Cleveland Clinic

Epilepsies and Electroclinical Syndromes: Adolescents and Adults

2020 Epilepsy Update & Review Course

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Disclosures

None

Objectives

- **Recognize and diagnose electroclinical and epilepsy syndromes in the adolescent and adult**
- **Summarize treatment strategies and prognostic implications in these epilepsy syndromes**

NEONATAL/INFANTILE

- Self-limited neonatal and familial neonatal epilepsy
- Self limited familial and nonfamilial infantile epilepsy
- Early myoclonic encephalopathy
- Ohtahara syndrome
  West Syndrome
- Dravet syndrome
- Myoclonic epilepsy in infancy
- Epilepsy of infancy with migrating focal seizures
- Myoclonic encephalopathy in non-progressive disorders

ADOLESCENT/ADULT

- Juvenile absence epilepsy
- Juvenile myoclonic epilepsy
- Epilepsy with generalized tonic-clonic seizures alone
- Autosomal dominant epilepsy with auditory features
- Other familial temporal lobe epilepsies

CHILDHOOD

- Epilepsy with myoclonic-atonic seizures
- Epilepsy with eyelid myoclonias
- Lennox-Gastaut syndrome
- Childhood absence epilepsy
- Epilepsy with myoclonic absences
- Panayiotopoulos syndrome
- Childhood occipital epilepsy (Gastaut type)
- Photosensitive occipital lobe epilepsy
- Childhood epilepsy with centrotemporal spikes
- Atypical childhood epilepsy with centrotemporal spikes
- Epileptic encephaloapthy with continuous spike-and-wave during sleep
- Landau-Keffner Syndrome
- Autosomal Dominant nocturnal frontal lobe epilepsy

VARIABLE

- Reflex epilepsies
- Progressive myoclonic epilepsies
- Familial focal epilepsy with variable foci

AGE OF ONSET

- Juvenile absence epilepsy (JAE)
- Juvenile myoclonic epilepsy (JME)
- Epilepsy with generalized tonic-clonic seizures alone
- Progressive myoclonic epilepsies
- Autosomal dominant epilepsy with auditory features (ADEAF)
- Other familial temporal lobe epilepsies
- Reflex epilepsy

Road Map

Definitions

- **Generalized seizure** **"**engage or involve networks on both sides of the brain at the onset**"**

- **Epilepsy Syndrome** "cluster of features incorporating seizure types, EEG and imaging features that tend to occur together…often has age-dependent features…seizures triggers, diurnal variation, sometimes prognosis…distinctive comorbidities…It may have associated etiologic, prognostic, and treatment implications."

- Never a formal classification of epilepsy syndromes by ILAE

Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 2017; 58 (4): 522 – 530

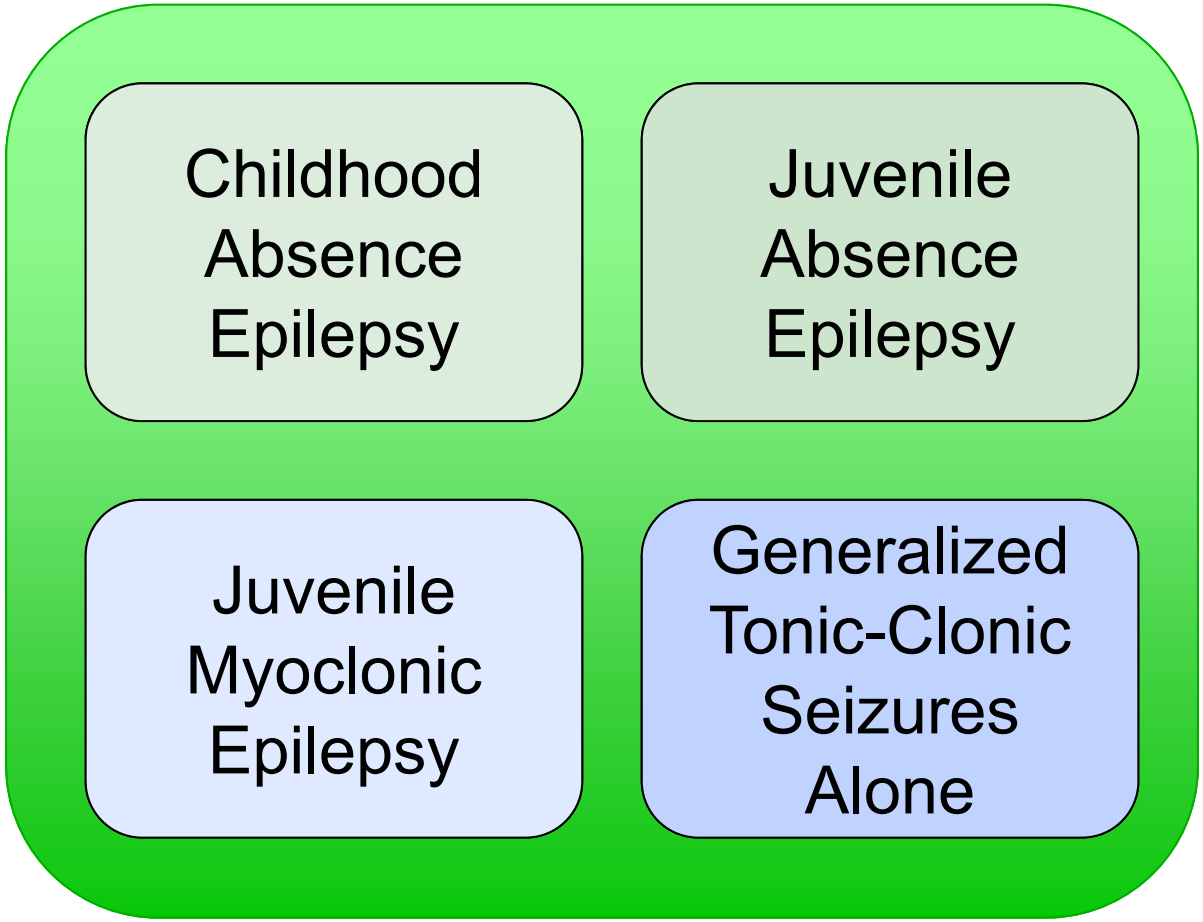
CASE: 12-year-old healthy boy who presents with first convulsive seizure without aura. He has also had weekly staring episodes over the past year that were treated originally as ADHD.

JUVENILE ABSENCE EPILEPSY (JAE)

~~Primary Generalized Epilepsies (PGE)~~

~~Idiopathic Generalized Epilepsies (IGE)~~

Genetic Generalized Epilepsy (GGE)



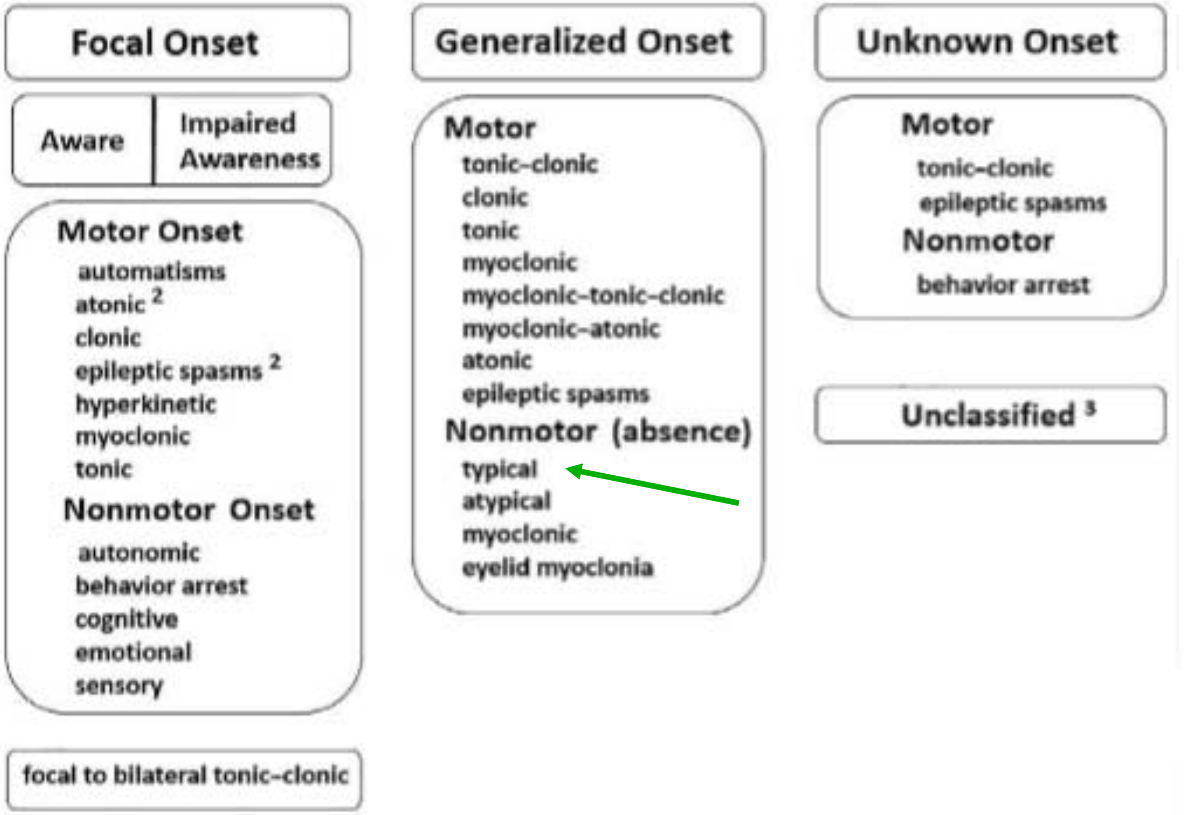
ILAE POSITION PAPER

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, 58(4):522–530, 2017
doi: 10.1111/epi.13670

