EPILEPSY SYNDROMES OF ADOLESCENCE AND ADULTHOOD

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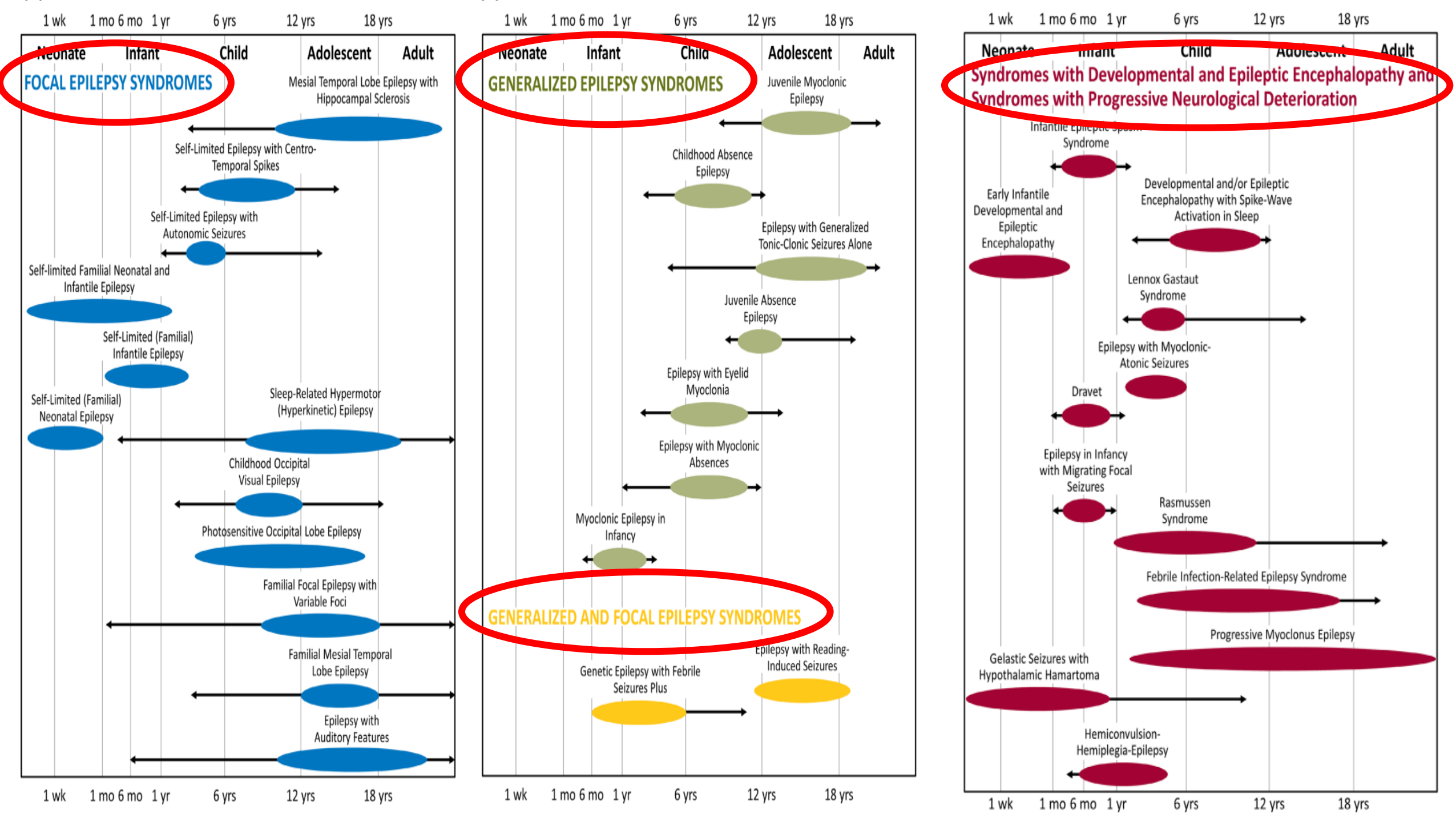
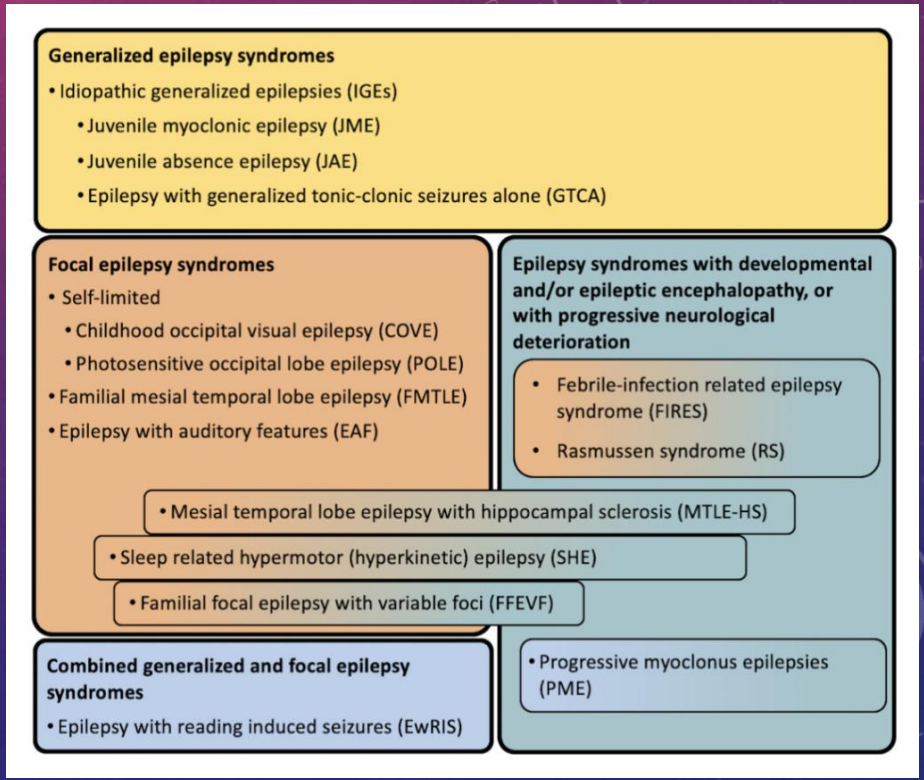
EPILEPSY SYNDROME CLASSIFICATION 2022

- Onset: neonatal/infant (up to 2 years), childhood, adolescent/adult (IGEs), variable age (ped & adult)
- Epilepsy type: focal, generalized, combined
- Associated with developmental and/or epileptic encephalopathy (DE and/or EE) or progressive neurological deterioration


1 wk
1 mo 6 mo
1 yr
6 yrs
12 yrs
18 yrs
Neonate
Infant
Child
Adolescent
Adult
FOCAL EPILEPSY SYNDROMES
Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis
Self-Limited Epilepsy with Centro-Temporal Spikes
Self-Limited Epilepsy with Autonomic Seizures
Self-limited Familial Neonatal and Infantile Epilepsy
Self-Limited (Familial) Infantile Epilepsy
Self-Limited (Familial) Neonatal Epilepsy
Sleep-Related Hypermotor (Hyperkinetic) Epilepsy
Childhood Occipital Visual Epilepsy
Photosensitive Occipital Lobe Epilepsy
Familial Focal Epilepsy with Variable Foci
Familial Mesial Temporal Lobe Epilepsy
Epilepsy with Auditory Features
GENERALIZED EPILEPSY SYNDROMES
Juvenile Myoclonic Epilepsy
Childhood Absence Epilepsy
Epilepsy with Generalized Tonic-Clonic Seizures Alone
Juvenile Absence Epilepsy
Epilepsy with Eyelid Myoclonia
Epilepsy with Myoclonic Absences
Myoclonic Epilepsy in Infancy
GENERALIZED AND FOCAL EPILEPSY SYNDROMES
Genetic Epilepsy with Febrile Seizures Plus
Epilepsy with Reading-Induced Seizures
Syndromes with Developmental and Epileptic Encephalopathy and Syndromes with Progressive Neurological Deterioration
Syndrome
Early Infantile Developmental and Epileptic Encephalopathy
Developmental and/or Epileptic Encephalopathy with Spike-Wave Activation in Sleep
Lennox Gastaut Syndrome
Epilepsy with Myoclonic-Atonic Seizures
Dravet
Epilepsy in Infancy with Migrating Focal Seizures
Rasmussen Syndrome
Febrile Infection-Related Epilepsy Syndrome
Progressive Myoclonus Epilepsy
Gelastic Seizures with Hypothalamic Hamartoma
Hemiconvulsion-Hemiplegia-Epilepsy

OUTLINE: EPILEPSY SYNDROME OF ADOLESCENCE AND ADULT

- **Focal epilepsy syndrome**
  - Sleep related hypermotor epilepsy (SHE)
  - Familial mesial temporal lobe epilepsy (FMTLE)
  - Epilepsy with auditory feature (EAF)
  - Familial focal epilepsy with variable foci (FFEVF)
  - MTLE-HS
- **Generalized epilepsy syndrome**
  - IGE: JAE, JME, GTCA
- **Combined generalized and focal epilepsy**
  - Epilepsy with reading induced seizure (EwRIS)
- **Epilepsy syndrome with DE and/or EE or with progressive neurological deterioration**
  - NORSE & Febrile infection related epilepsy syndrome (FIRES)
  - Rasmussen syndrome (RS)
  - Progressive myoclonic epilepsy (PME)



Epilepsia. 2022;63:1443–74.

FOCAL EPILEPSY SYNDROME

- Sleep related hypermotor epilepsy (SHE)
- Familial mesial temporal lobe epilepsy (FMTLE)
- Epilepsy with auditory feature (EAF)
- Familial focal epilepsy with variable foci (FFEVF)
- MTLE-HS

SLEEP RELATED HYPERMOTOR EPILEPSY (SHE)

SLEEP RELATED HYPERMOTOR (HYPERKINETIC) EPILEPSY (SHE)

- Previously known as AD nocturnal frontal lobe epilepsy
- Attacks are associated with sleep rather than time of day
- Seizures may arise from extrafrontal sites
  - Insulo-opercular, temporal, parietal
- Motor aspects of seizures are characteristic
- Age at seizure onset mostly in first 2 decades of life
  - Typically in adolescence (11–14 yrs), range 2 months to 64 years

CLINICAL FEATURES

- Brief (<2 minutes) seizures with stereotyped motor patterns within individuals
- Abrupt onset and offset
- Most common clinical expression consists of hypermotor events
  - Vigorous hyperkinetic features (complex body movements with kicking or cycling of limbs and rocking body movements), usually with vegetative signs, vocalization, emotional facial expression
  - Asymmetric tonic/dystonic seizures with or without head/eye deviation
- Seizures occur predominantly during sleep (non-REM)
- Seizure frequency may be very high , every night, usually many times per night
- Clustering is characteristic but not obligatory for diagnosis

