MAHIDOL UNIVERSITY
Wisdom of the Land

# Justification of Seizure Management based on EEG Findings: Focusing on Epilepsy Syndromes

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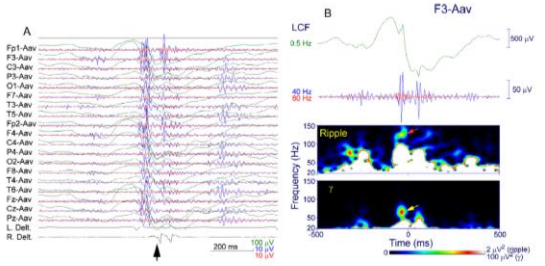
## Myoclonic Seizure

- A single or series of jerks (brief muscle contractions)
- Duration in each jerk: typically milliseconds
- Status epilepticus
  - Myoclonic status epilepticus: ongoing (> 30 minutes) irregular jerking, often with partially retained awareness
  - Generalized clonic seizure:
    - lost of consciousness
    - jerking is sustained & rhythmic
- Myoclonic seizures can result in a "drop attack" (other causes of drop attacks: tonic, atonic, myoclonic-atonic seizures)

https://www.epilepsy.com/article/2016/12/2017-revised-classification-seizures
Robert S. Fisher MD, PhD, Patricia O. Shafer RN, MN, & Carol D'Souza MA Psych on 12/2016

ใช้ประกอบการบรรยายในการประชุมวิชาการ2562-7-31 เพื่อการให้ความรู้ทางการแพทย์ไม่มีการเผยแพร่ในทางพาณิชย์ใด ๆ

Fast oscillations (40-150 HZ) were found to represent at least part of the cortical pathophysiological process in the generation of myoclonic seizures that should involve the thalamocortical network system




The filtered ictal EEG data of a myoclonic seizure (A, black arrow) and corresponding time-frequency analysis in Cz-Aav (B)
Low-cut frequency (LCF) filters were set at 0.5 Hz (green), 40 Hz (blue), and 80 Hz (red).
A ripple blob at 91.8 Hz is indicated by a red arrow in the spectrum (B). Delt., deltoid muscle.

Kobayashi K., et al. Brain Dev 2018;40: 397– 405.

ILAE POSITION PAPER

## ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology

[1,2,3]Ingrid E. Scheffer, [1]Samuel Berkovic, [4]Giuseppe Capovilla, [5]Mary B. Connolly, [6]Jacqueline French, [7]Laura Guilhoto, [8,9]Edouard Hirsch, [10]Satish Jain, [11]Gary W. Mathern, [12]Solomon L. Moshé, [13]Douglas R. Nordli, [14]Emilio Perucca, [15]Torbjörn Tomson, [16]Samuel Wiebe, [17]Yue-Hua Zhang, and [18,19]Sameer M. Zuberi

*Epilepsia*, **(*):1–10, 2017
doi: 10.1111/epi.13709

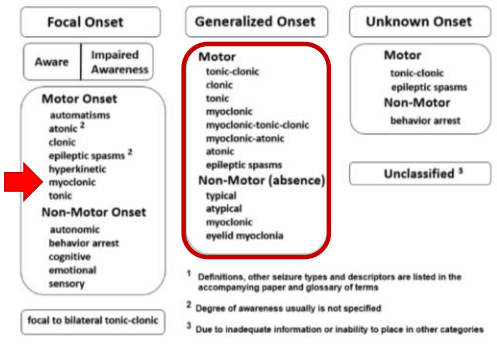
ILAE POSITION PAPER

## Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology

*Robert S. Fisher, †J. Helen Cross, ‡Jacqueline A. French, §Norimichi Higurashi, ¶Edouard Hirsch, #Floor E. Jansen, **Lieven Lagae, ††Solomon L. Moshé, ‡‡Jukka Peltola, §§Eliane Roulet Perez, ¶¶Ingrid E. Scheffer, and ##***Sameer M. Zuberi

*Epilepsia*, **(*):1–9, 2017
doi: 10.1111/epi.13670

## ILAE 2017 Classification of Seizure Types Expanded Version [1]




https://www.epilepsy.com/article/2016/12/2017-revised-classification-seizures

## Myoclonic Seizure: D/Dx.

- Non-epileptic seizures
- Non-epileptic myoclonus
- Movement disorders
- Seizures
  - Myoclonic atonic seizure
  - Atonic seizure
  - Focal motor with negative myoclonus

## Myoclonic Seizure & Related Epilepsy Syndromes: "Infancy"

- Early myoclonic epilepsy
- Myoclonic epilepsy in Infancy
- Metabolic encephalopathy
  - Pyridoxine and pyridoxal-5-phosphate disorders
  - Non-ketotic hyperglyinemia
  - Amino and organic acidopathies
  - Urea cycle disorders
  - Mitochondrial disorders
  - Molybdemum cofactor deficiency
  - Sulfite oxidase deficiency, etc.
- Myoclonic epilepsy in nonprogressive disorders:
  - Structural, chromosomal, genetic, etc.....
- Ohtahara syndrome
- Dravet syndrome