ILAE 2017 Classification of Seizure Types Expanded Version [1]

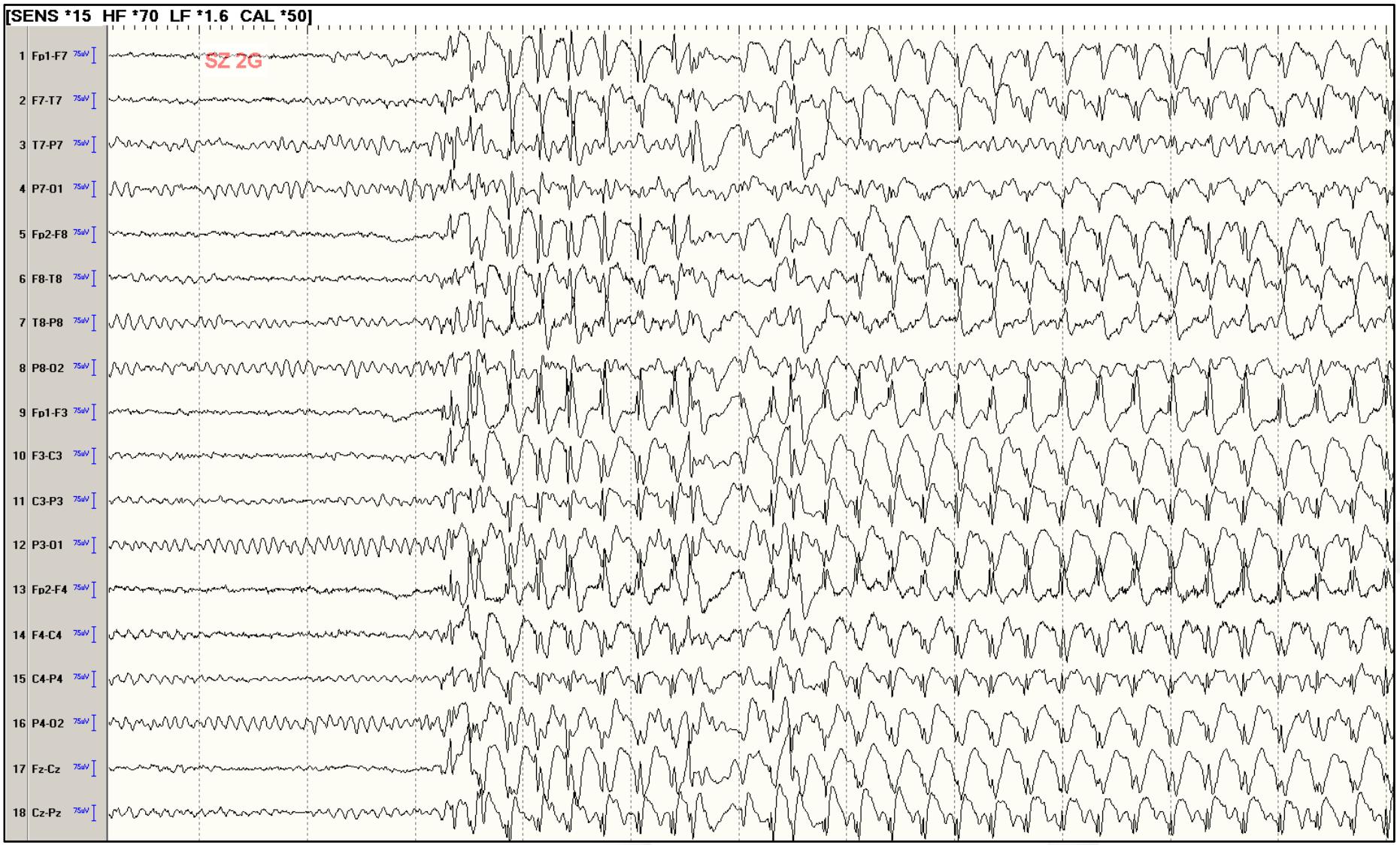


Juvenile Absence Epilepsy

- Development: normal
- Onset: around puberty, 8 to 16 years (peak 10-12)
- Seizure Types:
  - Absence seizures predominate but not as frequent as CAE and not typically triggered by hyperventilation
  - GTC seizure
  - Rare myoclonic seizures
- Can be inherited (positive family history in 1/3)

JAE Electrical Features

Generalized spike wave complexes 3 to 4 Hz



JAE Electrical Features

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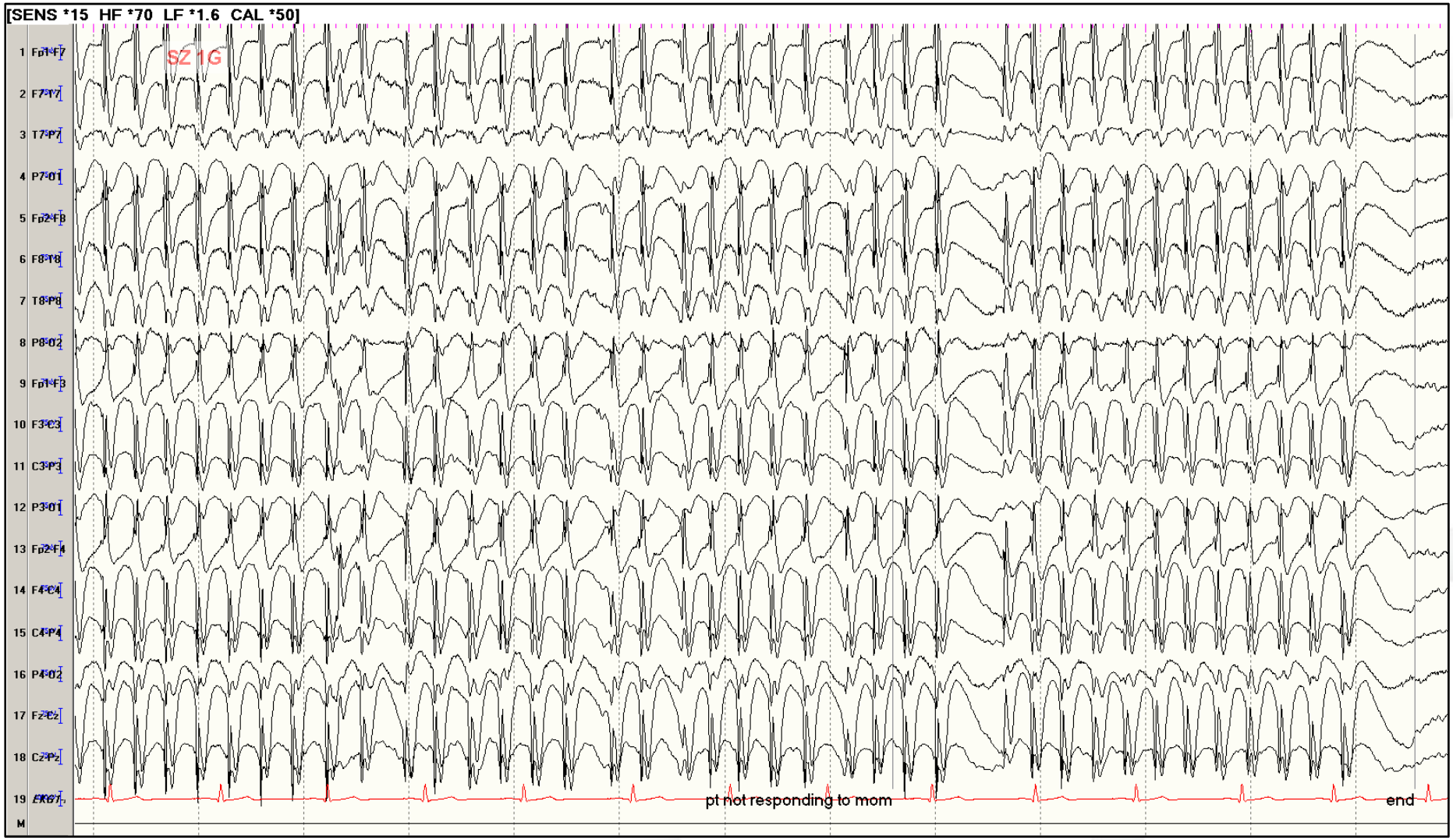


CASE: 16-year-old healthy girl who presents with first convulsive seizure at school after staying up until 3am studying for an exam. On further history you find she has been having morning myoclonic jerks for a while and that she has to close her eyes for flashing lights as they make her feel “jumpy”.