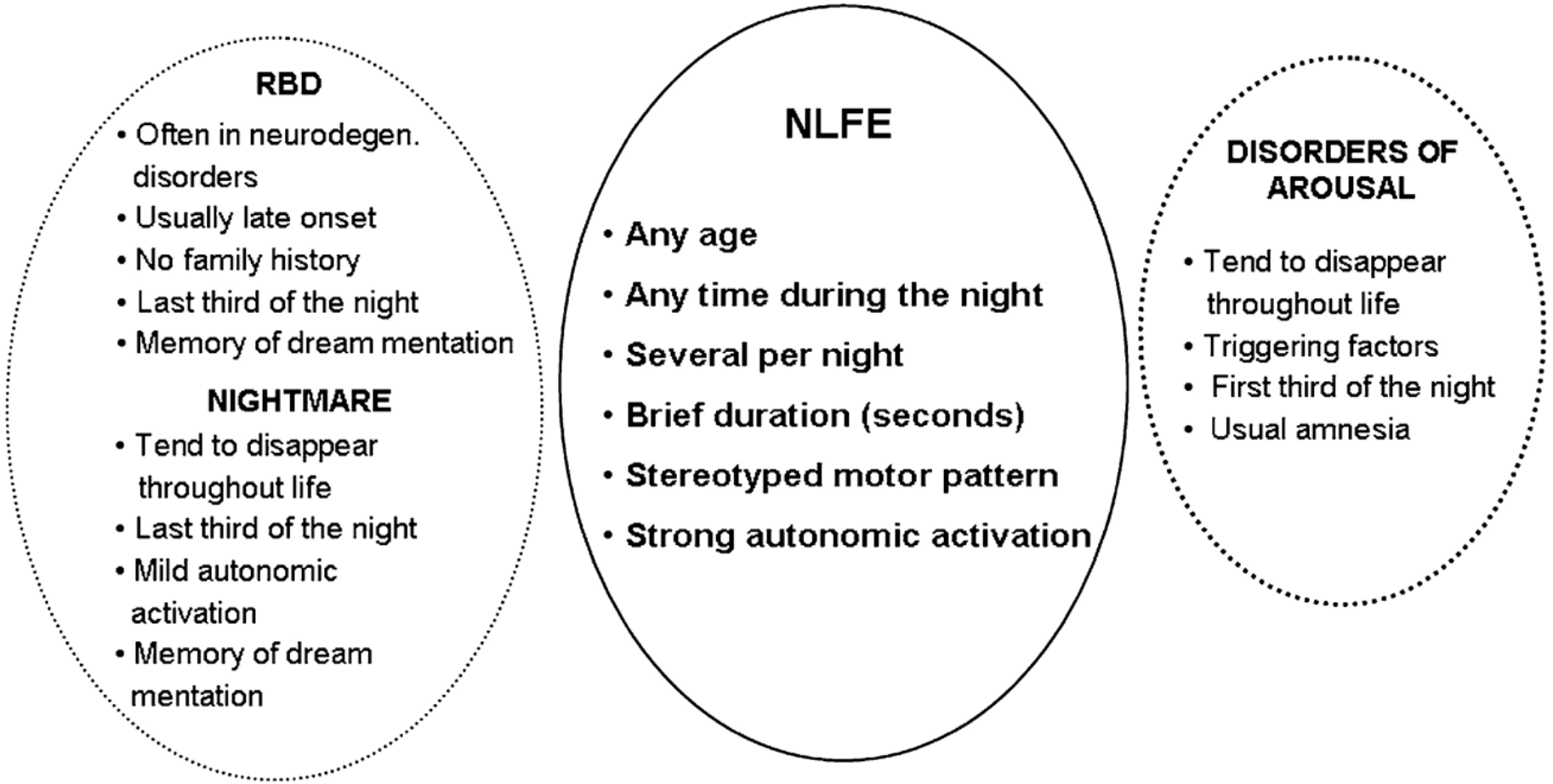
CLINICAL FEATURES

- Clinical features range from abrupt stereotyped arousals (paroxysmal arousal or minor motor events), repeated throughout the night or arising intermittently, with almost periodic pattern, to complex hypermotor seizures

- More seldom, protracted ambulatory behavior known as epileptic nocturnal wandering

- Events can last longer than 2 minutes

TYPICAL FEATURES DISTINGUISHING NOCTURNAL PAROXYSMAL EPISODES



Sleep Med Rev. 2007;11(4):255-67.

SHE

- Duration: Brief < 2 min
- Frequent, clustering
- Stereotyped
- Hypermotor/hyperkinetic
- Non-REM: N1/N2, transition between sleep stage

Arousal parasomnia

- Longer: Several minutes
- Infrequent, sporadic
- Not stereotyped
- Less frenetic, more goal-oriented
- Stage 3 non-REM, most often first half of the night

Table 2 Distinctive clinical features of nocturnal frontal lobe seizures and the most common parasomnias.

	Disorders of arousal	Nightmares	RBD	NFLS
Age at onset (yrs)	3–8	Usually 3–6	After 50	Any age
Gender	Either	Either	Male predominance	Male predominance
Family history of parasomnias	+	+	–	+
Spontaneous evolution	Tend to disappear	Tend to disappear	Rare spontaneous remission	Increased frequency?
Episodes/month	Sporadic	Sporadic	Almost every night	Almost every night
Occurrence during the night	First third	Last third	At least 90 min after sleep onset	Any time
Sleep stage onset of episodes	NREM sleep (st. 3–4)	REM sleep	REM sleep	NREM (mainly st. 2)
Triggering factors	++ (Sleep deprivation, febrile illness)	++ (Stress, traumatic events)	–	±
Episodes/night	Usually one	Usually one	From one to several	Several
Episodes duration	1–10 min	3–30 min	1–2 min	sec to 3 min
Stereotypic motor pattern	–	–	–	+
Autonomic discharge	+++	+	–	++(+)
Consciousness if awakened	Impaired	Normal	Normal	Normal
Recall of the episode if awakened	No	Yes	Yes	Inconstant

Sleep Med Rev. 2007;11(4):255-67.

SHE

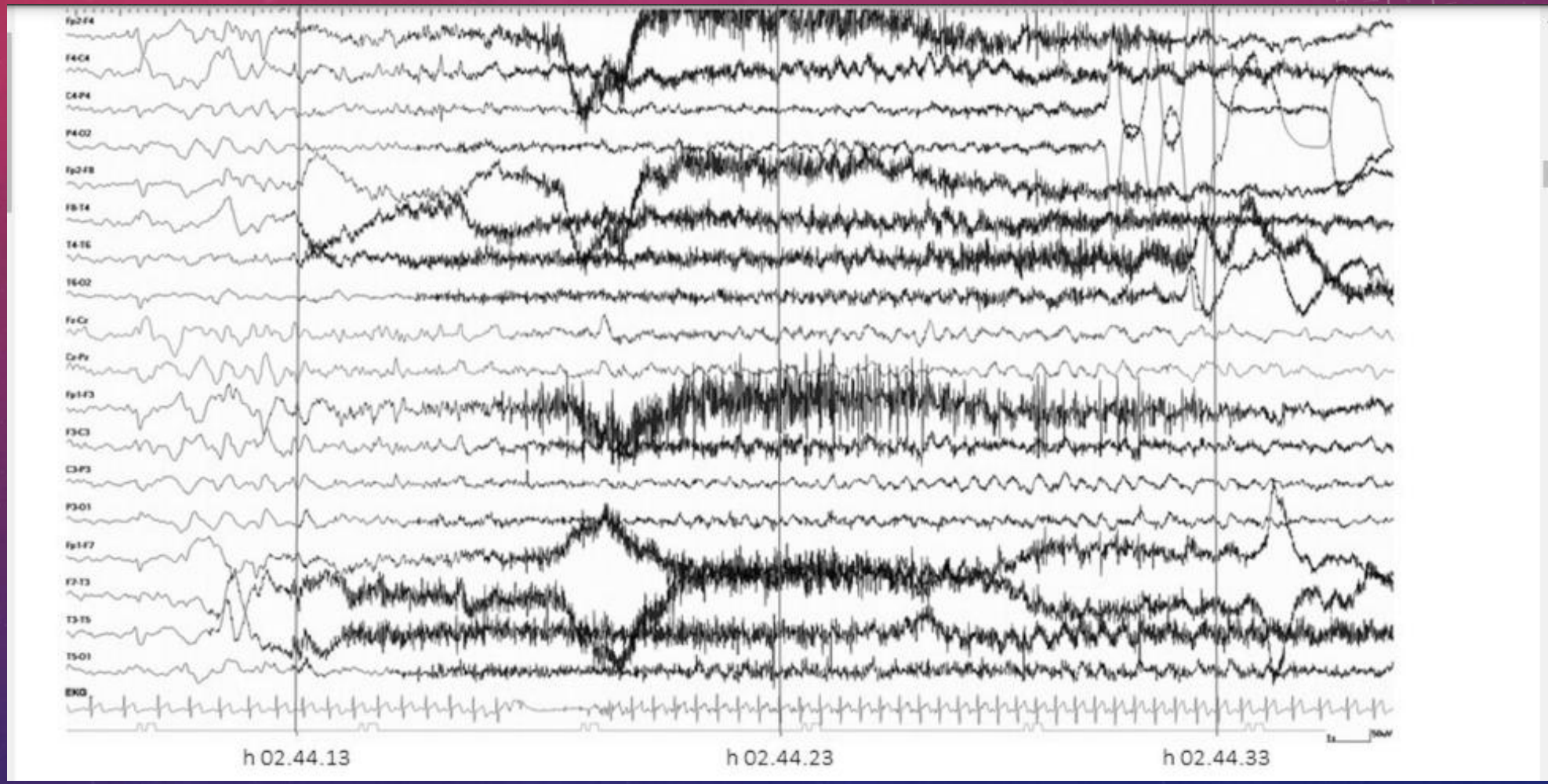
- Etiology: Structural (FCD), genetic (CHRNA4, CHRNA2, CHRNB2, KCNT1, DEPDC5, NPRL2, NPRL3, PRIMA1), acquired

- Course of illness: related to underlying etiology

EEG

- Awake: Normal BG, non-epileptiform in most (50%–90%) patients
- Sleep: IEDs over frontal areas in approximately 50%
- Ictal EEG
  - May not show definitive ictal patterns, obscured by movement artifact
  - Evolving sharp or spike-and-wave discharges, rhythmic slow activity
  - Diffuse background flattening over frontal areas
- Postictal focal slowing
- Prolonged video EEG: best diagnostic test to identify events with stereotyped semiology from sleep to confirm diagnosis

ICTAL EEG



Curr Treat Options Neurol. 2020;22(1):1.

MESIAL TEMPORAL LOBE EPILEPSY WITH HIPPOCAMPAL SCLEROSIS

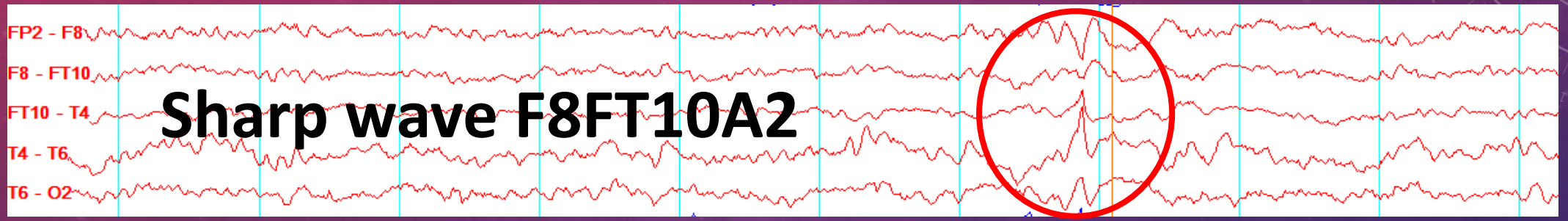
MTLE WITH HS

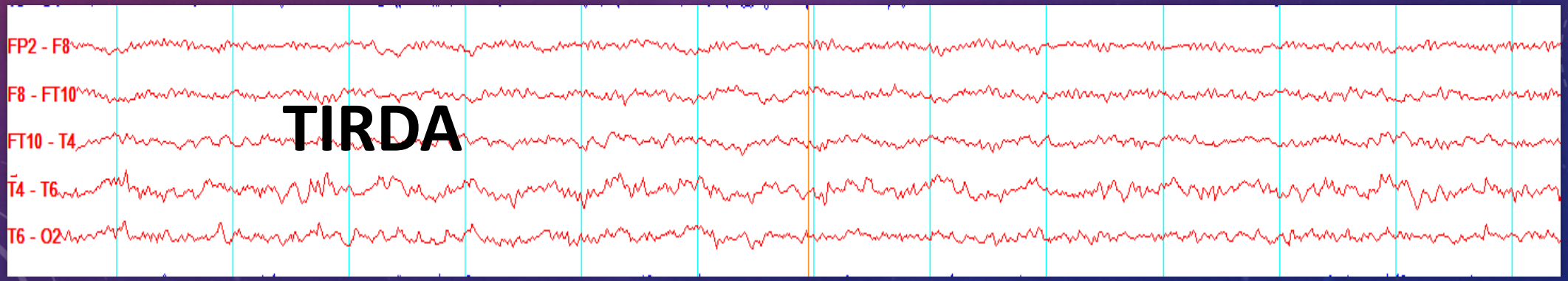
- Age at seizure onset is typically in adolescent and young adult years
- Seizure is gradual onset and offset
- Focal aware or impaired awareness seizures with semiological features referable to medial temporal lobe networks
  - Focal aware seizures: autonomic (rising epigastric sensation, abdominal discomfort, nausea, retching, pallor, flushing, tachycardia), cognitive (déjà vu, jamais vu), emotional (fear), or sensory (olfactory, gustatory)
  - FIAS:
    - Behavioral arrest, often automatisms may be oral (chewing, lip- smacking, swallowing), vocal, or gestural, upper limb automatisms may be unilateral and may lateralize to ipsilateral hemisphere
    - Contralateral upper limb dystonia may develop
    - Aphasia is common with dominant MTLE- HS