## Myoclonic Seizure & Related Epilepsy Syndromes: "Toddlers & Children"

- Dravet syndrome
- Lennox-Gastaut syndrome
- Epilepsy with myoclonic-atonic seizures
- Epilepsy with myoclonic absence
- Progressive myoclonic epilepsy
- Juvenile myoclonic epilepsy

## Myoclonic Seizure & Related Epilepsy Syndromes

- Early myoclonic epilepsy
- Lennox-Gastaut syndrome
- Dravet syndrome
- Epilepsy with myoclonic-atonic seizures
- Juvenile myoclonic epilepsy
- Progressive myoclonic epilepsy

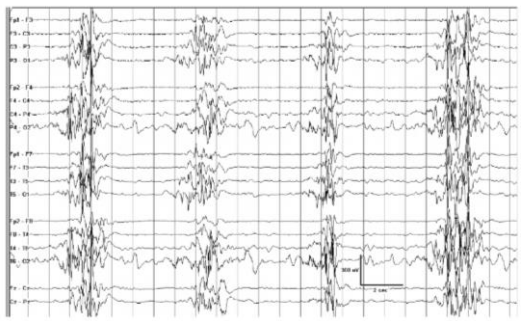
## Early Myoclonic Epilepsy

- Frequent intractable seizures & severe early encephalopathy in the first two month of life (50% in 10 days)
- Seizure:
  - Frequent fragmentary erratic myoclonus, migrating from one part of body towards others, asynchronously
  - In later stage:
    - Focal seizure,
    - Epileptic spasms, or
    - Generalized tonic-clonic

## Early Myoclonic Epilepsy EEG

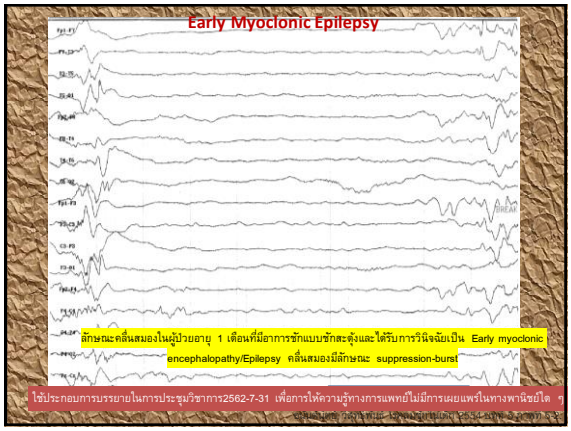
- **Background EEG**
  - Abnormal in all stages
  - With a suppression-burst pattern
  - High voltage bursts (150-300 uV) of spikes or sharp and slow waves, lasting 1-5 sec. with inter-burst intervals of 3-10 sec.
- **EEG**
  - May evolve to hypsarrhythmia pattern (as seen in West syndrome) or multifocal spikes and sharp waves at 3-4 month-old

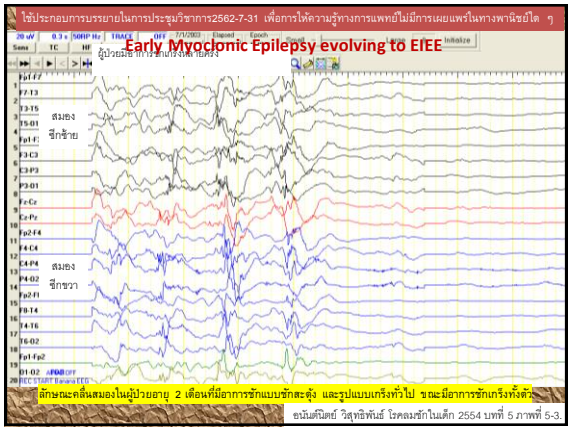
## Early Myoclonic Epilepsy





Korff CM, Nordli DR Jr. Pediatr Neurol. 2006;34(4):253-63




## Lennox-Gastaut Syndrome

- Onset of seizures from age 1 to 7 yrs (peak 3 to 5 yrs)
- Triad
  - Multiple types of intractable seizures (tonic seizure in sleep)
  - Cognitive and behavioral impairments
  - EEG with diffuse slow spike-and-wave and paroxysms of fast activity
- Up to 30% of cases of LGS evolve from earlier onset epilepsy syndromes
- Causes
  - Structural abnormality 70%
  - Genetics and others 30%