JUVENILE MYOCLONIC EPILEPSY (JME)

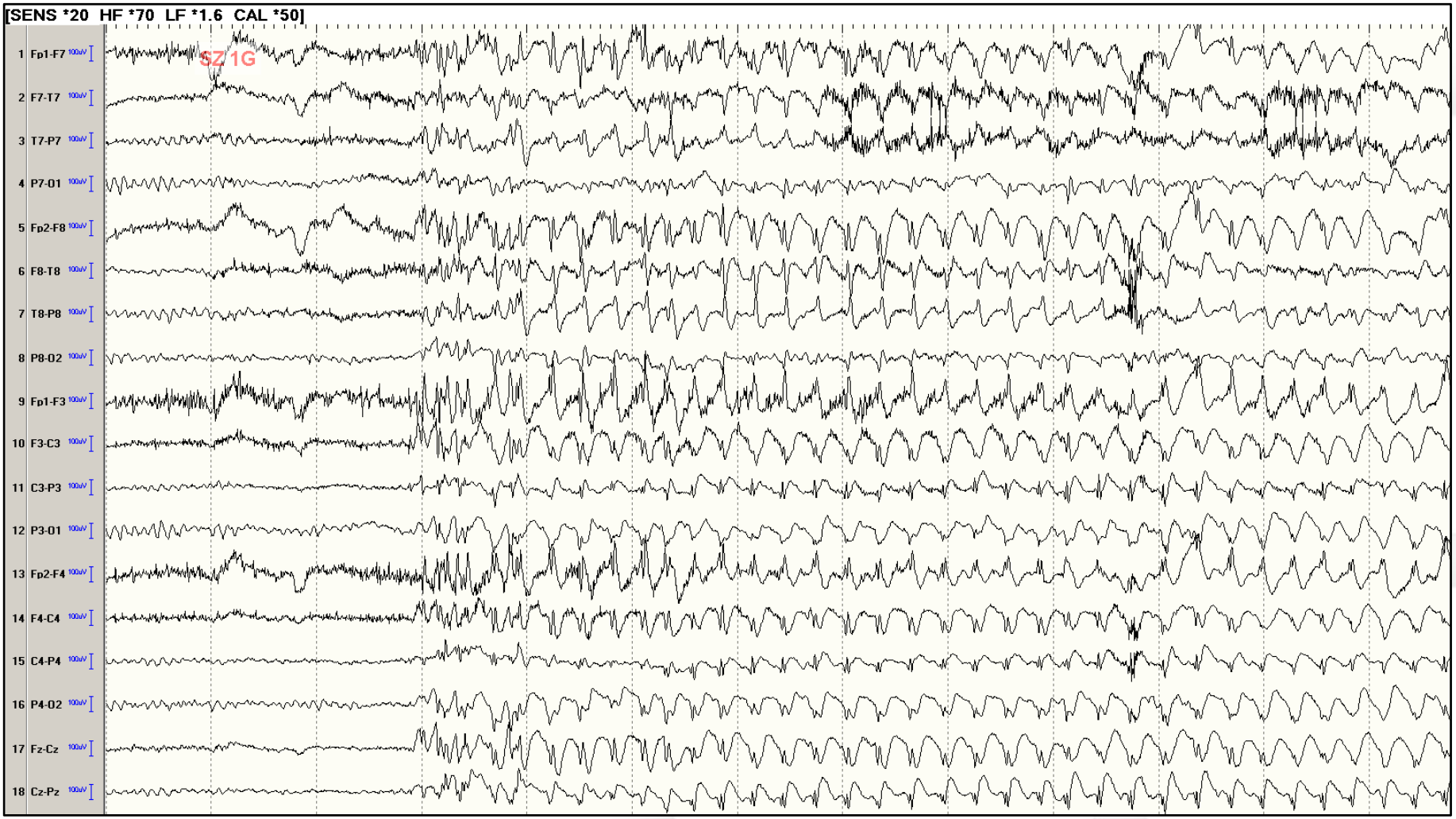
Juvenile Myoclonic Epilepsy

- Development: normal
- Onset: Later adolescence, 12 to 18 years (peak 15)
- Seizure Types:
  - Myoclonic seizures
    - Upper extremity prominence, typically extensors
    - Single or repetitive
  - GTC seizures
  - Absence in 1/3 but infrequent[1]
- Can be inherited (positive family history in 1/3)
- Sensitivity to light, sleep deprivation, alcohol
- Often requires long term treatment

[1]Panayiotopoulos CP, et al. Absences in juvenile myoclonic epilepsy: a clinical and video-electroencephalographic study. *Ann Neurol* 1989;25(4): 391 - 397