EEG

- Focal slow over temporal area
- Temporal intermittent rhythmic delta activity
- Epileptiform abnormality over ipsilateral anterior temporal region, may be bilateral and independent, or bilaterally synchronous
- Ictal EEG changes are marked by rhythmic temporal alpha or theta activity within 30 seconds of clinical onset

INTERICTAL EEG



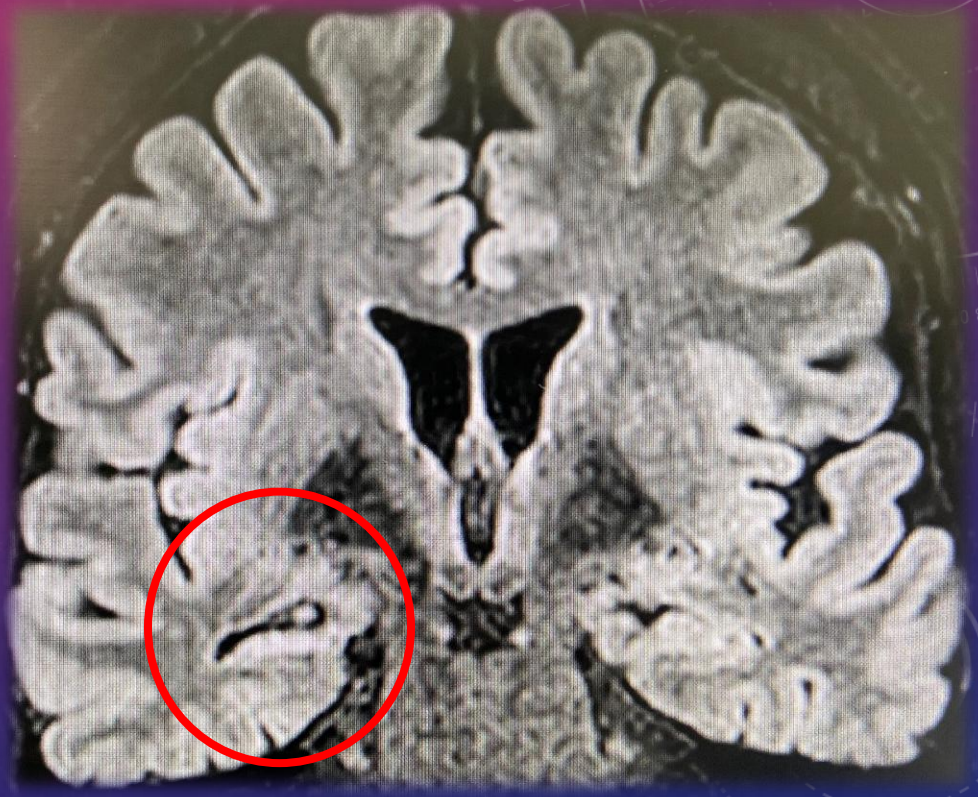


MTLE WITH HS

- Imaging: hippocampal sclerosis, increased signal and loss of volume

  (15% dual pathology)

- Often drug resistance, may full remission after epilepsy surgery



FAMILIAL MESIAL TEMPORAL LOBE EPILEPSY

FMTLE

- Typically onset in adolescence or adulthood (3-63 yr)
- Clinical seizure: focal aware seizures with mTLE semiology
  - Clinical vary between mild syndrome with prominent déjà vu (most common) to more severe phenotype with febrile seizures and HS
- Typical form, seizures are mild and occur infrequently
- FH of individuals with focal seizures arise from mesial temporal lobe
- Normal intellectual development and no associated neurological abnormalities
- History of febrile seizures is uncommon with typical presentation
- Normal MRI or HS/atrophy: exclude other pathology

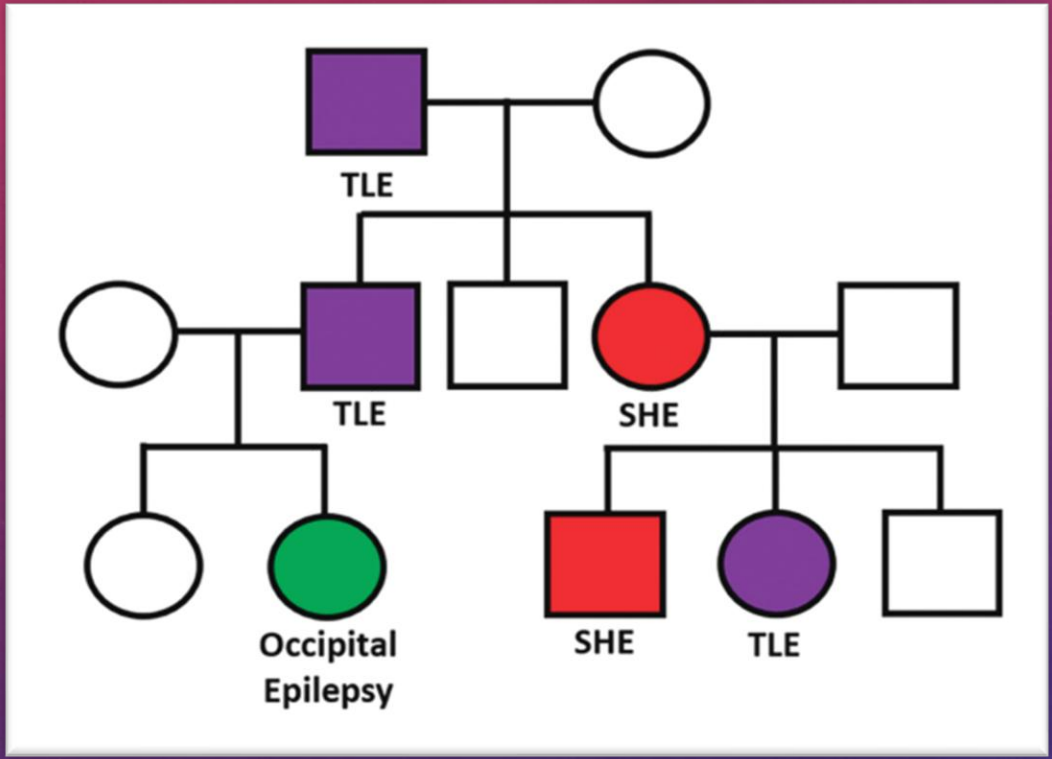
EPILEPSY WITH AUDITORY FEATURES

EAF

- Mostly sporadic, also ADEAF (related gene LGI1, RELN, MICAL1)
- Onset adolescence or early adulthood
- Focal aware seizures with auditory symptoms and/or receptive aphasia
- Rarely may have focal to bilateral tonic–clonic seizures
- Some patients have seizures precipitated by specific sounds
- 1/3 are drug resistant
- MRI: normal or FCD

FAMILIAL FOCAL EPILEPSY WITH VARIABLE FOCI

FFEVF



Example pedigree
Continuum (Minneap Minn). 2022;28(2):339-362.

- Rare AD familial focal epilepsy syndrome
- Focal seizures arising from different cortical regions (most common frontal or temporal) in different family members with variable severity
- Every individual in family have single focal seizure type
- Most cases are responsive to ASMs
- Selected patients with DRE and FCDII, epilepsy surgery may result in full remission

Focal Epilepsy Syndrome (SHE, FMTLE, FFEVF, EAF)

Syndrome	Onset (usual)	Clinical	Interictal EEG	Imaging
SHE	Second decade of life	From sleep, brief hyperkinetic or asymmetric tonic/dystonic motor seizures	Background interictal EEG is usually normal; focal (usually frontal) epileptiform abnormality can be seen	Normal, FCD, or acquired structural abnormality
FMTLE	Adolescence or adulthood	Typically, focal aware seizures with intense déjà vu and associated features, e.g., dreamy perceptions, fear or panic, slow motion, visual or auditory illusions, and autonomic manifestations	Background interictal EEG is usually normal or may show mild temporal slowing; temporal epileptiform abnormality can occasionally be seen	Normal, rarely hippocampal atrophy or increased T2 signal
FFEVF	First or second decade of life	Focal seizures, semiology dependent on focal cortical area involved in an individual, but constant in that individual	Background interictal EEG is usually normal; focal epileptiform abnormality can be seen	Normal or FCD
EAF	Second or third decade of life	Sensory seizures (auditory), cognitive seizures with receptive aphasia	Background interictal EEG is usually normal; focal (usually temporal) epileptiform abnormality can be seen	Usually normal, although posterior temporal FCD reported

Epilepsia. 2022;63:1443–74.

Focal Epilepsy Syndrome (SHE, FMTLE, FFEVF, EAF)

Focal epilepsy syndrome	Related genes
SHE	*CHRNA4, CHRNA2, CHRNB2, DEPDC5, KCNT1, NPRL2, NPRL3, PRIMA1*
FMTLE	*DEPDC5* (Mendelian inheritance is rare, FMTLE typically displays complex inheritance)
FFEVF	*TSC1, TSC2, DEPDC5, NPRL2, NPRL3*
EAF	*LGI1, RELN, MICAL1*

Abbreviations: EAF, epilepsy with auditory features; FFEVF, familial focal epilepsy with variable foci; FMTLE, familial mesial temporal lobe epilepsy; SHE, sleep-related hypermotor (hyperkinetic) epilepsy.