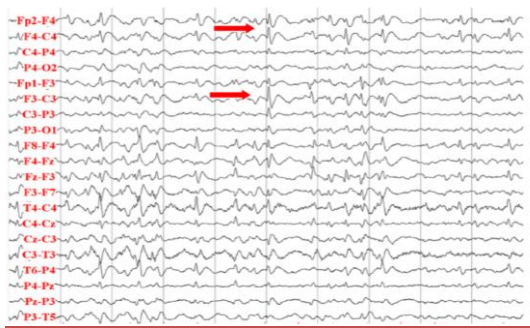
## Lennox-Gastaut Syndrome

- **Seizure type**
  - Tonic seizure in sleep
  - Other seizure types
    - GTC, atypical absence, atonic, focal, epileptic spasms
    - Myoclonic
      (if predominate, consider Dravet syndrome)
    - Myoclonic-atonic
      (if predominate, consider Epilepsy with Myoclonic-atonic seizure)

## Lennox-Gastaut Syndrome

- **EEG background**
  - Abnormal in all cases
  - Generalized or focal slowing
  - Bi-parietal rhythmic theta → Epilepsy with myoclonic-atonic seizure
- **Interictal**
  - Focal or multifocal spike-and-wave or sharp-slow waves (anterior predominance)
  - Slow (<2.5 Hz) spike-and-wave and paroxysmal fast activity (10 Hz or greater) in slow sleep (**A must finding**)
  - Periods of suppression may present
- **Ictal EEG patterns**
  - According to individual seizure types

**Slow spike-wave in Lennox-Gastaut syndrome**

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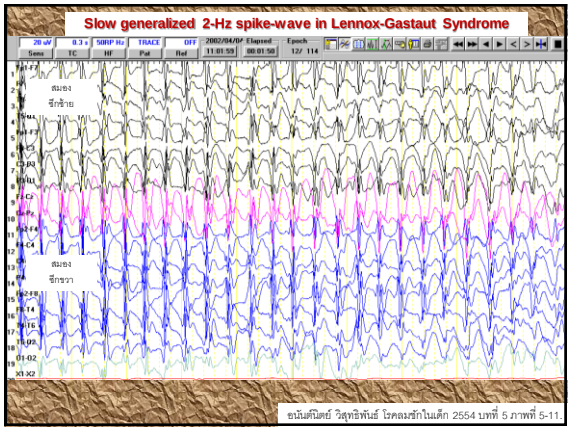
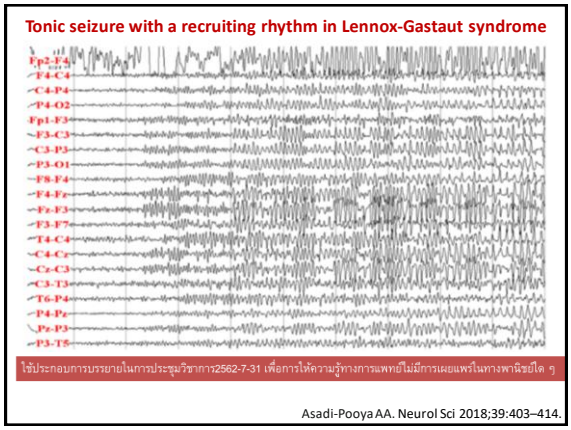
Asadi-Pooya AA. Neurol Sci 2018;39:403–414.




## Dravet Syndrome

### (Severe Myoclonic Epilepsy of Infancy, SMEI)

- Typically presents in the first year of life in a normal child age between 1 - 4 yrs
- Onset of seizures typically around age of 6 mo.
- Prolonged Seizure with febrile and afebrile,
  - Focal (usually **hemiclonic** -> sustained rhythmic jerking rapidly involves one side of the body at seizure onset)
  - Generalized tonic-clonic seizures
  - Other seizure types: myoclonic, atypical absence seizures
- Seizures are usually intractable and from age of one yr
- Cognitive & behavior impairments
- Clinical diagnosis:
  - Abnormalities in Na channel gene SCN1A (75% of cases)

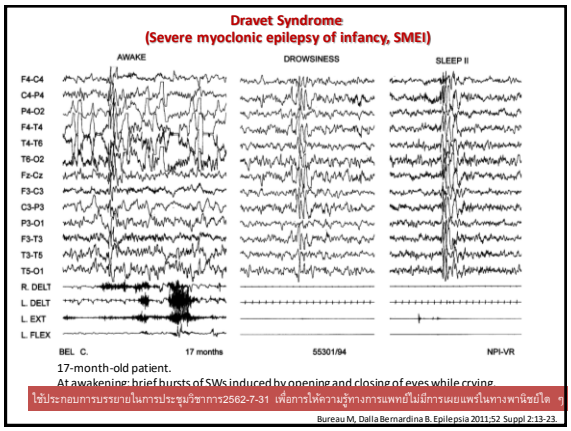
Bureau M, Dalla Bernardina B. Epilepsia 2011;52 Suppl 2:13-23.