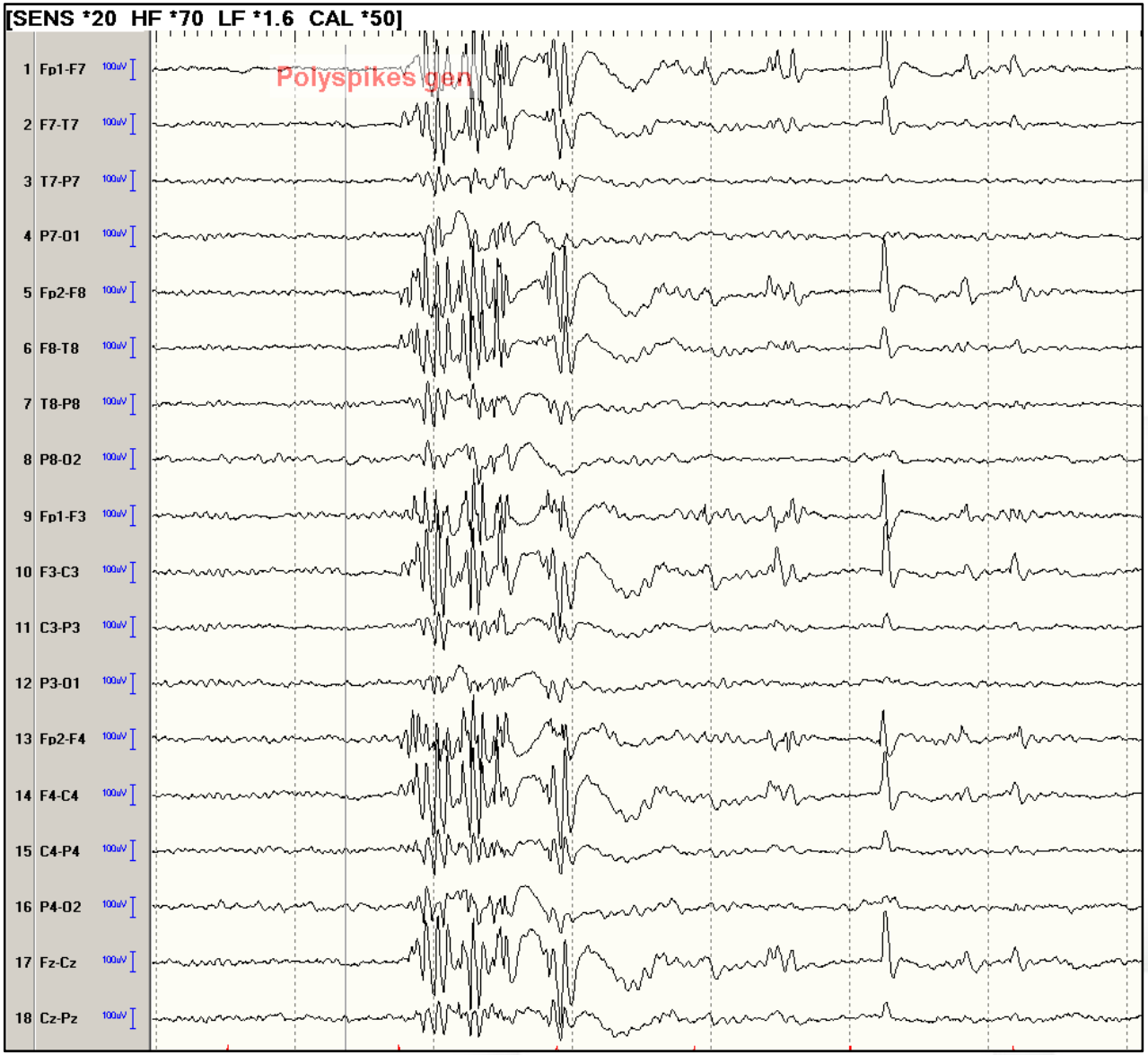
JME Electrical Features

Generalized spike wave complex, often polyspike components



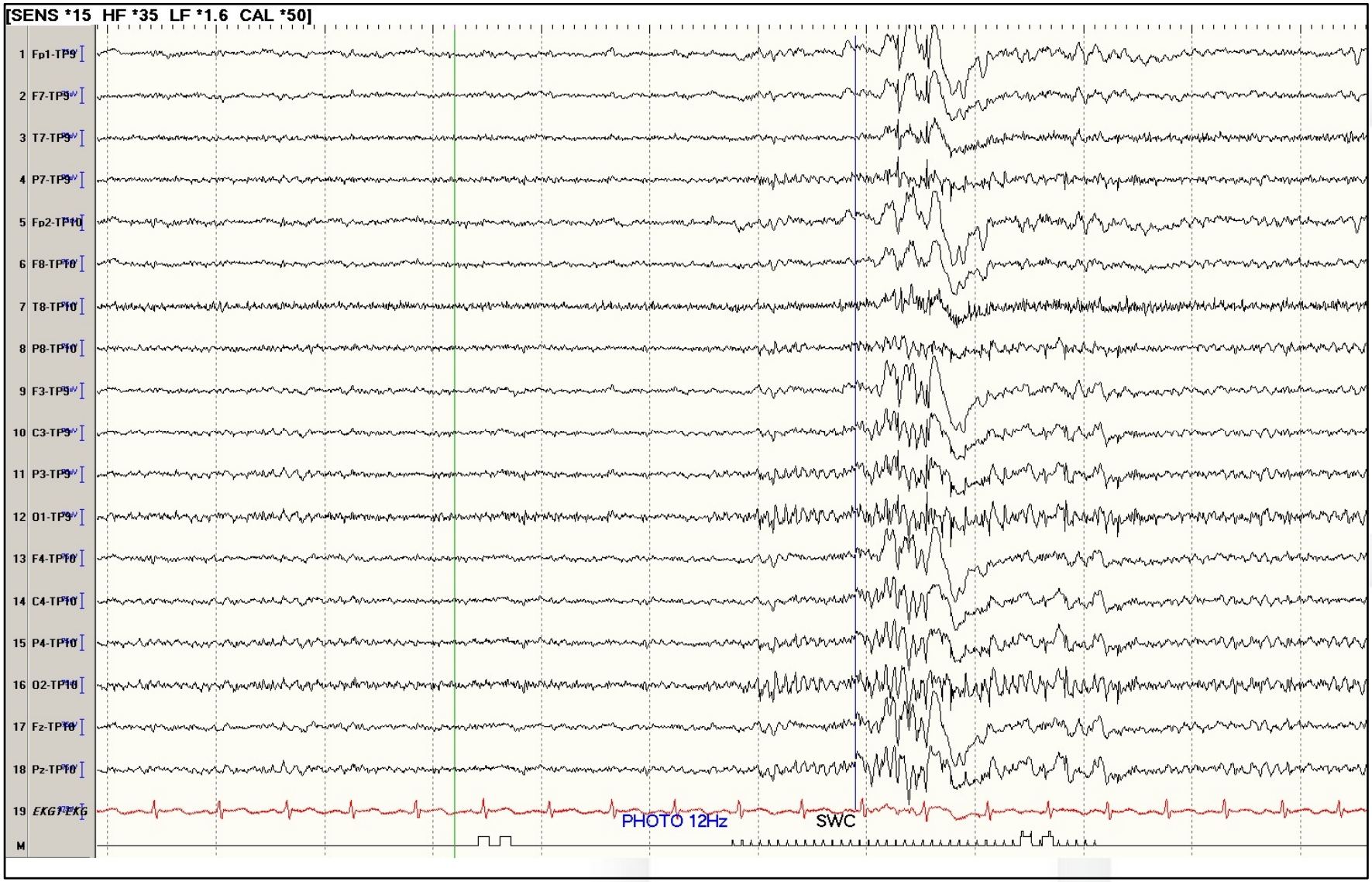
JME Electrical Features

Generalized Polyspikes



JME Electrical Features

Photoparoxysmal Response



CASE: 28-year-old man presents for increasing frequency (now monthly) generalized tonic clonic seizures usually occurring in the morning before work. No myoclonic jerks, photosensitivity, or other seizure types. His paternal grandfather and one of his paternal cousins also has epilepsy.

EPILEPSY WITH GENERALIZED TONIC-CLONIC SEIZURES ALONE

GTC seizures alone

- Development: normal
- Onset: second decade: 5 to 50 years (peak 15)
- Worsens with age
- Seizure Types:
  - Predominantly GTC on awakening
  - Less frequent myoclonic or absence
- Sensitive to light, sleep deprivation, alcohol

GGE Summary & Genetics

	Absence	Myoclonic	GTC	Onset	Identified Genes
CAE	+++	-	-	Childhood 4 to 10	GABRG2, GABRA1, GABRB3, CACNA1H
JAE	++	+	++	Puberty 8 to 16	GRIK 1
JME	+/-	+++	+++	Late adolescence 12 to 18	EFHC1, GABRA1 BRD/RING3, Cx-36, CACNB4, GABRD, CASR, ME2, SCN1B, EFHC2 CLCN2, BRD2
GTC only	+/-	+/-	+++	Second decade 5 to 50	CLCN2

Risk to first degree relative of GGE patients ~ 7%, but remains a generic prediction.[1]

[1]Peljto AL, Barker-Cummings C, Vasoli VM, Leibson CL, Hauser WA, Buchhalter JR, Ottman R. Familial risk of epilepsy: A population-based study. *Brain* 2014;137:795–805

Take home points GGE

- Genetic ≠ Inherited
- Normal development
- Typically good prognosis: Not progressive, can resolve, typically well-controlled, no neurological deficits
- Adult onset is not rare
  - 28% of GGE have onset after age 20[1]

[1]Marini C, et al. *J Neurol Neurosurg Psychiatry* 2003; *74:192-6*

The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial

Anthony G Marson, Asya M Al-Kharusi, Muna Alwaidh, Richard Appleton, Gus A Baker, David W Chadwick, Celia Cramp, Oliver C Cockerell, Paul N Cooper, Julie Doughty, Barbara Eaton, Carrol Gamble, Peter J Goulding, Stephen J L Howell, Adrian Hughes, Margaret Jackson, Ann Jacoby, Mark Kellett, Geoffrey R Lawson, John Paul Leach, Paola Nicolaides, Richard Roberts, Phil Shackley, Jing Shen, David F Smith, Philip E M Smith, Catrin Tudur Smith, Alessandr a Vanoli, Paula R Williamson, on behalf of the SANAD Study group

Lancet 2007; 369: 1016–26

- ✓ Valproate and topiramate have better seizure control than lamotrigine

- ✓ Valproate better tolerated than topiramate

“valproate should remain the drug of first choice for many patients with generalized and unclassified epilepsies. However, because of known potential adverse effects of valproate during pregnancy, the benefits for seizure control in women of childbearing years should be considered."

Ask the Experts

Special Communication

Epilepsy treatment in adults and adolescents: Expert opinion, 2016

Jerry J. Shih [a,*], Julia B. Whitlock [a], Nicole Chimato [b], Emily Vargas [b], Steven C. Karceski [c], Ryan D. Frank [b]

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- ✓ Valproate for all GGE (except women of child-bearing age)
- ✓ Lamotrigine or levetiracetam women of child-bearing age with GGE
- ✓ Ethosuximide in patient with absence only
- ✓ Levetiracetam in patients with GGE with GTC & myoclonic

2018 AAN / AES Practice Guidelines

Monotherapy in adults and children with new-onset GE or unclassified GTC seizures

Level	Recommendation
No Recommendation	Evidence is insufficient to compare efficacy of LTG and TPM with that of valproic acid (VPA) in children and adults with new-onset or relapsing GE (1 Class III study).