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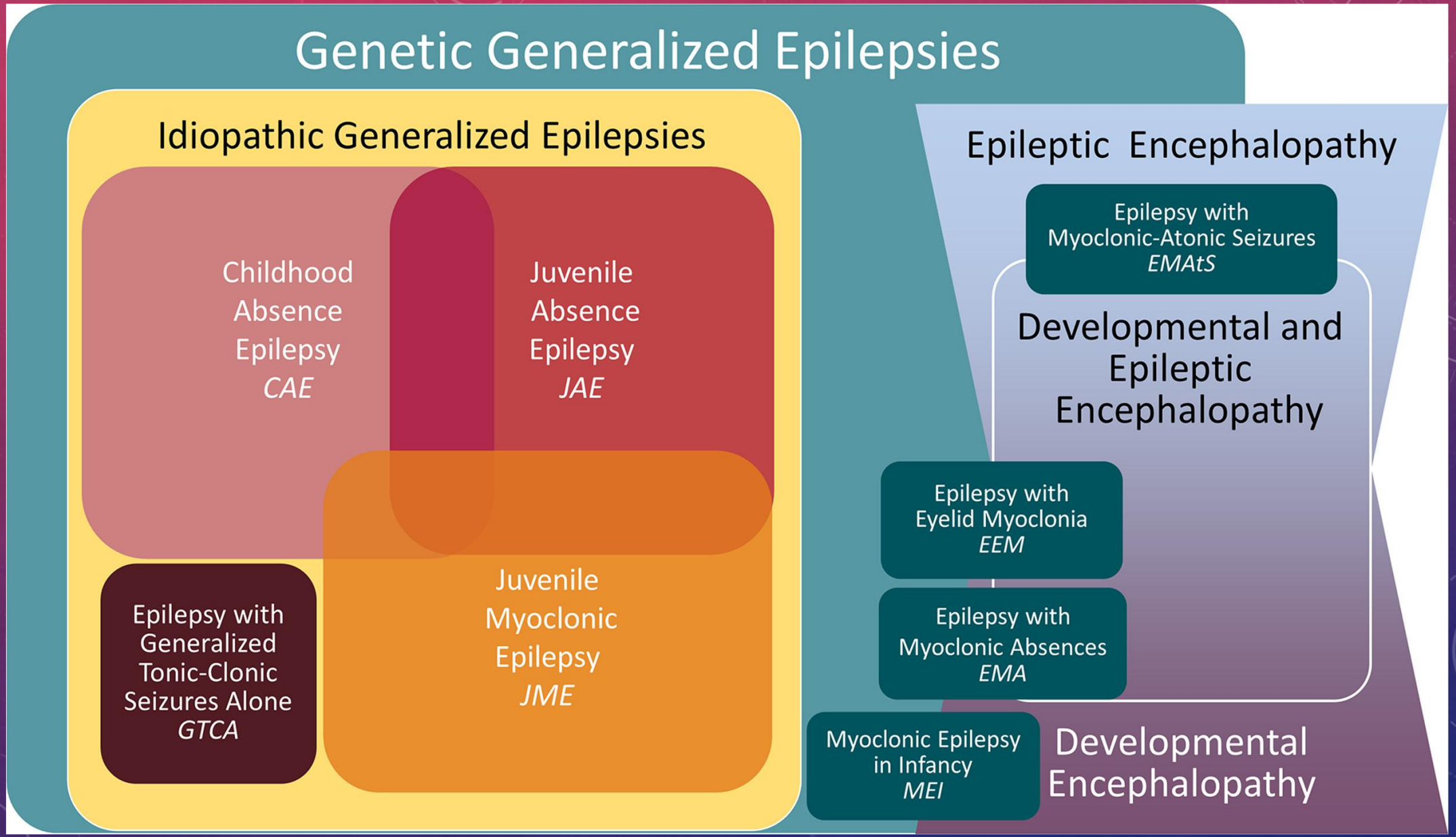
GENERALIZED EPILEPSY SYNDROME

GENERALIZED EPILEPSY SYNDROME

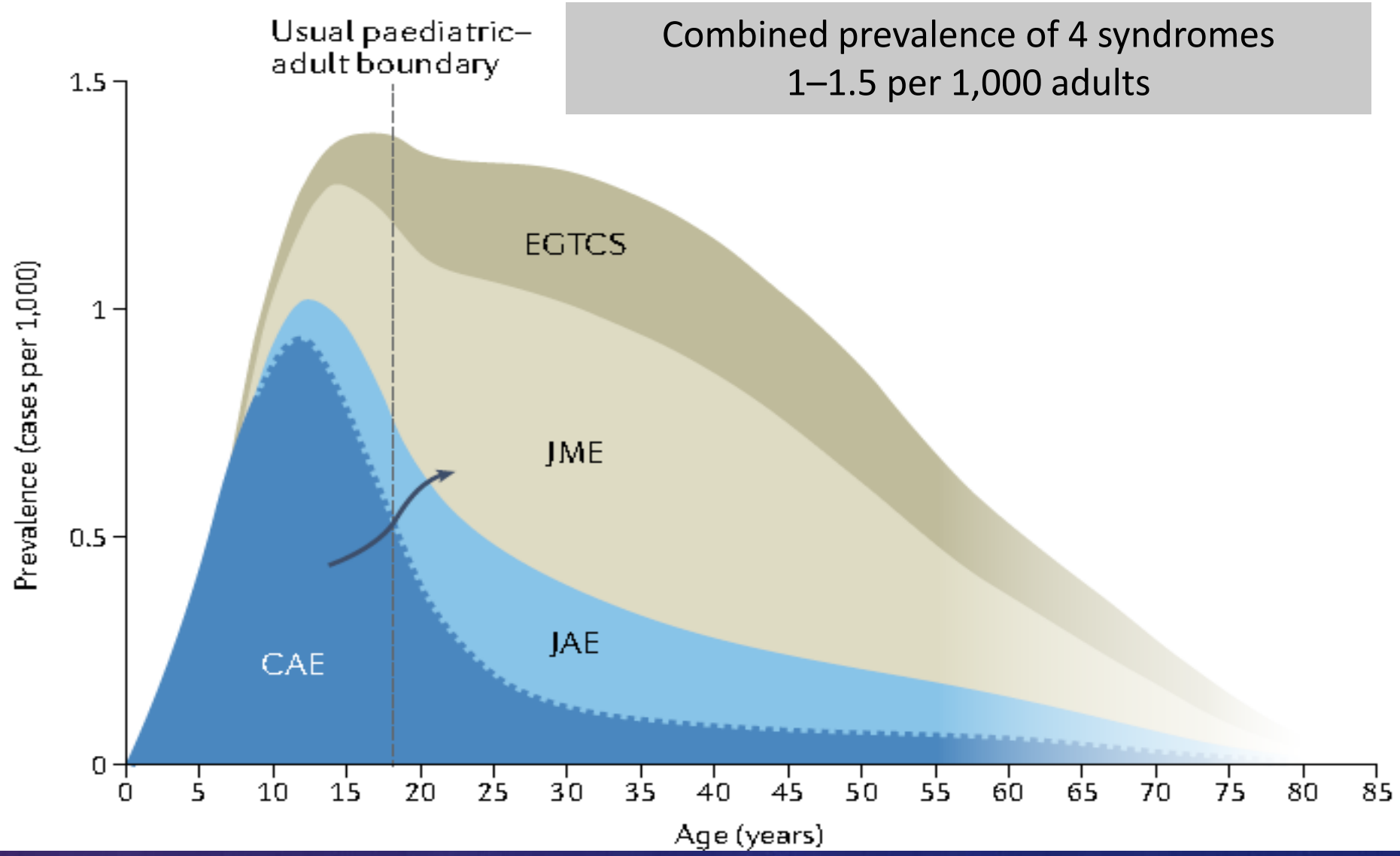
- JAE
- JME
- GTCA



Epilepsia. 2022;63:1475–1499.

Prevalence of active GGE syndromes across the lifespan

Combined prevalence of 4 syndromes
1–1.5 per 1,000 adults



Nat Rev Neurol. 2022;18(2):71–83.

GGE

- Functional imbalance of bilateral frontothalamocortical networks → seizure & cognitive impairment
- Neuropsychological deficits and psychiatric traits
    - Poorer academic performance
    - Dysfunctional social cognition
    - Personality disorder: impulsivity, emotional instability
    - Affective & anxiety disorder
- Genetic: Polygenic modes of inheritance (combinations of multiple gene alterations)

  ** esp. GABA receptor subunit **

GENETIC DEFECT IN SOME GGE

Gene	Locus	Protein	Phenotype
GABRG2	5q31–33	$GABA_A$ receptor γ_2-subunit	CAE and FS
GABRA1	5q34–35	$GABA_A$ receptor α_1-subunit	JME, CAE
CLCN2	3q26	ClC-2 voltage-gated Cl channel	CAE, JAE, JME, EMA
EFHC1	6p11–12	Myoclonin1	JME
CACNA1H	16p13.3	T-type Ca^{2+} channel α_{1H}-subunit	CAE
CACNB4	2q22–23	Ca^{2+} channel β_4-subunit	JME, JAE
CACNA1A	19p13	P/Q-type Ca^{2+} channel α_{1A}-subunit	CAE with ataxia
RORB	9q21.13	Transcriptional factors	Eyelid myoclonia with Ab
List of loci from genome-wide linkage analyses of small multiplex families			
1p, 2q36, 3q26, 5q12-q14, 5q34, 6p21, 8q24, 8p, 9q32–33; 10q25–26, 10p11, 11q13, 13q22–31, 14q23, 15q14, 18q21, 19q13			IGE, CAE, JME
List of CNVs, risk factors of IGE			
Microdeletions: 15q13.3, 15q11.2, 16p13.11			IGE, JME
Duplication: 1q21.3			Early onset CAE

CAE, childhood absence epilepsy; *EMA*, myoclonic–astatic epilepsy; *FS*, febrile seizures; *IGE*, idiopathic generalized epilepsy; *JAE*, juvenile absence epilepsy; *JME*, juvenile myoclonic epilepsy.

Guerrini R. Handb Clin Neurol. 2019;161:3-15.

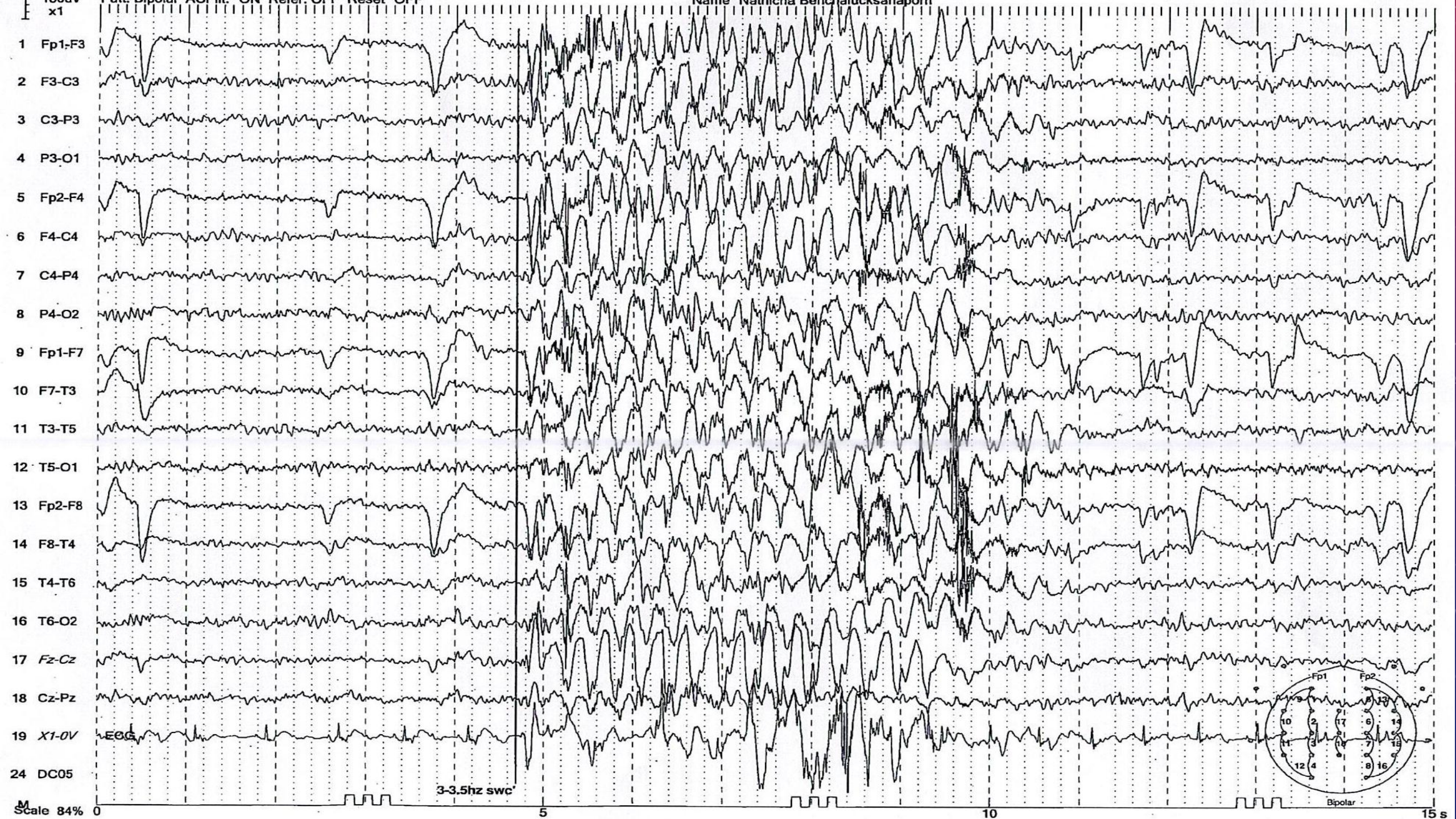
JUVENILE ABSENCE EPILEPSY

JAE

- Age of onset 9-13, range 8-20 years
- Absence seizure, less than daily
- GTCs > 90% shortly after absence seizure
- Triggers: sleep deprivation, alcohol, HV
- Normal development and cognition (+/-ADHD, LD)