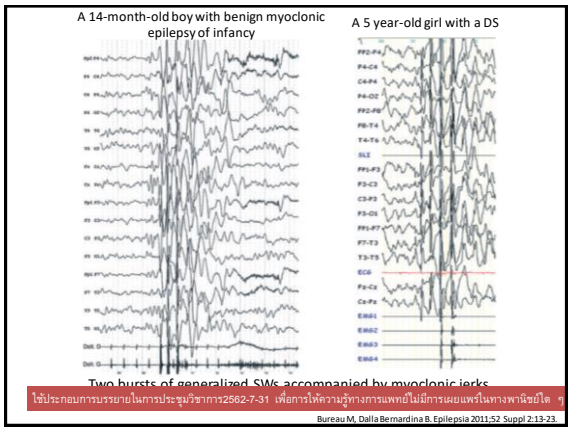
## Dravet Syndrome

### (Severe Myoclonic Epilepsy of Infancy, SMEI)

- **Background EEG**
  - Typically normal in during first year of age
  - Post-ictal slowing at initial stage
  - Diffuse slowing may present
- **Interictal**
  - Generalized spike-and-wave and multifocal discharges
- **Photic and pattern stimulations**
  - Precipitate generalized spike-and-wave, with or without seizure
- **Ictal**
  - According to the type of seizure
  - Should not presence:
    diffuse electrodecremental patterns or paroxysmal fast activity
    **(seen in LGS)**

Bureau M, Dalla Bernardina B. Electroencephalographic characteristics of Dravet syndrome. Epilepsia 2011;52 Suppl 2:13-23.



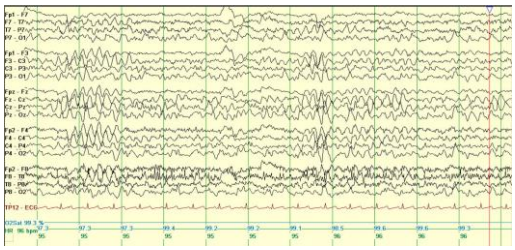
## Epilepsy with Myoclonic-atonic Seizures
**(Epilepsy with myoclonic astatic seizures, Doose syndrome)**

- Onset between 6 mo. and 6 yr. (peak 2 - 4 years)
- 2/3 had febrile seizures and generalized tonic-clonic seizures preceding to onset of myoclonic-atonic / atonic seizures
- Glucose transporter disorders must be considered and excluded

## Epilepsy with Myoclonic-atonic Seizures
**(Epilepsy with myoclonic astatic seizures, Doose syndrome)**

- **Background**
  - May be normal or show generalized slowing. Background bi-parietal theta

## Epilepsy with Myoclonic-atonic Seizures
**(Epilepsy with myoclonic astatic seizures, Doose syndrome)**
"bi-parietal theta"





## Epilepsy with Myoclonic-atonic Seizures
**(Epilepsy with myoclonic astatic seizures, Doose syndrome)**

- **Background**
  - May be normal or show generalized slowing. Background bi-parietal theta
- **Interictal**
  - Generalized spike-and-wave and polyspike-and-wave
- **Photic stimulation**
  - may trigger generalized spike-and-wave and polyspike-and-wave, and myoclonic-atonic seizures
- **Sleep deprivation & sleep**
  - Fragmented generalized spike-and-wave
- **Ictal**
  - Myoclonic component is associated with a generalized spike or polyspikes
  - Atonic component is associated with the after-going high voltage slow wave

ขณะที่ม

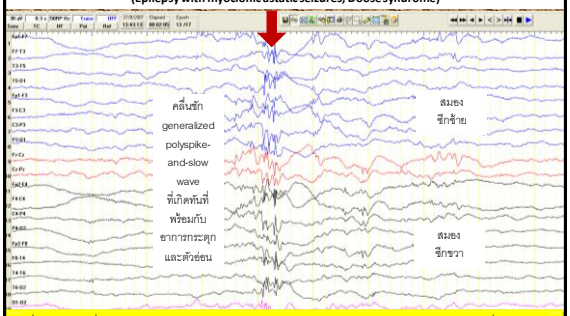
**Epilepsy with Myoclonic-atonic Seizures**
**(Epilepsy with myoclonic astatic seizures, Doose syndrome)**


คลื่นไฟฟ้าสมองที่พบในผู้ป่วยกลุ่มอาการ Doose อายุ 4 ปีพบ generalized polyspike-and-slow wave ความถี่ 2.5 Hz เกิดพร้อมกับอาการชักสะดุ้งและตัวอ่อนทันที ขณะที่หมดอาการชักสะดุ้งและตัวอ่อนทันที

อนันต์นิตย์ วิสุทธิพันธ์ โรคลมชักในเด็ก 2554 บทที่ 5 ภาพที่ 5-11.