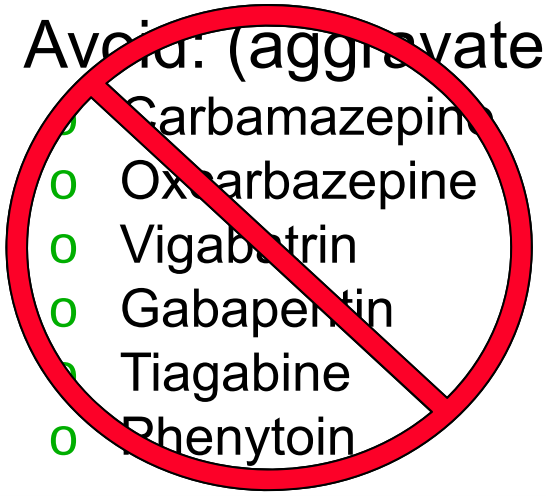
For adult and pediatric patients with TR generalized epilepsy (GE), are these AEDs effective in reducing seizure frequency when used as adjunctive therapy (compared with no adjunctive therapy)?

Level	Recommendation
Level B	For add-on therapy for GE, immediate-release and extended-release lamotrigine use should be considered as add-on therapy to decrease seizure frequency in treating adults with TR generalized tonic-clonic (GTC) seizures secondary to GE.
Level B	Levetiracetam (LEV) use should be considered to decrease seizure frequency as add-on therapy for TR GTC seizures and for TR juvenile myoclonic epilepsy.

Kanner AM, Ashman E, Gloss D et al. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new-onset epilepsy**.** *Neurology.* 2018; 91 (2)

Generalized Epilepsy Treatment

- First Line: **Valproate** (consider teratogenicity)
- Second Line: **Topiramate, Lamotrigine**
  - Lamotrigine could exacerbate myoclonus *level F*
- Third Line:
  - Levetiracetam (good for myoclonus) *class B*
  - Zonisamide *case series*
- Possibly Effective: Benzodiazepines, Primidone, Phenobarbital
- Avoid: (aggravate seizures) *class IV*[2]
  - Carbamazepine
  - Oxcarbazepine
  - Vigabatrin
  - Gabapentin
  - Tiagabine
  - Phenytoin



Glauser T et al. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic syndromes. *Epilepsia* 2013; 54 (3): 551 – 563.

[2]Guerrini et al., 1998; Genton, 2000; Somerville, 2009

Long Term Outcome of JME

First Author	Pub. Year	n	Outcome
Delgado	1984	43	28%(12) relapse with medication withdrawal after 2 yr seizure free
Camfield	2009	23	17% seizure free at 25 yrs f/u
Seneviratne	2012	review	< 20% remain in remission without treatment
Geithner	2012	31	68% seizure free at 25-63 yr f/u
Senf	2013	66	59% seizure free > 5 years at 45 yr f/u
Hofler	2014	175	8% seizure free > 10 yr
Vonderwulbecke	2017	176	60% > 5 years seizure free at 43 yr f/u

Prognosis of GGE

- Response to treatment overall good (but not complete)
- Previous reports long term remission rates higher in CAE than JAE/JME

Long-term outcome in adolescent-onset generalized genetic epilepsies

Bernd J. Vorderwülbecke, Alexander B. Kowski, Andrea Kirschbaum, Hannah Merkle, Philine Senf, *Dieter Janz, and Martin Holtkamp

Epilepsia, 58(7):1244–1250, 2017
doi: 10.1111/epi.13761

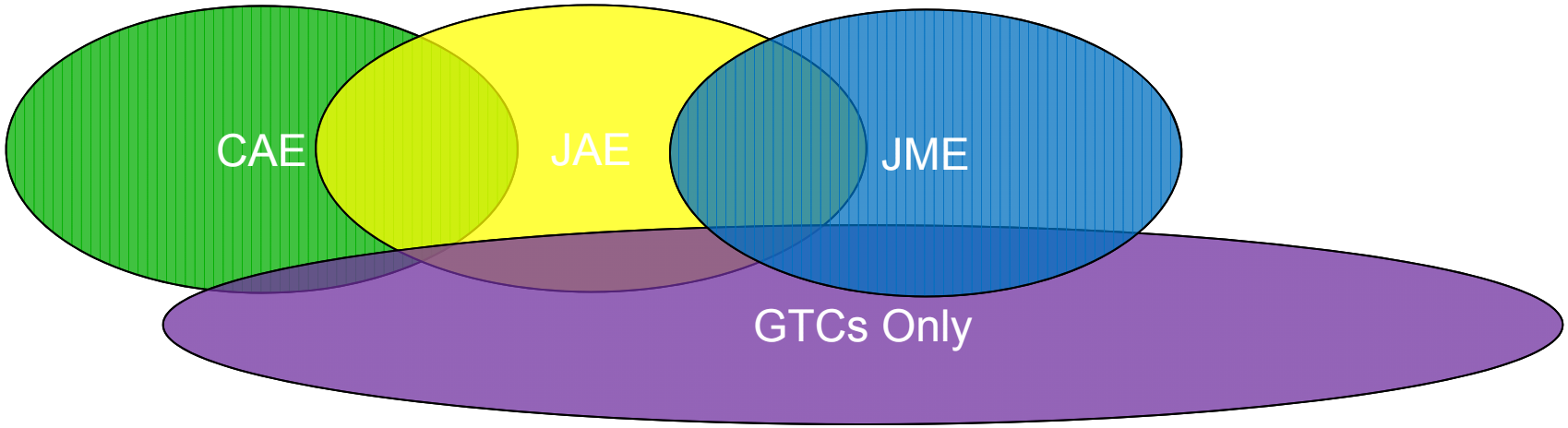
- ✓ Long term seizure outcome hardly differed between the three subsyndromes
- ✓ 60% seizure free 5 years
- ✓ 14% > 10 years seizure free with 5 years off medication

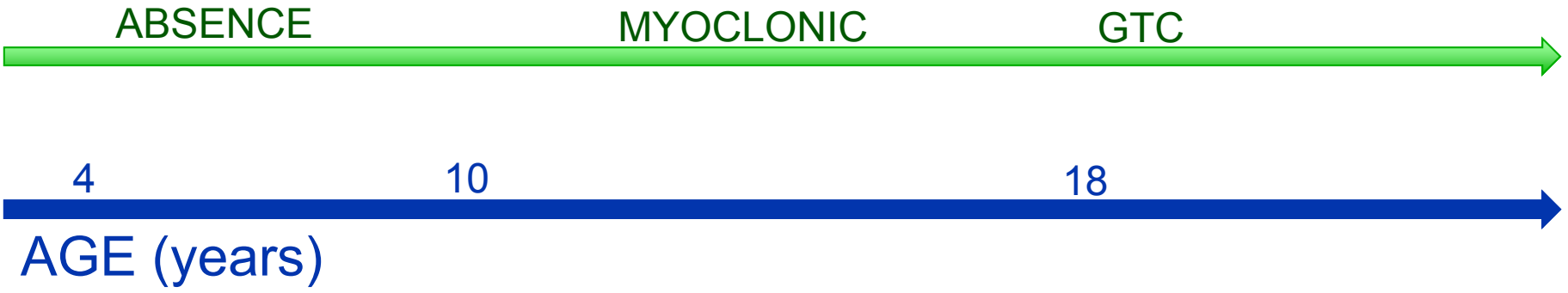
13-year-old developmentally normal teenage boy:

- First generalized tonic clonic seizure at age 9
- Myoclonic jerks started age 12
- Absence seizures started at age 8 (not having currently)
- Older brother with similar history controlled on medications

What is the best diagnosis?