JAE EEG

- Interictal
  - 3-5.5 Hz Generalized spike/polyspike, may show focal abnormality, asymmetrical burst of spike/polyspike waves
  - SW: less organized, more fragmented than CAE
- Ictal
  - Generalized 3-5.5Hz spike/polyspike waves elicit by hyperventilation
  - Absences may have a faster rhythm of GSW at 4–5Hz, esp. at onset
- Photoparoxysmal response 25%


Name: Nathicha Benchalucksanaporn
1 Fp1-F3
2 F3-C3
3 C3-P3
4 P3-O1
5 Fp2-F4
6 F4-C4
7 C4-P4
8 P4-O2
9 Fp1-F7
10 F7-T3
11 T3-T5
12 T5-O1
13 Fp2-F8
14 F8-T4
15 T4-T6
16 T6-O2
17 Fz-Cz
18 Cz-Pz
19 X1-0V
ECG
24 DC05
3-3.5hz swc'
Scale 84%
0
5
10
15 s
Fp1
Fp2
Bipolar

	CAE	JAE
Age at onset	2 to 13 years (4-10)	8-20 years (9-13)
Absence seizure	More frequent (10s-100s/day) Cluster Shorter duration 3-20s Severe loss of awareness	Less frequent (1-10/day) Sporadic Longer duration 5-30s Less complete impaired awareness
GTCs	Less common	More common
EEG	Bilateral, 3Hz (2.5-4) synchronous, symmetrical SW Irregular generalized SW uncommon OIRDA 21%	Generalized spike/PSW 3-5.5 Hz Irregular generalized SW more common

JAE

- Typically pharmacoresponsive syndrome
  - ETX, VPA, LTG
- Avoided PHT, CBZ, GBP, pregabalin, vigabatrin
- Lifelong requirement for medication expected

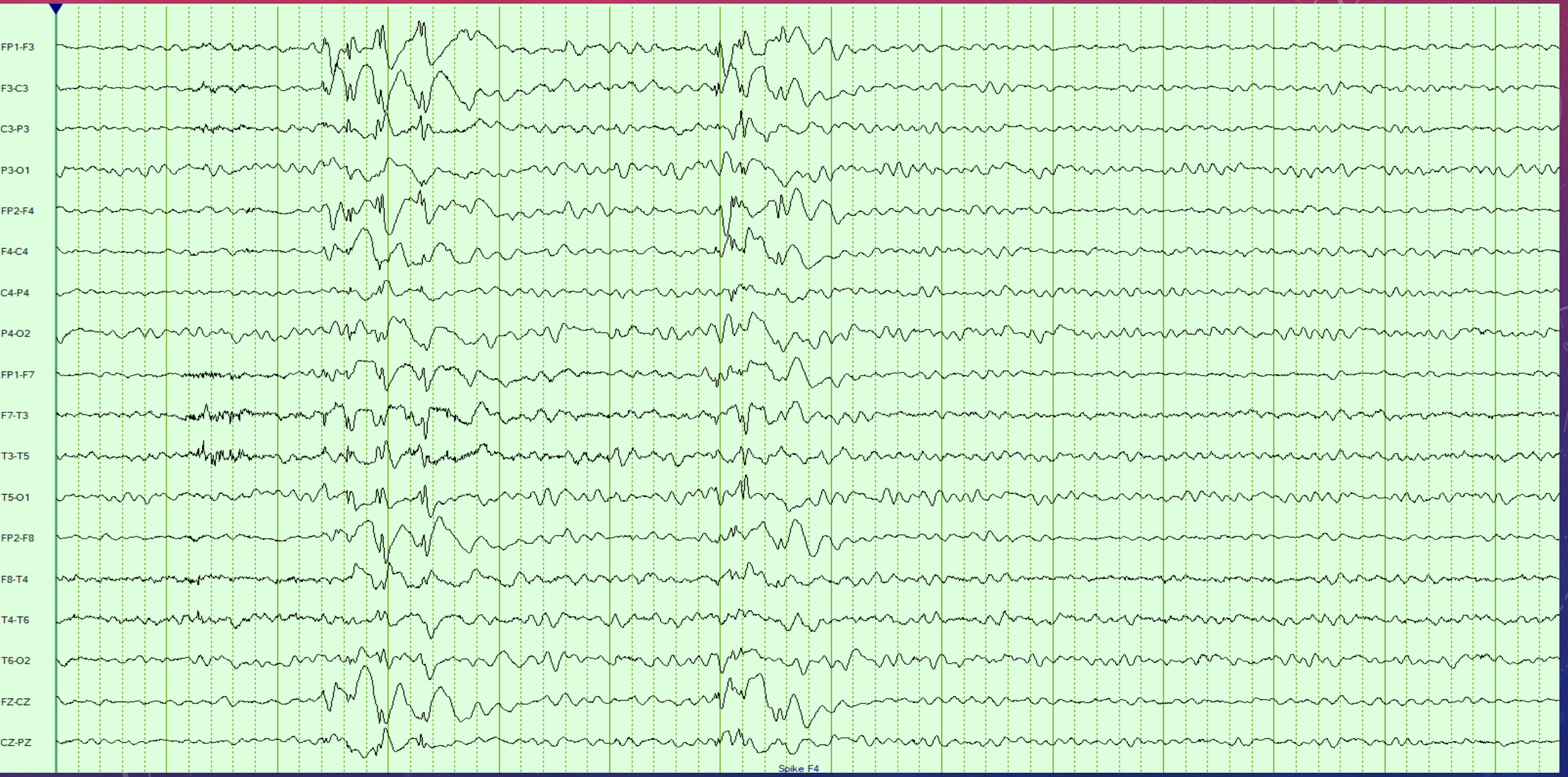
JUVENILE MYOCLONIC EPILEPSY

JME

- 5% to 10% of all epilepsy, onset 10-24 years (8-40)
- Most constant clinical feature is **myoclonic seizures**
  - Predominantly involving upper extremities (shoulder, arm, rarely distal)
  - Generally bilateral
  - Especially upon awakening, within 2 hour after awakening
  - 25% asymmetrical
- Majority develop **GTCs**, usually shortly after awakening
  - Often preceded by series of myoclonic seizures → **myoclonic-tonic-clonic seizure**
- At least 1/3 experience **absence seizures**

JME: EEG

- Normal EEG background
- Abrupt paroxysmal generalized 4-6 Hz spike or PSW (fast spike and wave)
  - More frequent in the morning than evening
  - Increased in frequency during sleep (most prominent N1, N2)
  - Transition from sleep to awake, arousal
- +/- Focal spike
- Potentiated by sleep/sleep deprivation, alcohol use, menses, photic stimulation (>1/3 PPR, typically at 10-30Hz PS), HV
- Improved yield of EEG: total or partial sleep deprivation, cont. at least 30 min after awakening, PS, HV, EMG


FP1-F3
F3-C3
C3-P3
P3-O1
FP2-F4
F4-C4
C4-P4
P4-O2
FP1-F7
F7-T3
T3-T5
T5-O1
FP2-F8
F8-T4
T4-T6
T6-O2
FZ-CZ
CZ-PZ
Spike F4

JME MANAGEMENT

ASMs

- VPA is efficacious
  - Avoid in women of child-bearing age
- LEV, LTG may be effective
- Myoclonic seizure worsened by CBZ, OXC, PHT, GBP, VGB

Counselling

- Lifestyle modification
- Medication compliance
- Avoid alcohol & illicit drug
- Avoid sleep deprivation
- Avoid flashing lights (40-90% photosensitive)

NATURAL HISTORY

- 65%– 92% of patients are drug responsive
- Sodium channel blockers often aggravate myoclonic and absence seizures
- Lamotrigine may aggravate myoclonic seizures in some patients
- Usually considered a lifelong disorder, often requiring lifelong therapy
  - Occasional cases may successfully discontinue ASMs later in life

EPILEPSY WITH GENERALIZED TONIC-CLONIC SEIZURES ALONE

EPILEPSY WITH GTCS ALONE

- Typical age of onset of 16 years (6-28)
- Seizure peak in early morning
- Small peak upon falling sleep/naps or in the evening
- EEG: 4-5 Hz generalized spike/polyspike-and-slow-wave
- Triggers: sleep deprivation, photic stimulation, stress, alcohol
- Pharmacoresponsive, but lifelong predisposition to seizure expected

Summary clinical presentation of GGE

Table 1 | **Typical clinical presentations of GGE syndromes**

Syndrome	Approximate proportion of adults with GGE (%)	Seizure types	Typical age at onset (peak) (years)	Sex ratio
Childhood absence epilepsy	15	Absence (100%)[a] Tonic–clonic (20%)	4–12 (6)	F > M
Juvenile absence epilepsy	15	Absence (100%)[b] Tonic–clonic (90%)[c]	8–20 (14)	F = M
Juvenile myoclonic epilepsy	45	Myoclonic (100%) Absence (30%)[b] Tonic–clonic (90%)[d]	6–25 (14)	F ≥ M
Epilepsy with generalized tonic–clonic seizures alone	25	Tonic–clonic (100%)	5–40 (17)	F = M

Overlaps:
CAE & JAE

Phonotypic inconclusive in about 1/5

Evolving:
CAE → JME

Nat Rev Neurol. 2022;18(2):71–83.

EPILEPSY WITH READING INDUCED SEIZURE

EWRIS

- Rare combined generalized and focal epilepsy syndrome
- Reflex myoclonic seizures affecting orofacial muscles triggered by reading +/- → BTC
- Triggers: reading, language related task (talk, writing, making complex decision)
- Typically in late teens (median=17.5 years, range = 10–46 years)
- Developmental, neuro exam, MRI: normal
- Favorable prognosis

EPILEPSY SYNDROME WITH DE AND/OR EE OR WITH PROGRESSIVE NEUROLOGICAL DETERIORATION

- NORSE & Febrile infection related epilepsy syndrome (FIRES)
- Rasmussen syndrome (RS)
- Progressive myoclonic epilepsy (PME)

NEW ONSET REFRACTORY STATUS EPILEPTICUS (NORSE)
&
FEBRILE INFECTION RELATED EPILEPSY SYNDROME (FIRES)