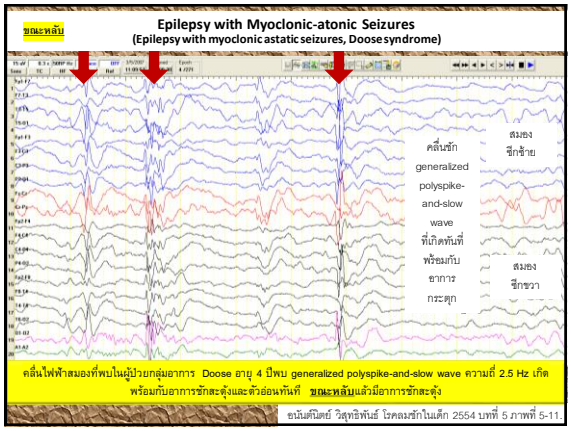
ขณะช่วง

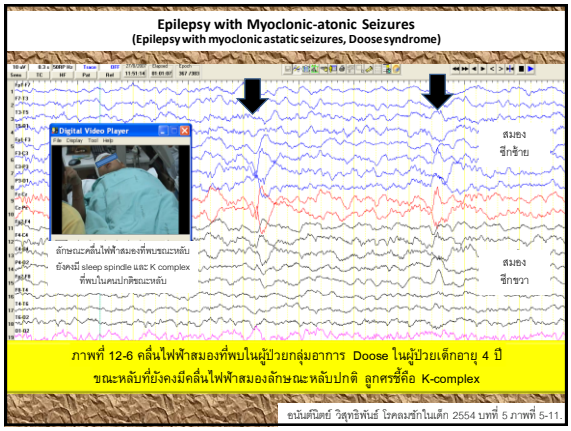
**Epilepsy with Myoclonic-atonic Seizures**
**(Epilepsy with myoclonic astatic seizures, Doose syndrome)**

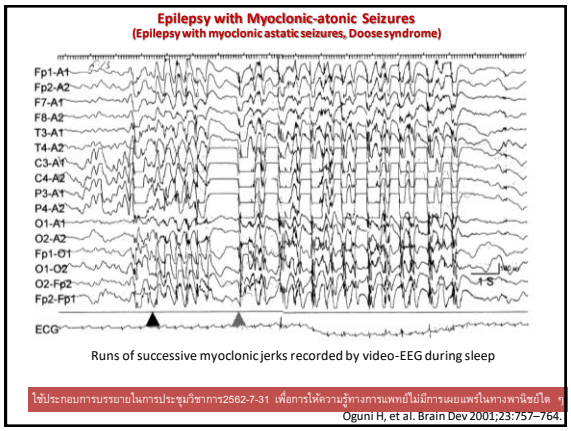


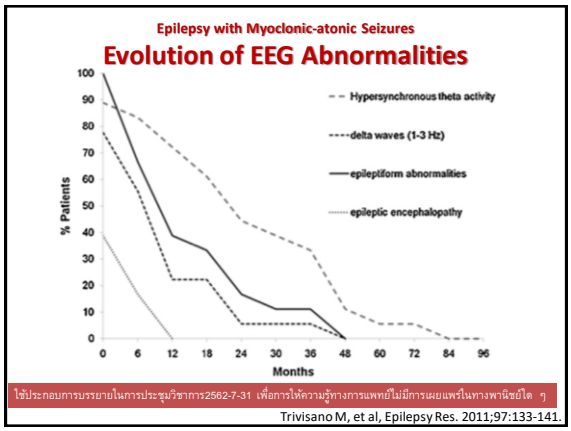

คลื่นไฟฟ้าสมองที่พบในผู้ป่วยกลุ่มอาการ Doose อายุ 4 ปีพบ generalized polyspike-and-slow wave ความถี่ 2.5 Hz เกิดพร้อมกับอาการชักสะดุ้งและตัวอ่อนทันที ขณะช่วงอาการชักสะดุ้งและตัวอ่อนทันที

อนันต์นิตย์ วิสุทธิพันธ์ โรคลมชักในเด็ก 2554 บทที่ 5 ภาพที่ 5-11.




## Juvenile Myoclonic Epilepsy

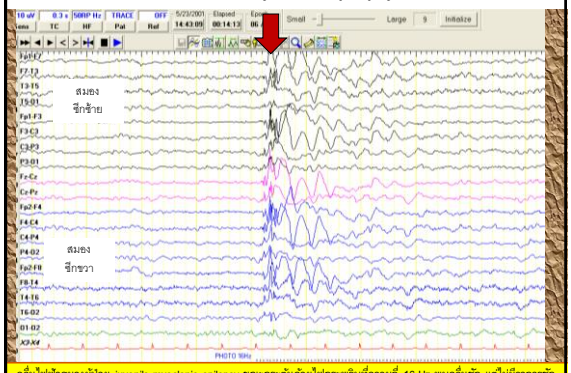
- Characterized by
  - Myoclonic seizures
  - Generalized tonic-clonic seizures
- Onset between 8 (or 10) to 25 years of age
  - Approximately 5% evolve from childhood absence epilepsy
  - Both males & females are equally affected
- Antecedent and birth history: normal
- Development and cognition: typically normal
- Neurological examination and head size: normal
- History of febrile seizures: 5-10%

https://www.epilepsydiagnosis.org/syndrome/jme-overview.html
Yacubian EM. Seizure. 2017;44:48-52.