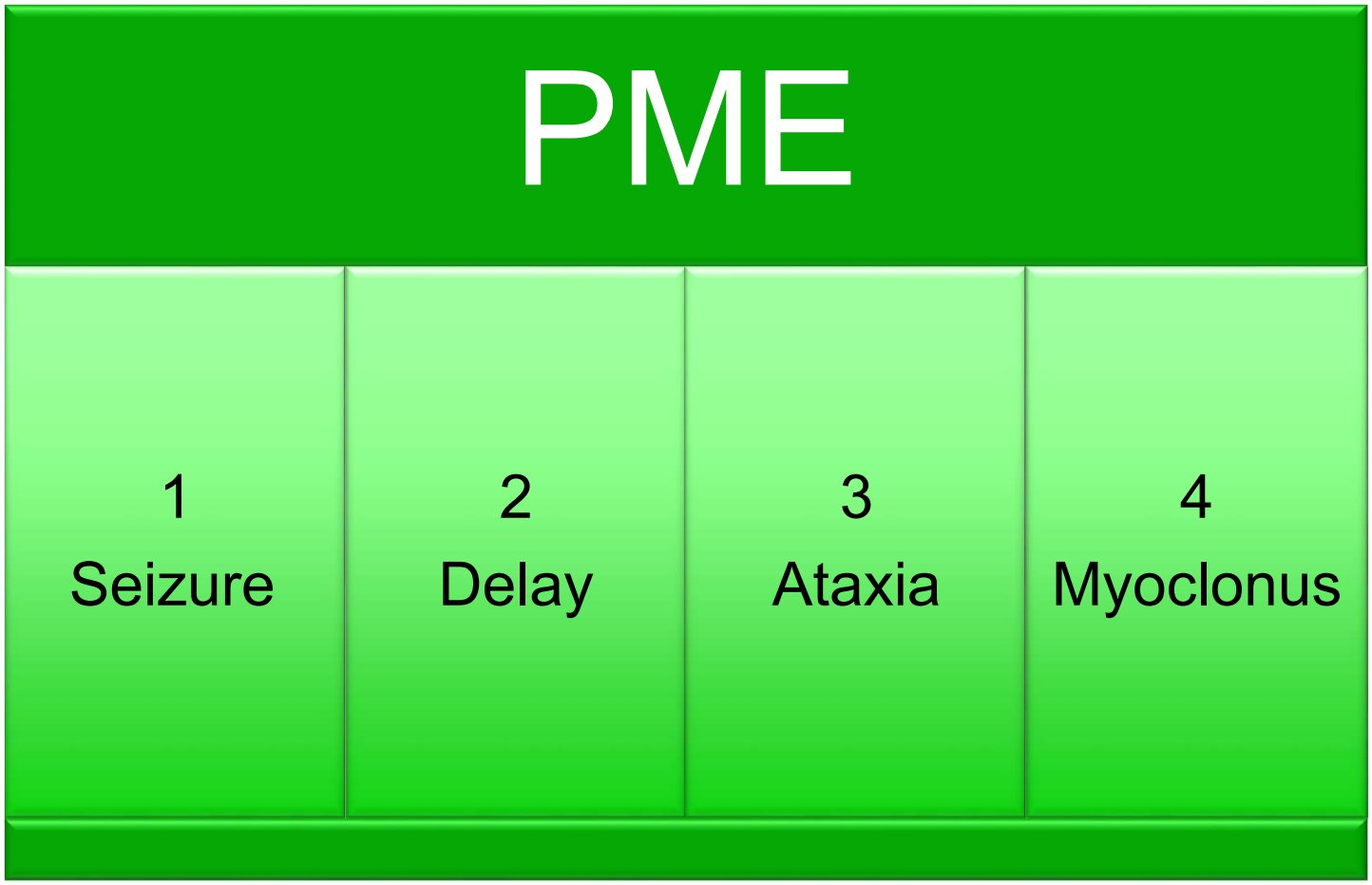
Continuum of GGE





Same patient returns at age 15 refractory to levetiracetam and zonisamide. He develops unsteady gait and tremor, as well as worsening myoclonus that now occurs for hours and with startle. He begins to have decline in school performance, becoming more withdrawn. What is the diagnosis?

PROGRESSIVE MYOCLONIC EPILEPSY (PME)



Progressive Myoclonic Epilepsy

- Heterogenous conditions that manifest clinically in a similar way
- Rare
- Genetic
- Progressive, neurodegenerative with poor outcome
- Childhood or adolescence
- EEG: Slow, generalized spikes and wave 2.5 to 6 Hz, polyspikes, focal sharp waves
- Photosensitivity (lower frequency than GGE)

Progressive Myoclonic Epilepsy (PME)

Autosomal Recessive

- **Unverricht-Lundborg (ULD)**
  CSTB (EPM1)
- **Lafora Disease**
  EPM2A, NHLRC1
- **Sialidoses**
  NEU1
- **Neuronal Ceroid Lipofucinosis (NCL)**
  TPP1 CLN3, CLN5, CLN6

Autosomal Dominant

- **DRPLA**
  DRPLA
- **Adult onset NCL (Kuff's)**

Mitochondrial

- **Myoclonic epilepsy with ragged red fibers (MERRF)**
  MTTK

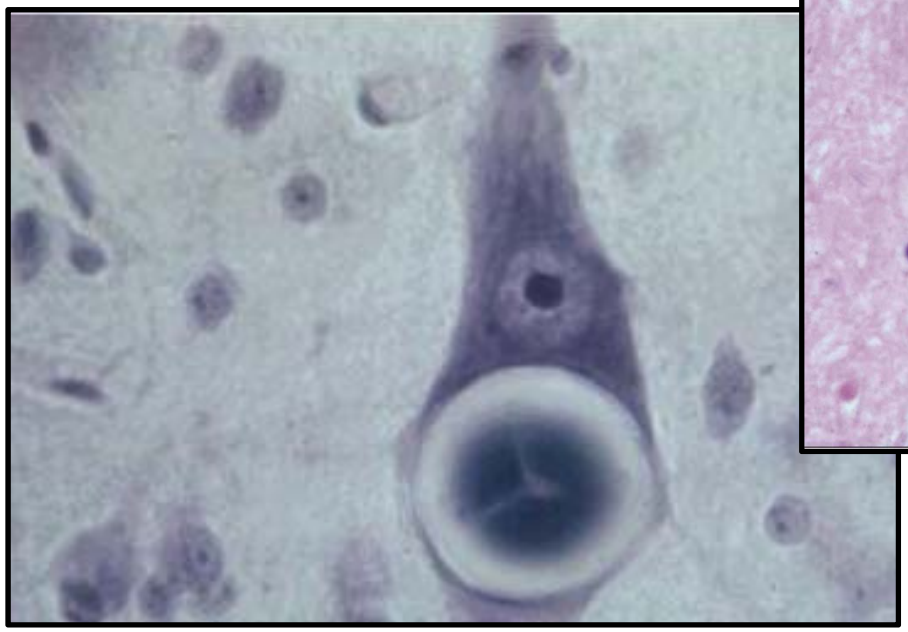
Shahwan et al. Lancet Neurol 2005
Girard JM et al. Handb Clin Neurol 2013

Unverricht-Lundborg Disease (ULD)

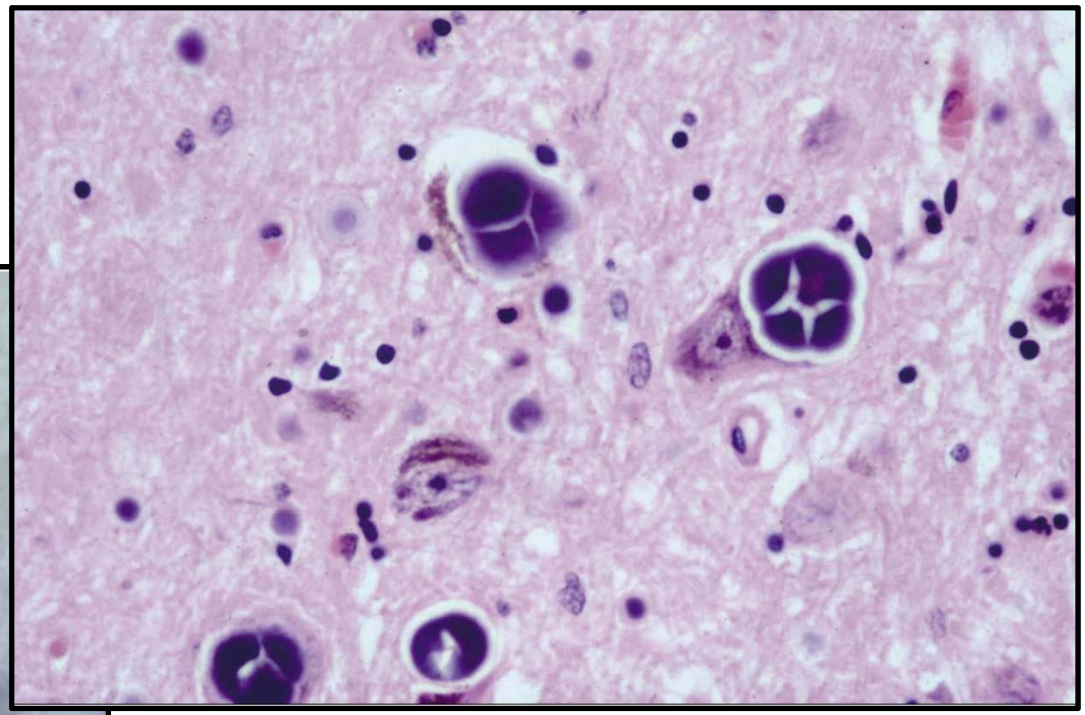
- Onset: 6 to 18 years, stabilize by 40, can live to 60s
- Seizures: Stimulus sensitive myoclonus + GTC/absence
- Other Features:
  - Progressive ataxia, dysarthria, intention tremor
  - Mild dementia (late feature)
- Genetics: autosomal recessive, mutation in cystatin B gene (CSTB, previously EPM1)
- Treatment tips: Phenytoin dramatically worsens ataxia
- EEG: generalized spikes and polyspikes with photosensitivity
- MRI: mild cerebellar / brainstem and less often cerebral atrophy

Lafora Bodies

Periodic-acid-Schiff (PAS) positive intracellular polyglucosan inclusion body in neurons, heart, skeletal muscle, liver, sweat gland ducts



Jeffrey A. Golden & Brian N. Harding. (2004). Developmental Neuropathology. *The International Society of Neuropathology*.