NEW-ONSET REFRACTORY STATUS EPILEPTICUS

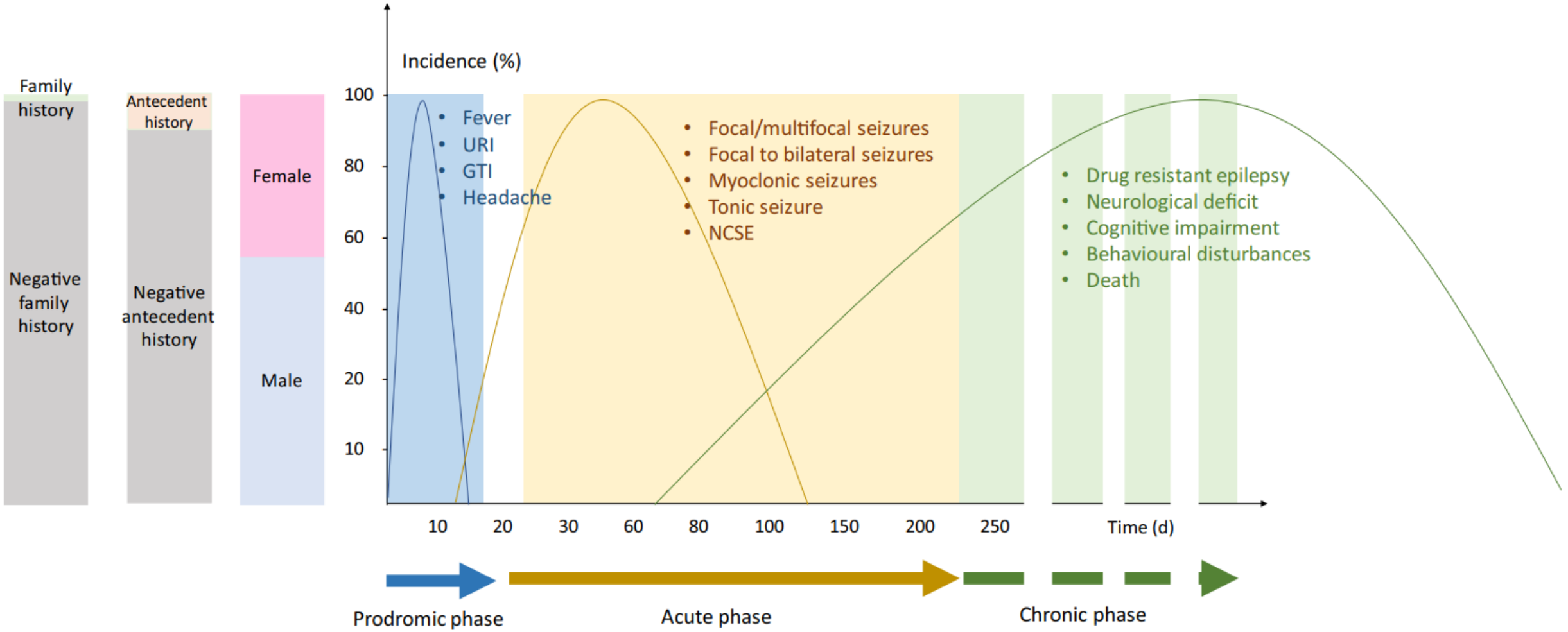
- Rare clinical presentations characterized by **de novo onset of RSE** in patient without active epilepsy and without clearly identifiable acute or active structural, toxic, or metabolic cause

- FIRES is considered a subcategory of NORSE, diagnosis requires prior **febrile infection starting between 2 weeks and 24 hours** before onset of RSE

NORSE & FIRES

- Mainly affect school-age children and young adults
- **Acute phase**: high seizure burden, lasts 1–12 weeks
- **Chronic phase**: drug-resistant multifocal epilepsy and intellectual disability or learning difficulties

Clinical findings of FIRES & NORSE



Developmental Medicine & Child Neurology 2020,62: 897–905.

Etiology assessment

Etiology

Unknown 50%

Infection 10%

Inflammatory, autoimmune 40%

Genetic: rare Mitochondrial, POLG1, SCN1A, PCDH19, CADASIL

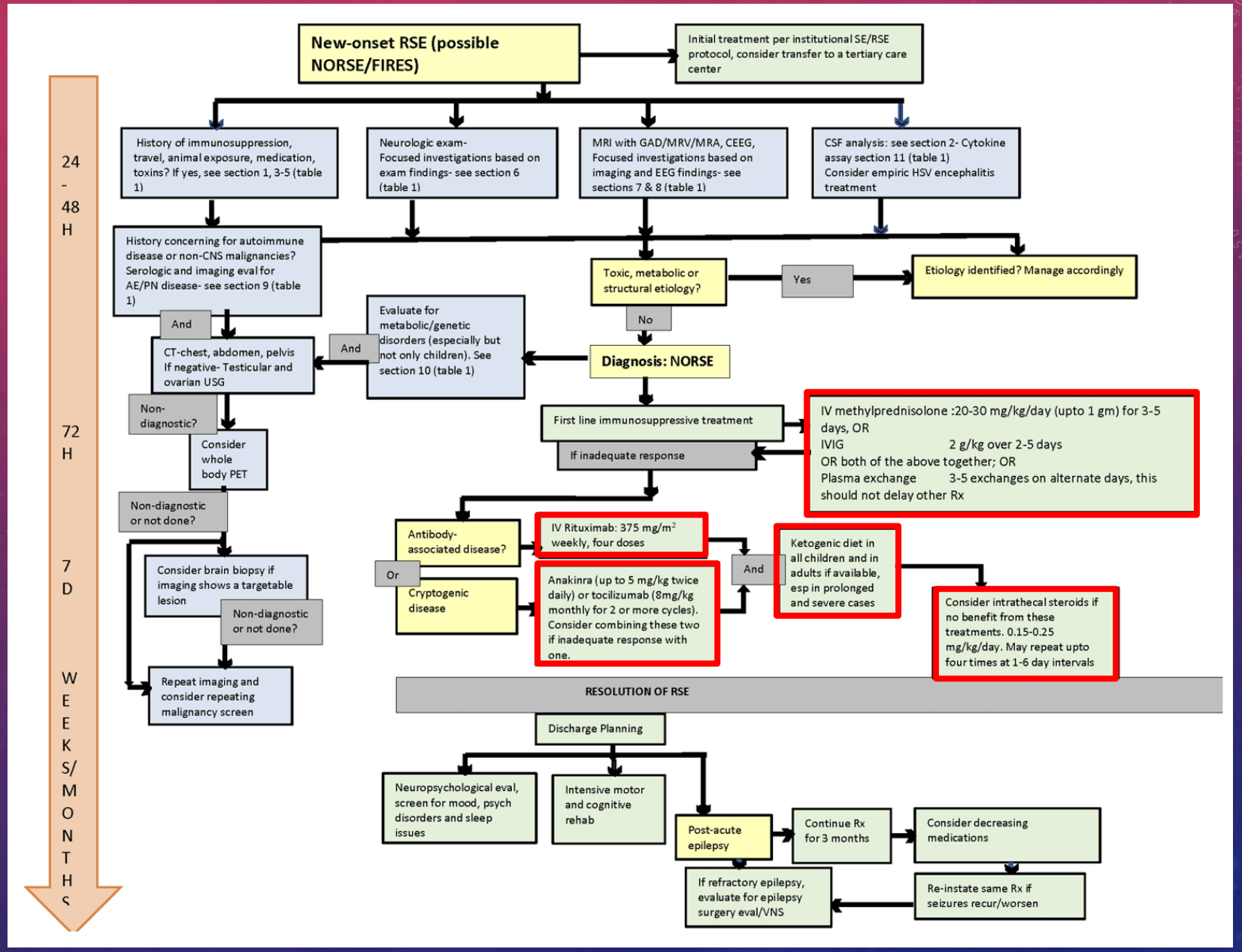
Seizure 2019;68:72-8.

Table 1 – Aetiological assessment. Adapted from [14,40].

Recommended in all patients	
MRI brain with contrast angiography and venography	
Blood and serum analysis	Standard biological assessment
	Autoimmune antibody panel: ANA, ANCA, anti-thyroid, anti-neuronal surface antigens, onconeuronal antibody panel
	VDRL, HIV 1-2, bacterial and fungal cultures
	Bacterial serologies: Chlamydia pneumoniae, Bartonella henselae, Mycoplasma pneumonia, Coxiella burnetii, Shigella sp. and Chlamydia psittaci
Nasopharyngeal swab	Respiratory viral DFA panel; SARS-CoV2 PCR
Gastrointestinal pathogens	Multiplex PCR
CSF	Cell counts, protein, and glucose, immunoelectrophoresis
	Bacterial and fungal stains and cultures including *Mycobacterium tuberculosis*
	RT-PCR for HIV, PCR for HSV1-2, VZV, EBV
	PCR for *Chlamydia pneumoniae*, *Bartonella henselae*, *Mycoplasma pneumonia*, *Coxiella burnetii*, *Shigella* sp.
	VDRL, Lyme
	Paraneoplastic and autoimmune epilepsy antibody panel
EEG	
Immunocompromised patients	
Serum analysis	Serology for cryptococcus species, *Histoplasma capsulatum*, *Toxoplasma gondii*
CSF	Stain for fungi, PCR for *Toxoplasma gondii*, JC Virus, CMV, HHV6, parvovirus ± West Nile Virus
Risk of exposure to specific pathogens according to geographical factors	
Oncological screening	
Serum analysis	Cancer serum markers
CSF	CSF cytology and flow cytometry
CT chest-abdomen-pelvis, pelvic or scrotal ultrasound, pelvic MRI, mammogram whole body PET CT	
Screening for inborn error of metabolism and mitochondrial disorders	
Ammonia, acute porphyria screen, LDH, urine analysis	
Plasma and CSF lactate, pyruvate, muscle biopsy	
Genetic screening	
Panel, whole exome, CGH array, mitochondrial genome sequencing	
Brain biopsy	

Rev neurol (Paris). 2022;178:74 – 83.

Flow diagram for evaluation and management of NORSE/FIRES



Front Neurol. 2023;14:1150496.

TREATMENT OF FIRES & NORSE

- Management of seizures in initial 24–48 h should be like any case of RSE
- First-line immunotherapy should begin within 72 h using steroids, IVIG, or plasmapheresis
- If no improvement, ketogenic diet and second-line immunotherapy should start within seven days
  - Rituximab if strong suggestion or proof of antibody-mediated disease
  - Anakinra or tocilizumab for cryptogenic cases
- Intensive motor and cognitive rehab are usually necessary
- Some may need continued immunologic treatments and epilepsy surgery evaluation

Front Neurol. 2023;14:1150496.

RASMUSSEN SYNDROME

RASMUSSEN SYNDROME

- Rare, severe chronic unilateral inflammation of cerebral cortex, drug-resistant epilepsy, and progressive neurological and cognitive deterioration

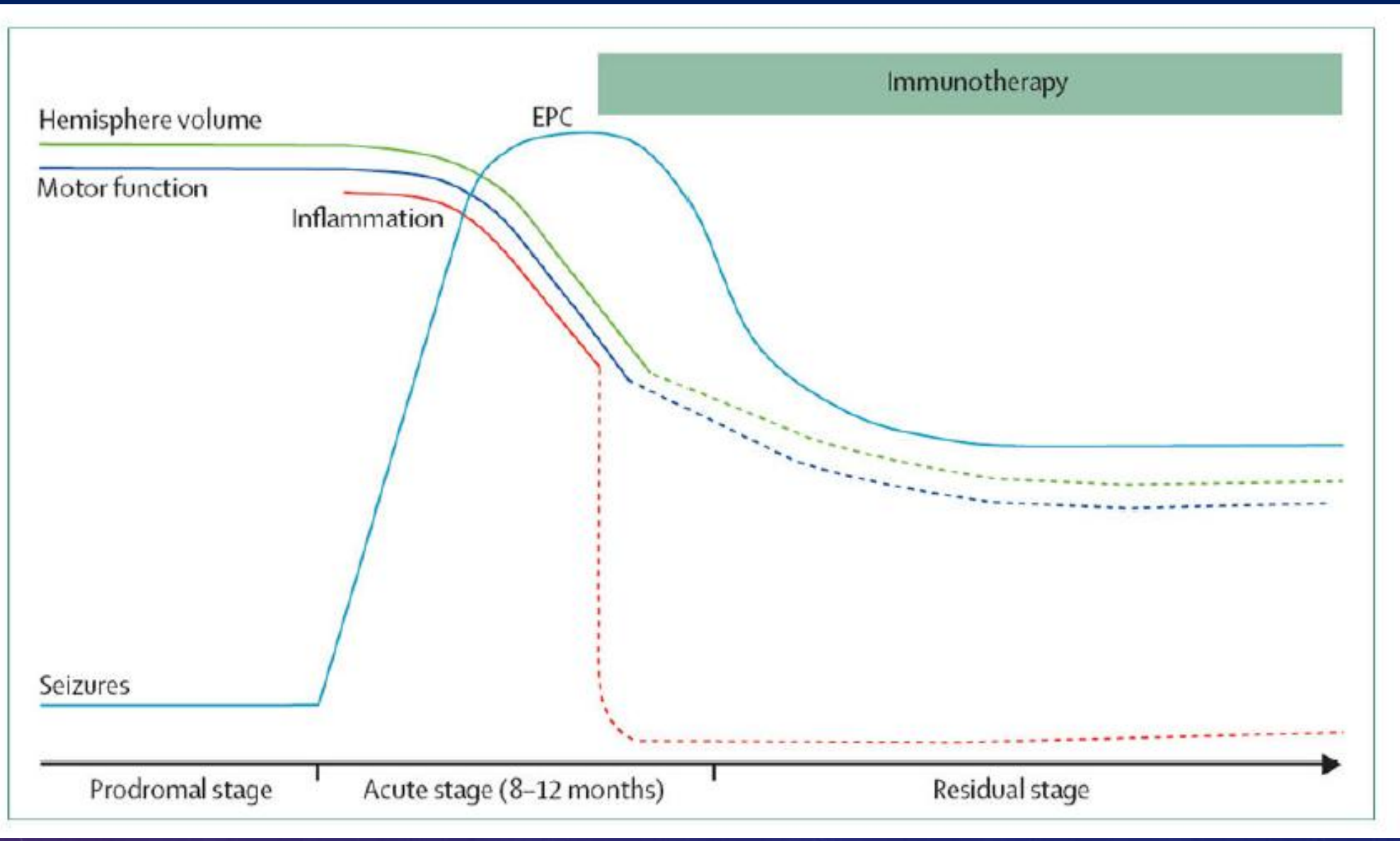
- Typical age of onset at 1–10 years (median 6 yrs)

