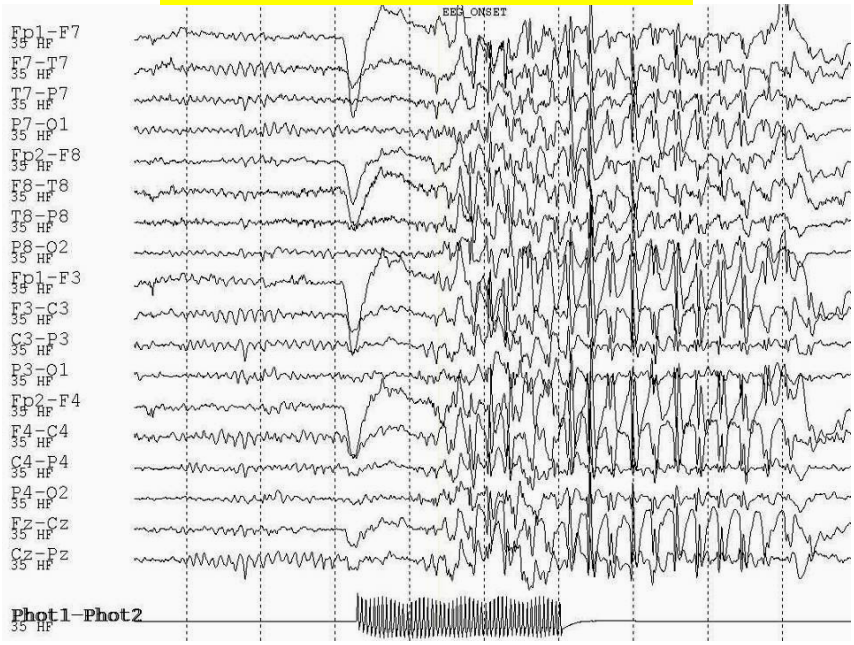
Seizures

- Myoclonic seizures- distal part of limbs, usually upon awakening (0.5-1 hour)
- Myoclonic status epilepticus can occur.
- GTC in 90% of cases, usually preceded by series of myoclonic jerks
- Absence seizure in 1/3 of cases (briefer; 3 seconds, less frequent (<daily) and less impairment of awareness compared to CAE or JAE.
- Seizures induced by visual stimuli, sleep deprivation, alcohol intake, fatigue

EEG

- Generalized spike-and-wave and polyspike-and-wave, usually at 3.5-6Hz
- Photoparoxysmal response to intermittent photic stimulation is seen in one third of cases
- Generalized spike-and-wave or polyspike-and-wave and clinical absences may be provoked by hyperventilation

Photic Stimulation



Juvenile Myoclonic Epilepsy: Available Evidence

- A total of 0 RCTs examined initial monotherapy of children with Juvenile Myoclonic Epilepsy
- Division of trials
  - Class I (n=0)
  - Class II (n=0)
  - Class IIII (n=1)

Juvenile Myoclonic Epilepsy : Recommendations

Level A: None

Level B: None

Level C: None

Level D: CZP, LTG*, LEV, TPM, VPA, ZNS

Level E: Others

Level F: CBZ*, GBP, OXC*, PHT*, TGB, VGB

*may aggravate myoclonic seizure types, should be used with caution

Juvenile Myoclonic Epilepsy

- Drugs to be avoided
- Clinical evidence has been provided that PHT, CBZ, OXC, VGB, TGB, GBP (PRE?) may aggravate absence and myoclonic seizures
- LTG has been shown to aggravate severe myoclonic epilepsies in infancy and in JME

Level of Evidence III-IV,

Recommendation C

Epilepsy with GTC alone

OVERVIEW

- Previously known as “epilepsy with grand mal seizures on awakening”
- Common genetic/idiopathic generalized epilepsy.
- Infrequent GTC seizures from the second decade of life, typically provoked by sleep deprivation. Exclusively occur upon awakening (1-2 hours)

Clinical context

- Onset between the ages of 5 to 40 years (peak 11-23 years, 80% of cases have their first tonic-clonic in the second decade).
- 20% of cases having more than one seizure per month prior to treatment.
- Treatment is required for life.
- Sleep deprivation, fatigue and alcohol lower threshold for seizures.
- Antecedent and birth history is normal. Family history of same syndrome in 20%.
- Some patients have a previous history of childhood absence epilepsy.
- Neurological examination, development and cognition are typically normal.

Epilepsy with GTC alone: EEG

Background

- Normal.

Interictal

- Generalized spike-and-wave or polyspike-and-wave is seen in the interictal EEG.
- 50% of patients have these abnormalities only in sleep.

Activation

- An intermittent photoparoxysmal response to photic stimulation may be seen.
- EEG abnormality is enhanced by sleep deprivation and in sleep.

Ictal- GTC

- Often obscured by artifact. Generalized fast rhythmic spikes are seen in the tonic stage. Bursts of spikes and after-coming slow waves are synchronous with clonic jerks. A postictal period of irregular slow activity follows.

Thank you for your attention.