Shahwan A, Farrell M, Delanty N. Progressive Myoclonic Epilepsies: a Review of Genetic and Therapuetic Aspects. *Lancet Neurology* 2005; 4: 239-248.

Lafora Disease

- Onset: 6 to 19 years, death < 10 years
- Seizures: GTC, clonic, myoclonic, astatic, atonic, absence, focal, and occipital seizures; often deteriorate to status
- Other Features:
  - Normal development until onset, isolated febrile or nonfebrile seizures in childhood
  - Progressive cognitive decline
  - Blindness
  - Ataxia
- Genetics: autosomal recessive, generalized polyglucosan storage disorder
  - EPM2A gene Laforin
  - EPM2B (*NHLRC1)* Malin
- Diagnosis: skin biopsy, lafora bodies, genetics
- EEG: low frequency photoparoxysmal response

Neuronal Ceroid Lipofuscinosis (NCL)

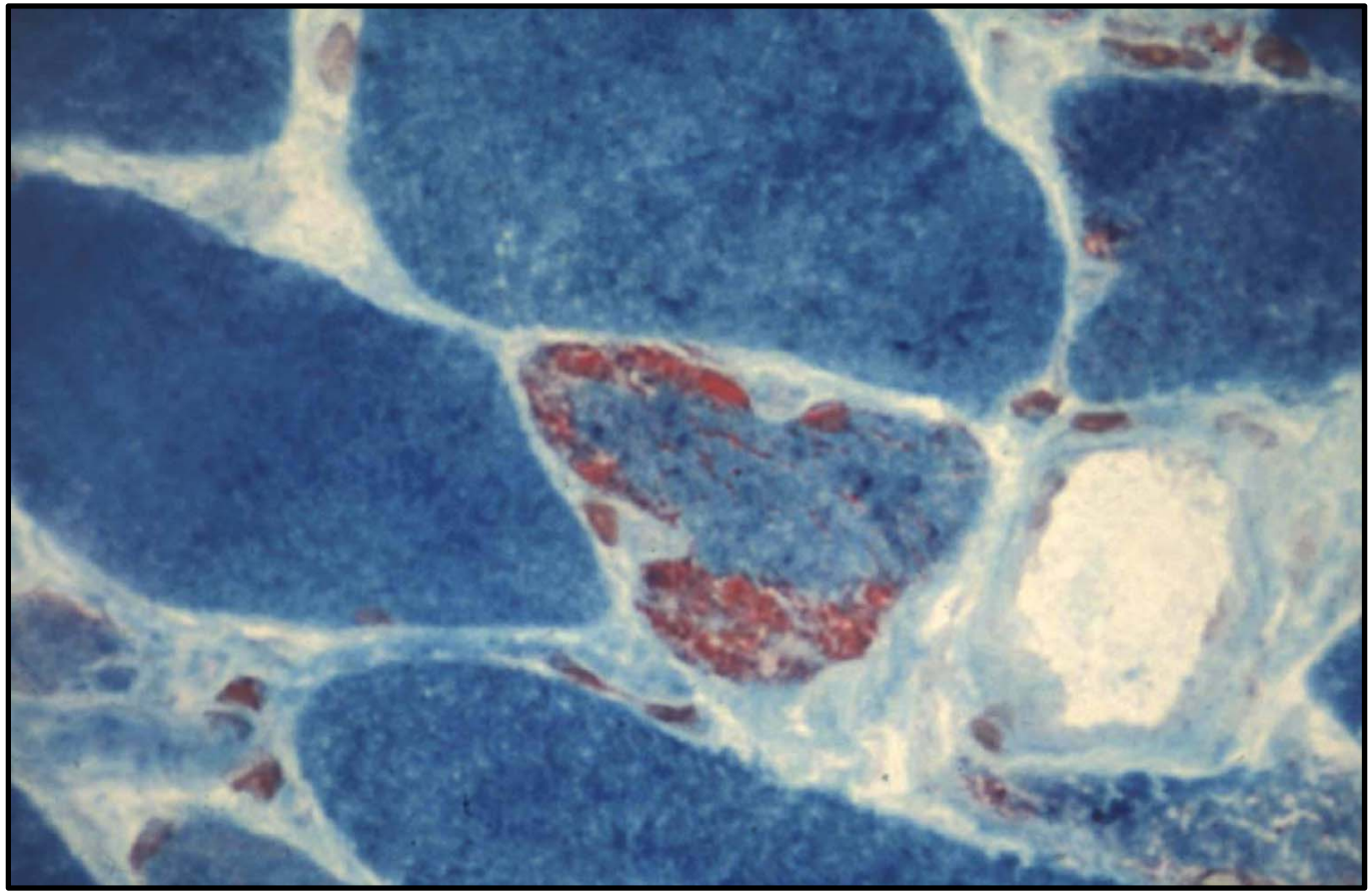
- Onset: varies with 5 subtypes, rapid progression, early death
- Seizures: + myoclonus, variable
- Other Features:
  - Progressive blindness characterized by retinal degeneration and optic atrophy
  - Progressive cognitive decline
- Genetics: autosomal recessive (except adult subtype can be dominant) accumulation of lipopigments in lysosomes
  - *PPT1,* CLN1, *TPP1,CLN3*, *CLN5*, *CLN6*, *MFSD8, CLN8, CTSD, DNAJC5, CTSF, ATP13A2, GRN, KCTD7*
- Diagnosis: intracellular inclusions (eccrine, conjunctival, muscle biopsy) or genetics
- EEG: Low frequency photic stimulation may induce occipital spikes, giant VEPs
- MRI: global atrophy, white matter T2 hyperintensities

NCL Subtypes

- **Type 2 Late infantile (Jansky-Bielschowsky)**
  - **Onset 2.5 to 4 years, death in 5 years**
  - **TPP1**
- **Type 3 Juvenile (Spielmeyer-Vogt-Sjogren or Batten)**
  - **Onset: 4 to 10 years**
  - **Prominent feature is loss of vision, seizures less prmonent**
  - ***CLN3***
- **Type 4 Adult (Kuf's or Parry)**
  - **Onset: adolescence or adulthood**
  - **no eye features**
  - **Can be autosomal recessive or dominant**
- **Type 5 Finnish variant late infantile**
  - ***CLN5***
- **Type 6 Late infantile variant**
  - ***CLN6***

Myoclonic Epilepsy with Ragged Red Fibers

Gomori trichrome with ragged red fibers



Shahwan A, et al. *Lancet Neurology* 2005

Myoclonic Epilepsy with Ragged Red Fibers (MERRF)