- 10% adolescent and young adult
  - Clinical course in adolescent and adult usually slower and less severe final deficits

RASMUSSEN SYNDROME: THREE STAGES

- **Initial prodromal phase (lasting months to years)**
  - Infrequent seizures and mild hemiparesis
- **Acute phase (lasting months to years)**
  - Increasingly frequent seizures, at times with EPC, progressive hemiparesis, hemianopia, cognitive, language deterioration
- **Chronic phase**
  - Permanent stable hemiparesis and other neurological disabilities, continued seizures (less frequent than in acute stage)

Natural clinical course and expected effect of immunotherapy

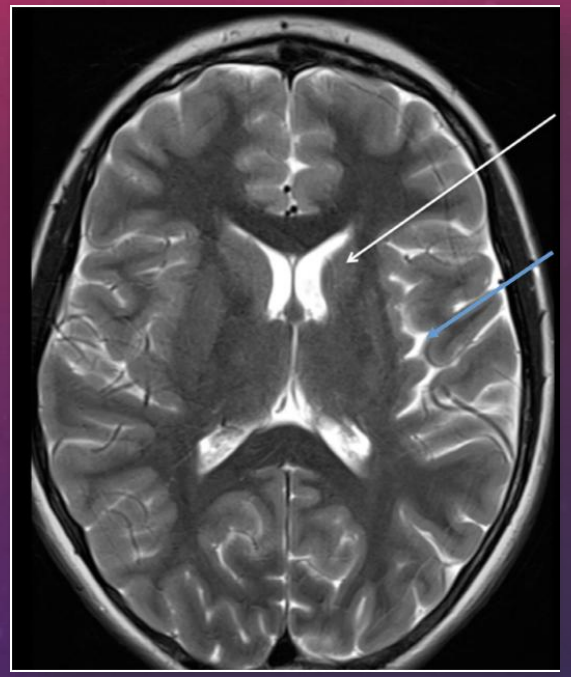


Lancet Neurol. 2014; 13(2):195–205.

MRI: Progressive hemispheric atrophy

Atrophy of head of caudate +

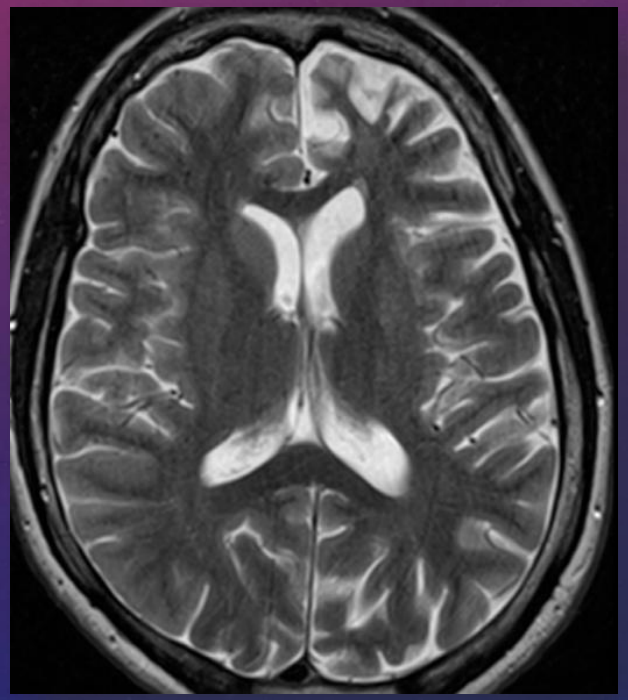
Subtle loss of volume of left insular region



‘FRONTO-INSULAR PREDILECTION’

Interval 8 years

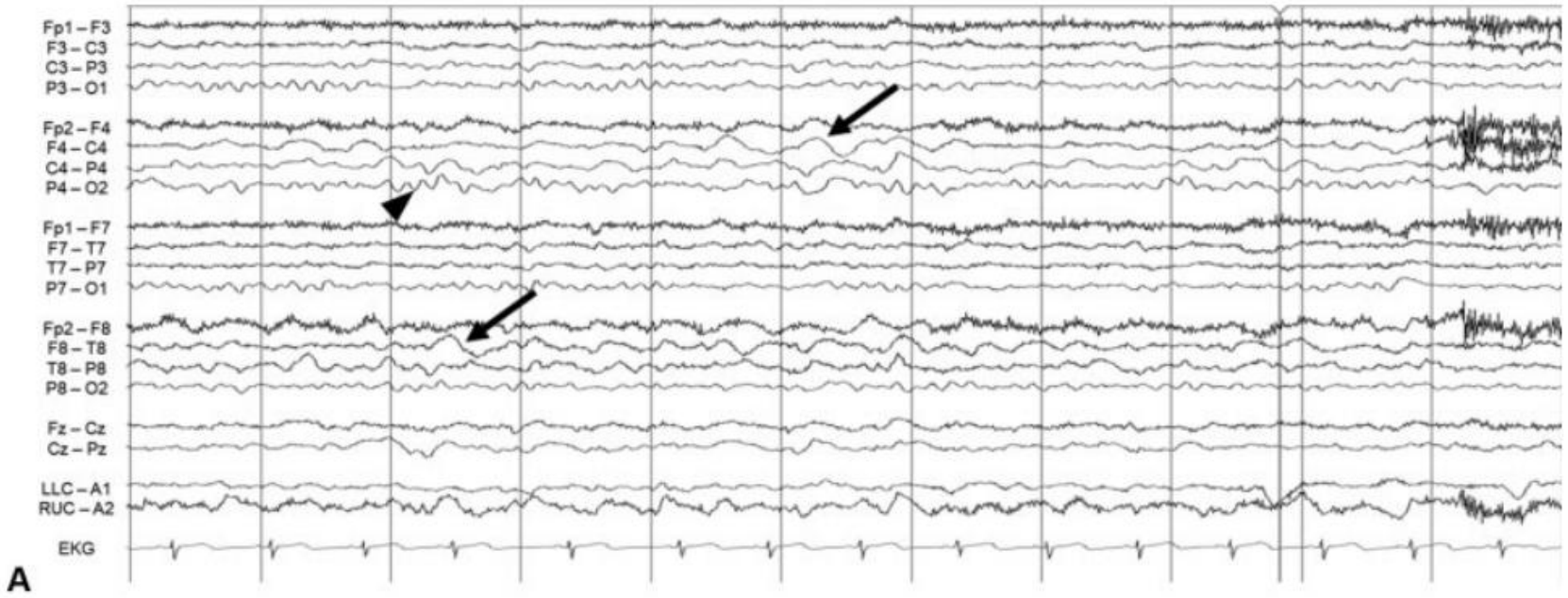
Increased atrophy of left hemisphere

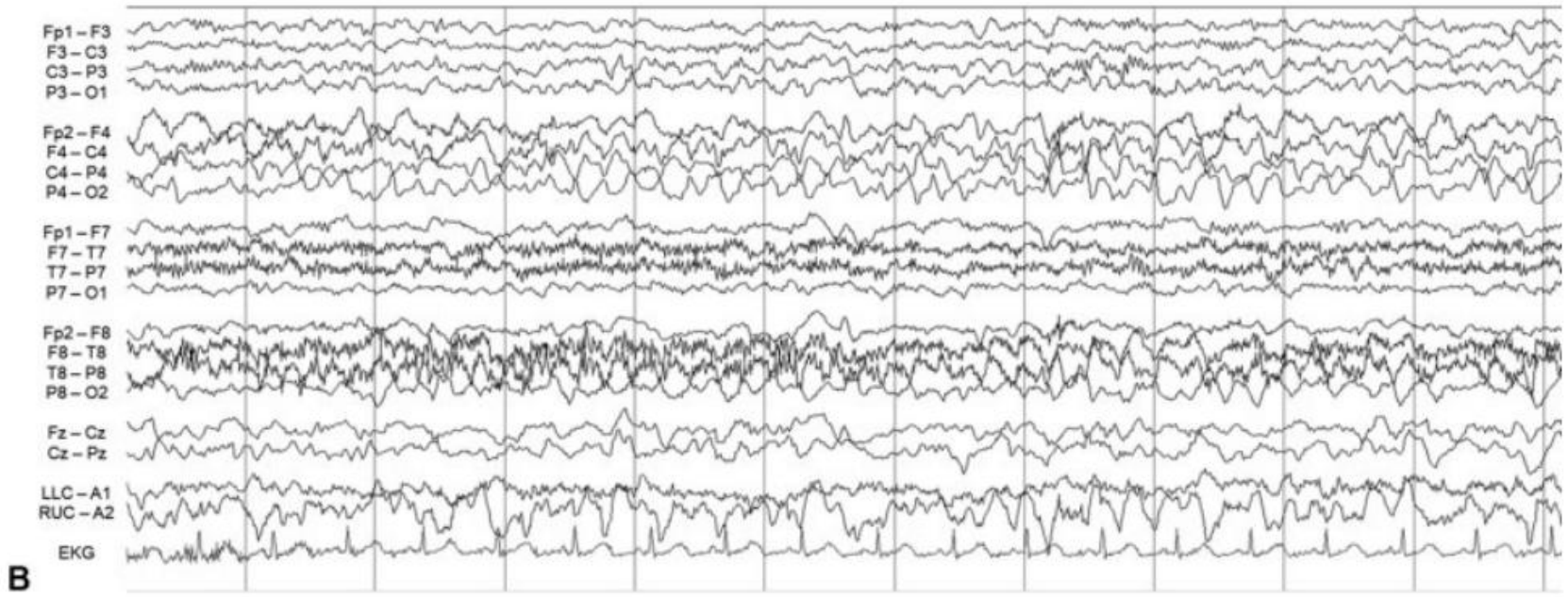


Epilepsia. 2022;63:1443–74.

EEG

- Unihemispheric slowing: first change
- Epileptiform discharges are present in affected hemisphere by 6 months
- Independent contralateral IED not present initially, seen increasingly after first few months, rising to 63- 94% by 4 to 5 years
- Unilateral seizure onset: Electro-clinical or NCS
  - EPC lack electrographic correlate in 43%





Semin Neurol 2020;40:201–210.