## Juvenile Myoclonic Epilepsy

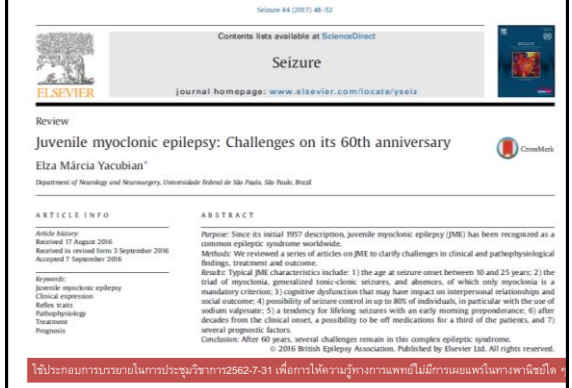
- **Background:** normal
- **Interictal**
  - Generalized spike-and-wave and polyspike-and-wave, usually at 3.5-6Hz
- **Photic stimulation**
  - Photoparoxysmal response in 1/3 of patients
- **Hyperventilation**
  - Generalized spike-and-wave or polyspike-and-wave and clinical absences
- **Ictal**
  - Myoclonic seizure: a single generalized polyspike-and-wave
  - Generalized tonic seizure: generalized fast rhythmic spikes
  - Clonic jerks: bursts of spikes and after-coming slow waves

**Juvenile Myoclonic Epilepsy**




คลื่นไฟฟ้าสมองผู้ป่วย juvenile myoclonic epilepsy ขณะกระตุ้นด้วยไฟกระพริบที่ความถี่ 16 Hz พบคลื่นซัก แต่ไม่มีอาการชัก

ชนันต์นิตย์ วิสุทธิพันธ์ โรคลมชักในเด็ก 2554 บทที่ 5 ภาพที่ 5-10.



Review

Juvenile myoclonic epilepsy: Challenges on its 60th anniversary

Elza Márcia Yacubian*

ABSTRACT

Purpose: Since its initial 1957 description, juvenile myoclonic epilepsy (JME) has been recognized as a common epileptic syndrome worldwide.

Methods: We reviewed a series of articles on JME to clarify challenges in clinical and pathophysiological findings, treatment and outcome.

Results: Typical JME characteristics include: 1) the age at seizure onset between 10 and 25 years; 2) the triad of myoclonia, generalized tonic-clonic seizures, and absences, of which only myoclonia is a mandatory criterion; 3) cognitive dysfunction that may have impact on interpersonal relationships and social outcome; 4) possibility of seizure control in up to 80% of individuals, in particular with the use of sodium valproate; 5) a tendency for lifelong seizures with an early morning preponderance; 6) after decades from the clinical onset, a possibility to be off medications for a third of the patients, and 7) several prognostic factors.

Conclusion: After 60 years, several challenges remain in this complex epileptic syndrome.

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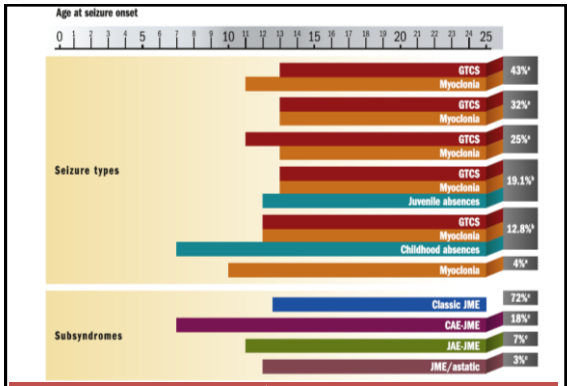
Yacubian EM. Seizure. 2017;44:48-52.

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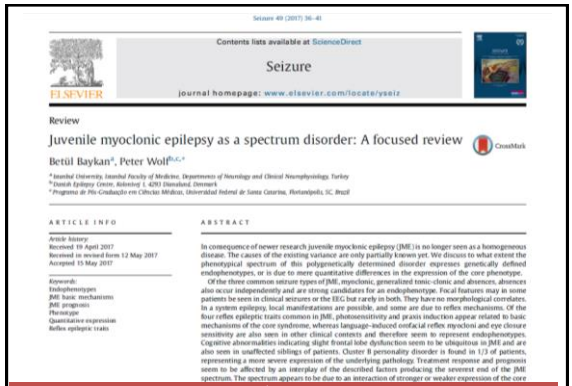

Review

Juvenile myoclonic epilepsy as a spectrum disorder: A focused review

Betül Baykan[a], Peter Wolf[b,c,*]

ABSTRACT

In consequence of newer research juvenile myoclonic epilepsy (JME) is no longer seen as a homogeneous disease. The causes of the existing variance are only partially known yet. We discuss to what extent the phenotypical spectrum of this polygenetically determined disorder expresses genetically defined endophenotypes, or is due to mere quantitative differences in the expression of the core phenotype.