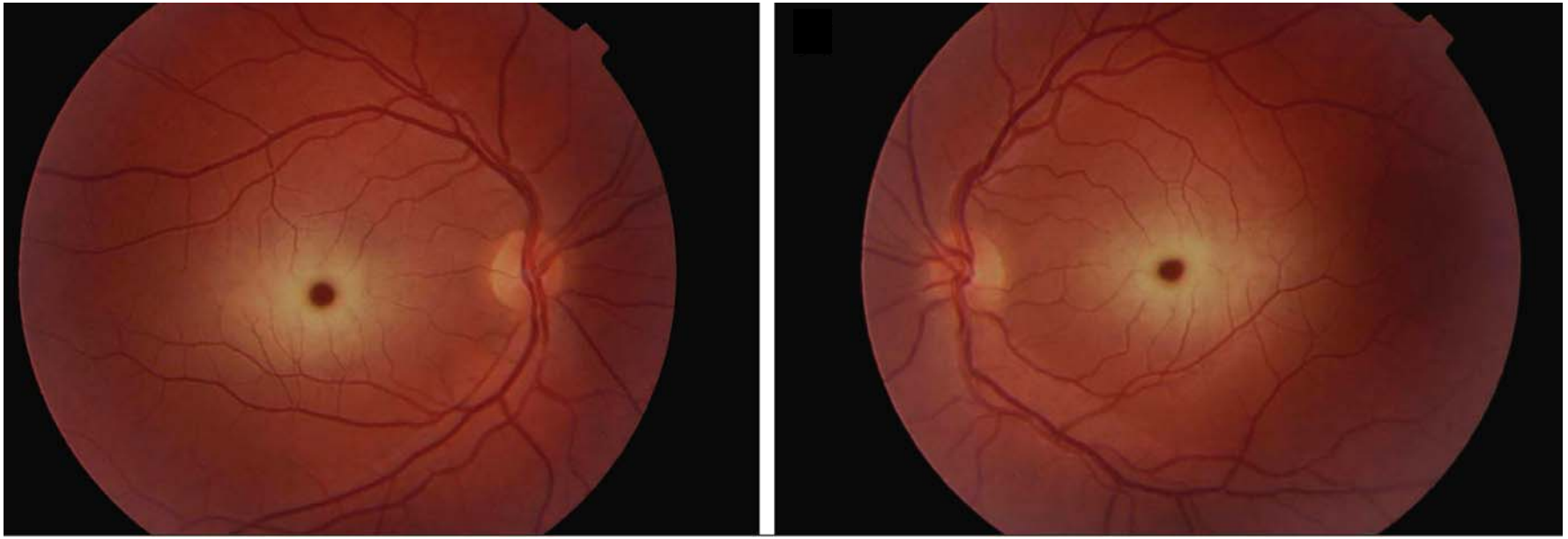
- Onset: childhood to young adult, insidiously or with metabolic crisis
- Genetics: Mitochondrial (maternal) or autosomal or sporadic tRNA Lys gene (MTTK) mutation
- Diagnosis: Ragged red fibers on muscle biopsy, genetics
- MRI: atrophy and calcificatins of basal ganglia, T2 grey matter intensity changes
- Treatment tips: Caution with valproate, sometimes emprically treated antioxidant vitamins, cofactors (coenzyme Q, L-carnitine)

Clinical Features:

- Epilepsy (myoclonus and GTCs)
- Ataxia
- Myopathy, neuropathy
- Deafness
- Optic atrophy
- Dementia
- Short stature
- Less common: diabetes mellitus, cardiomyopathy, retinopathy, ophthalmoparesis, multiple lipomas, pyramidal signs

Sialidosis

Fundus with Cherry – Red Spot



Heroman JW, Rychwalski P, Barr CC. Cherry Red Spot in Sialidosis (Mucolipidosis Type I). *Arch Ophthalmol.*2008;126(2):270–271. doi:10.1001/archophthalmol.2007.31 *http://jamanetwork.com/data/Journals/OPHTH/6864/esc70009f1.png*

Sialidosis I

- Onset: Juvenile
- Seizures: severe action/intention myoclonus, later GTC
- Other Features:
  - Cherry red spot, progressive visual failure
  - Gradual ataxia, spasticity
  - Painful sensory peripheral neuropathy
  - Dysmorphism: coarse faces, corneal clouding, skeletal dysplasia
  - Much less cognitive issue
- Genetics: autosomal recessive, neuroaminidase A, Nue1 gene
- Diagnosis: Vacuolate Kupffer cells, genetics

- TYPE II: similar but more severe, as early as neonatal onset, with hepatosplenomegaly and mental deterioration

Dentato-rubral-pallido-luysian atrophy (DRPLA)

- Onset: PME phenotype only if onset < age 20
- Seizures: myoclonic, GTC
- Other Features:
  - Extrapyramidal symptoms
  - Dementia
- Genetics: autosomal dominant with anticipation, unstable expansion of CAG trinucleotide repeats of DRPLA
- MRI: parasaggital atrophy esp. in pons and cerebellum

Summary of common PME

Disease	Age of onset	Seizures	Dementia	Ataxia	Distinctive features
ULD	6 to 18	Myoclonic ++++ GTC/absence	Minimal	Late	Milder, live to 60s No PHT!
Lafora	6 to 19	Myoclonic, GTC, atonic, focal ++ occipital (status)	Early and severe	Early	Death < 10 yr
NCL	Vary	Myoclonic ++, Variable	Progressive	Variable	Blindness, Visual abnormalities, early death
MERRF	Child to young adult	Myoclonus +, GTC	Variable, typically present	Variable, typically present	Ragged red fibers, can present in metabolic crisis, deafness, DM, myopathy, lipomas No VPA!
Sialidoses	Vary, juvenile II: neonate	Myoclonus +++, later GTC	I – absent II – learning disability	Gradual	Cherry red spot on fundus, progressive visual failure, dysmorphic
DRPLA	< age 20 (for PME)	Myoclonic +, GTC	Variable, but present	variable	

Adapted portions from Shahwan A, 2005.

Other Rare PME

- Gaucher III (glucocerebrosidase deficiency)
- SSPE (Subacute Sclerosing Panencephalitis)
- Juvenile GM2 gangliosidoses (Taysachs, Sandhoff, Hexosaminidase A&B deficiency)
- Pantothenate kinase-associated neurodegeneration (Hallervorden-Spatz)
- Ataxia-PME disease (PRICKLE1)
- Action myoclonus renal failure syndrome (SCARB2)
- SCARB2 without renal failure (ULD like)
- Neuroserpin mutations

Management of PME

Work-up

- MRI
- EEG
- Ophthalmology consultation
- Genetic testing

Treatment

- Seizure Management
  - No VPA in MERRF
  - No PHT in ULD
  - LEV for myoclonus
  - Try ZNS, VPA, PHB, benzodiazepines
  - Avoid: LTG, PHT, CBZ, GBP, VGB, TGB
- Rehabilitation
- Symptomatic, Palliation
- Genetic counseling

Autosomal Dominant Partial Epilepsy with Auditory Features

- Onset: 2 to 60 years (peak teens)[1]
- Isolated auditory auras or many evolve to loss of consciousness or generalized tonic clonic
- Seizure frequency low, can be reflexic
- Typically nonlesional MRI
- EEG often normal (vs temporal spikes)
- Responsive to treatment (96%)
- Genetics: RELN, LGI1 mutations[2]

[1]Bisulli et al, Brain 2004
[2]Michelucci et al, Epilepsy & Behavior, 2017

Other Familial Temporal Lobe Epilepsy

- Familial Mesial Temporal Lobe Epilepsy (FMTLE)
  - Heterogeneous
  - Onset: later childhood to early adult
  - Psychic, abdominal auras which can progress
  - Benign prognosis and good response to meds
  - Normal MRI or mesial temporal sclerosis
  - Varied genetics, autosomal dominant or recessive

Crompton et al, Brain 2010

Reflex Epilepsy

- Seizures not spontaneous but precipitated by stimulus
  - Should be objective and consistent
- ILAE in 1989: “epilepsies characterized by specific modes of seizure precipitation”
- Tasks/stimuli activate an area that may be hyperexcitable. If a large enough volume (or network) becomes activated it can reach “critical mass” and result in a seizure.
- Generalized or focal

Reflex Epilepsy Types

- Language or Reading Induced : Often cause jaw jerks or visual symptoms may progress to GTC, Inherited, onset late puberty, benign, typically no spontaneous seizures

- Startle: (sudden unexpected arousal), typically symptomatic to large brain lesions, often injury to sensorimotor and premotor cortex, many delayed

Elementary

- Visual: (most common), photosensitive, pattern sensitive, eye closure sensitivity idiopathic photosensitive occipital lobe epilepsy, occipital hyperexcitability
- Audiogenic: stimulus very specific, can be musicogenic (association with right temporal?), often also have spontaneous seizures
- Proprioceptive/Touch: can be active or passive movement, often involves sensorimotor of contralateral hemisphere

Situational

- Thinking: spatial or sequential, memory/pattern recognition, typically partial
- Bathing
- Praxis: generalized, more with challenging task
- Eating: Often temporolimbic, extratemporal symptomatic epilepsy

Koepp MJ, et al. *Lancet Neurol* 2016

HIGH YIELD POINTS

- Young adult with myoclonus, GTC = JME
- VPA drug of choice in GGE (teratogen)
- LTG may worsen myoclonus, LEV may help
- In GGE, no narrow spectrum CBZ, OXC, VGB, GBP, TGB, PHT
- PME can look like GGE initially
- Myoclonus, seizure, neurological deterioration, ataxia = PME
- Occipital epilepsy + PME = Lafora
- Mitochondrial + PME = MERRF ; no VPA
- Cherry-red-spot + PME = Sialidosis
- Mild PME that survives to adult = ULD ; no PHT
- ADLTE = LGI1, RELN

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