Of the three common seizure types of JME, myoclonic, generalized tonic-clonic and absences, absences also occur independently and are strong candidates for an endophenotype. Focal features may in some patients be seen in clinical seizures or the EEG but rarely in both. They have no morphological correlates. In a system epilepsy, local manifestations are possible, and some are due to reflex mechanisms. Of the four reflex epileptic traits common in JME, photosensitivity and praxis induction appear related to basic mechanisms of the core syndrome, whereas language-induced orofacial reflex myocloni and eye closure sensitivity are also seen in other clinical contexts and therefore seem to represent endophenotypes. Cognitive abnormalities indicating slight frontal lobe dysfunction seem to be ubiquitous in JME and are also seen in unaffected siblings of patients. Cluster B personality disorder is found in 1/3 of patients, representing a more severe expression of the underlying pathology. Treatment response and prognosis seem to be affected by an interplay of the described factors producing the severest end of the JME spectrum. The spectrum appears to be due to an interaction of stronger or weaker expression of the core

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Baykan B, Wolf P. Seizure. 2017;49:48-52.

## Progressive Myoclonus Epilepsy

- Patient with myoclonic seizures, with or without generalized tonic-clonic seizures with
  - Progressive cognitive decline
  - Myoclonus resulting in progressive motor impairment
  - Cerebellar signs
  - Background slowing on EEG (increasing over time)
  - Myoclonus refractory to trials of appropriate AEDs

Genton P, Striano P, Minassian BA. Epileptic Disord. 2016;18(S2):3-10.
Kälviäinen R. Semin Neurol. 2015;35(3):293-9.

## Progressive Myoclonus Epilepsy

- **Neurodegenerative conditions**
  - Unverricht-Lundborg disease, Lafora disease,
  - juvenile neuroaxonal dystrophy, pantothenate-kinase associated neurodegeneration, etc..
- **Metabolic disorders**
  - Mitochondrial disorders (MERRF), mitochondrial disorders (POLG1, MELAS, others),
  - Neuronal ceroid lipofuscinosis, sialidosis, GM2 gangliosidoses, tetrahydrobiopterin deficiency, non-infantile neuronopathic Gaucher's disease and Niemann Pick type C.
  - etc…
- **Immune etiologies**

Genton P, Striano P, Minassian BA. Epileptic Disord. 2016;18(S2):3-10.
Kälviäinen R. Semin Neurol. 2015;35(3):293-9.

## Progressive Myoclonus Epilepsy

- Background may be normal at onset, progressive slowing of the background occurs over time.
- Interictal EEG findings vary and depend on underlying etiology
- Ictal
  - Myoclonic seizure: a single generalized polyspike-and-wave
  - Tonic seizure: generalized fast rhythmic spikes
  - Clonic jerks: bursts of spikes and after-coming slow waves

## Justification of Seizure Management based on EEG Findings: Focusing on Epilepsy Syndromes

- Decision Making
  - Basic knowledge on seizure types, epilepsy syndrome
  - Good history taking and collection of evidence supporting diagnosis
  - Application of EEG recording, pertaining to the context and reality
  - Further stepwise investigations according to differential diagnosis

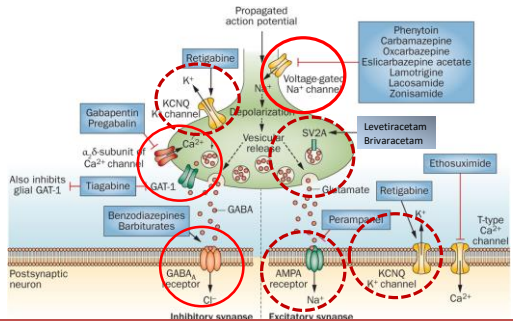
## Diagnostic Investigations in Different Progressive Myoclonus Epilepsies (PMEs)

| | |
|---|---|
| 1. Unverricht–Lundborg disease (EPM1) | Gene test: EPM1 (*CSTB*) mutation analysis |
| 2. Lafora body disease (EPM2) | Skin biopsy: Lafora bodies |
| | Gene tests: EPM2A or EPMP2B(*NHLRC1*) mutation analysis |
| 3. Neuronal ceroid lipofuscinoses (NCL) | Skin biopsy: Granular osmophilic deposit |
| | Leukocyte enzyme analyses: PPT1,TPP1, CTSD |
| | Gene tests: CLN1/*PPT1*, CLN2/*TPP1*, CLN3, CLN4/ *DNAJC5*, CLN5, CLN6, CLN7/*MFSD8*, CLN8, CLN10/*CTSD*, CLN11/*GRN*, CLN12/*ATP13A2*, CLN13/*CTSF*, CLN14/*KCTD7* mutation analysis |
| 4. Sialidosis | Urine: Sialo-oligosaccharides |
| | Leukocyte enzyme analysis: Neuraminidase |
| | Gene test: *NEU1* mutation analysis |
| 5. Myoclonus epilepsy and ragged-red fibers (MERFF) | Plasma lactate and pyruvate |
| | Muscle biopsy: Ragged-red fibers |
| | Gene test: MT-TK mutation analysis |
| 6. Type 3 neuronopathic Gaucher disease | Leukocyte enzyme analysis (β-glucocerebrosidase) |
| | Gene test: GBA mutation analysis |
| 7. Dentatorubral-pallidoluysian atrophy | Gene test: *DRPLA* mutation analysis |
| 8. Action myoclonus-renal failure syndrome (AMRF; EPM4) | Gene test: *SCARB2*/LIMP2 mutation analysis |
| 9. PME-ataxia syndrome (EPM5) | Gene test: *PRICKLE1* mutation analysis |
| 10. North Sea PME (EPM6) | Gene test: *GOSR2* mutation analysis |



Kälviäinen R. Sem Neurol. 2015;35:293–299

## Mechanisms of AEDs






Löscher W., Schmidt D. Nat Rev Neurol. 2012;8:661-2

## AEDs for Treatment of Myoclonic Seizures

| Epileptic Syndrome | Therapy | Remission |
|---|---|---|
| SMEI | VPA,TPM, BZD, Stiripentol,LTG, LEV, PER, KD | Never |
| MAE | VPA, LTG, BZD, LEV, PER, ZNS, KD | Vary (30-100 months) |
| LGS | Polytherapy, KD, Sx | Never |
| JME | VPA, LTG, LEV,PER, TPM , ZNS | With treatment |
| PME | Polytherapy | Never |

Stephani U. Epilepsia 2006;47(Suppl.2):53-55.
Baykan B, Wolf P. Seizure 2017;49:36-41.
Yacubian EM. Seizure 2017;44:36-41.

## Treatment for JME

| Antiepileptic drug | Daily usual doses in adults | Evidence |
|---|---|---|
| Valproate | 400–3000 mg | Most effective choice based on clinical experience; positive psychotropic effects |
| Phenobarbital | 60–180 mg | Before the availability of VPA, efficacy in up to 80% of patients |
| Levetiracetam | 500–3000 mg | Likely to be less efficacious than VPA in controlling absence seizures, which coexist with other seizure types in around 30% of patients with JME |
| Lamotrigine | 100–400 mg | Probably less effective than VPA. Synergistic effect with VPA. May worsen myoclonic seizures |
| Topiramate | 100–400 mg | May be effective in GTCS |
| Zonisamide | 100–500 mg | May be effective in myoclonia and GTCS |
| Perampanel | 6–12 mg | May be effective as adjunctive in GTCS |
| Clobazam | 10–40 mg | May be effective as adjunctive |
| Clonazepam | 4–8 mg | May be effective as adjunctive |
| Acetazolamide | 500–1000 mg | May be effective as adjunctive |



Yacubian EM. Seizure. 2017;44:48-52

## Treatment of PME

| Drugs useful in progressive myoclonic epilepsies | Drugs that exacerbate myoclonus |
|---|---|
| Sodium valproate* | Lamotrigine |
| Levetiracetam | Phenytoin |
| Topiramate | Carbamazepine |
| Clonazepam | Oxcarbazepine |
| Zonisamide | Tiagabine |
| Phenobarbital | Vigabatrin |

*Avoid valproate in myoclonic epilepsy with ragged-red fibres.

Malek N, et al. Pract Neurol 2015;15:164–171.

## Treatment Options in Common Encephalopathic Epilepsy Syndromes

| Epilepsy Syndrome | Hx Rx | US FDA Approved | Experiment Rx |
|---|---|---|---|
| West syndrome | ACTH gel, Vigabatrin | ACTH gel, Vigabatrin | **Cannabidiol** |
| Dravet Syndrome | Valproate, Stiripentol, Clobazam, Topiramate | | **Cannabidiol,** Fenfluramine, Stiripentol |
| LGS | Valproate | Felbamate, Topiramate, Lamotrigine, Clobazam, Rufinamide | **Cannabidiol** |

Mudigoudar E, et al. Seminar Ped Neurol 2016;23:167-179.

### Selection of AEDs

## "Factors for Decision Making"

- Efficacy on type of seizure
- Efficacy on epilepsy syndrome
- Safety & tolerability
- Pharmacokinetic property
- Availability
- Co-morbidity
- Pre-existing illness
- Cost
- Physician's experiences