RASMUSSEN' ENCEPHALITIS DIAGNOSTIC CRITERIA OF BIEN ET AL (2005), SUGGESTED REVISIONS

Step 1: Check fulfillment of clinical, EEG, and MRI criteria in Part A (all 3)	
Part A	
Clinical	Focal seizures and unilateral cortical deficits
EEG	*Markedly lateralized* slowing **and** unilateral seizure onset
MRI	*Markedly lateralized* focal cortical atrophy **and** at least one of the following: • Gray or white matter T2/FLAIR hyperintensity • Ipsilateral caudate head atrophy **or** T2/FLAIR hyperintensity
Step 2: If criteria from Part A not fulfilled, check criteria in Part B (2 of 3)	
Part B	
Clinical	EPC **or** progressive[a] unilateral cortical deficits
MRI	Progressive[a] *markedly lateralized* cortical atrophy
Histopathology	T-cell–dominated encephalitis with activated microglial cells (typically, but not necessarily, forming nodules) and reactive astrogliosis; numerous parenchymal macrophages, B-cells, or plasma cells or viral inclusion bodies exclude the diagnosis of RE

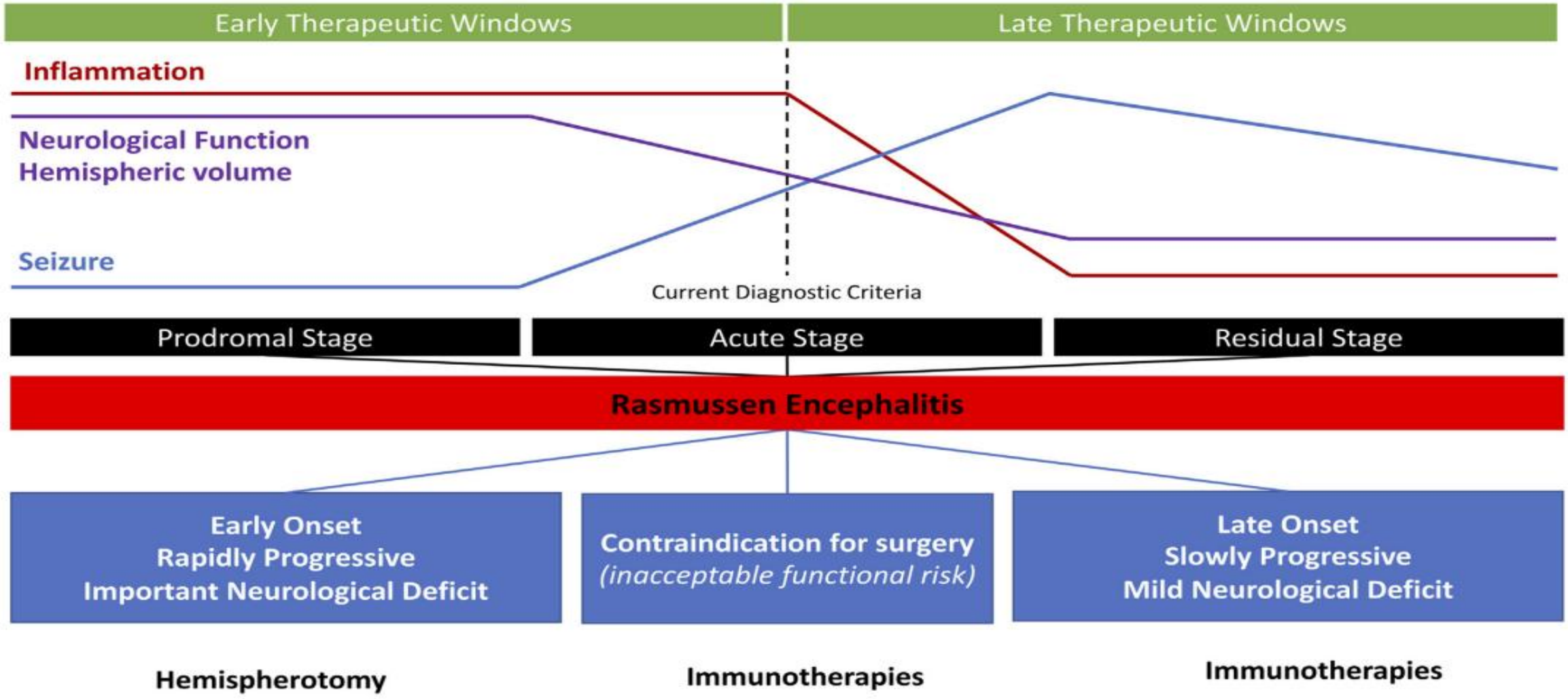
Semin Neurol 2020;40:201–210.

CORE DIAGNOSTIC CRITERIA FOR RASMUSSEN SYNDROME

Seizure	Focal/hemispheric seizures often increase in frequency over weeks to months
EEG	Hemispheric slowing and epileptiform abnormality
Imaging	Progressive hemiatrophy (early insula and head of caudate atrophy)
Long-term outcome	Drug-resistant epilepsy Progressive neurological deficits
MRI is required for diagnosis Ictal EEG is not required for diagnosis	

Epilepsia. 2022;63:1443–74.

Treatment: Medical therapy → Hemispheric disconnection surgery or hemispherectomy (only cure for seizure)



French Epilepsy congress 2021
Rev Neurol (Paris.)2022;178(7):675-691.

In case of immunotherapies failure -> re-evaluate surgical possibility
If surgery not considered -> change immunotherapy

PROGRESSIVE MYOCLONIC EPILEPSY

PME: GROUP OF NEURODEGENERATIVE DISEASE
DEBILITATING EVOLUTION, RESISTANCE TO TREATMENT, POOR PROGNOSIS

Key features

(1) Myoclonic seizure

(2) Progressive motor and cognitive impairment

(3) Sensory and cerebellar signs

(4) Abnormal background slowing on EEG, generalized spike/polyspike

(5) Prior normal development and cognition

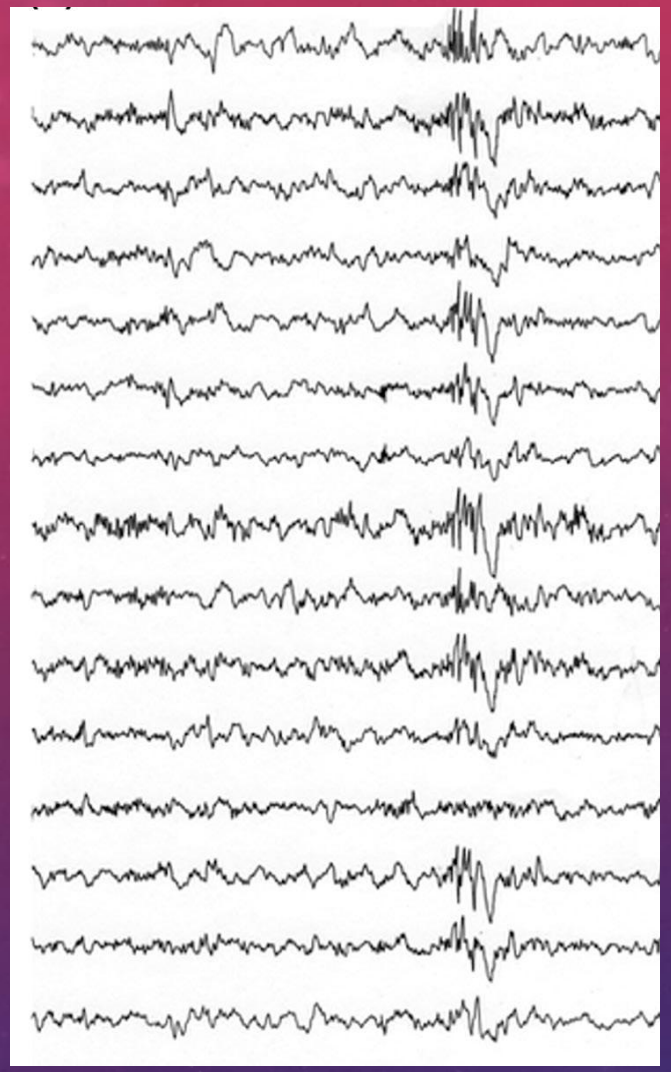
Photosensitivity is common feature

Other features: ataxia, dysarthria, vision loss, hearing loss, neuropathy, myopathy

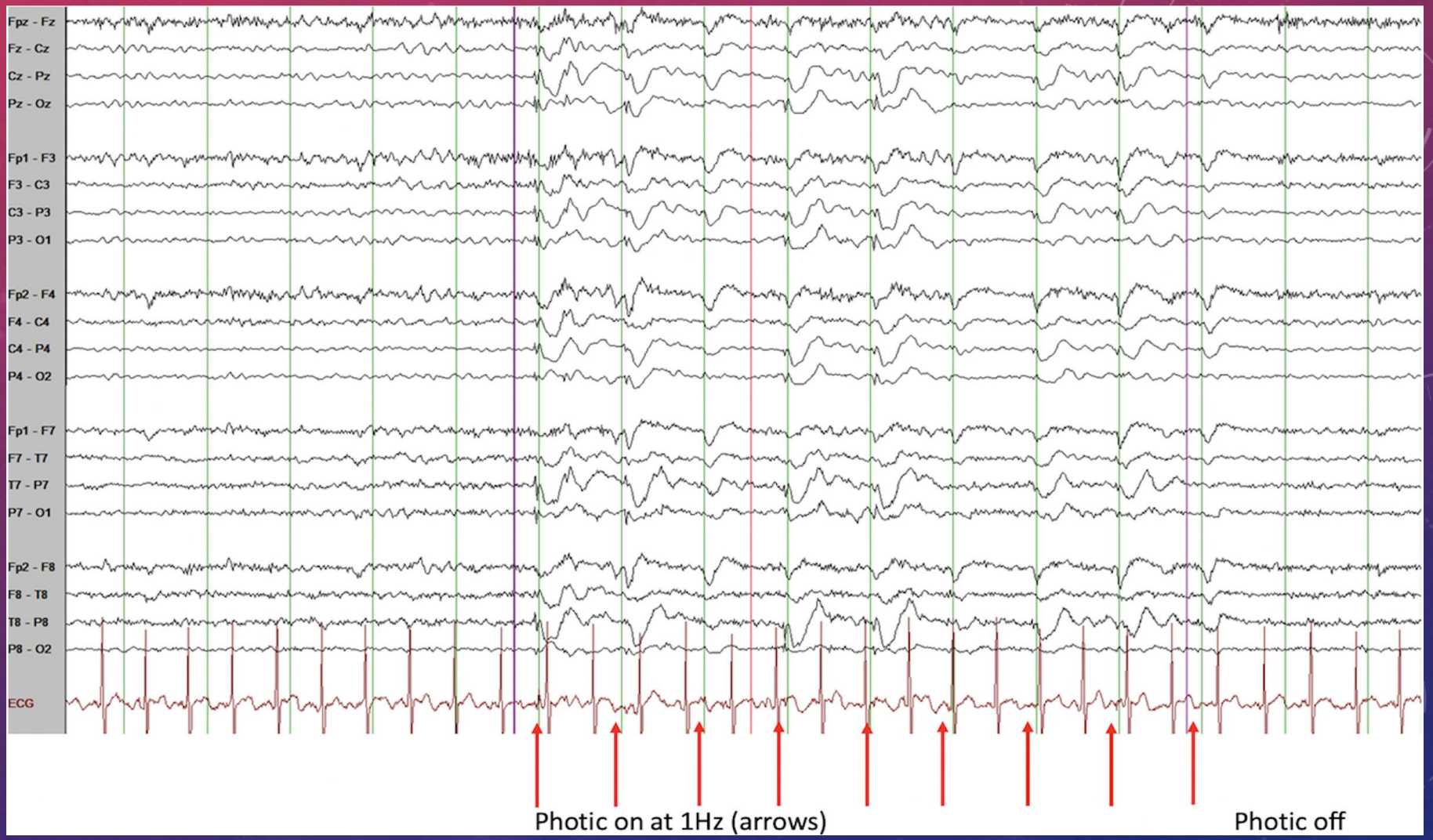
May be family history, AR inheritance in most cases, but can be sporadic

Usually childhood and adolescence onset

Severity and prognosis depend upon etiology



Generalized PSW



PPR at low frequency photic stimulation 1-3 Hz

Epilepsia. 2022;63:1443–1474.

PME (PROTOTYPES)

- Unverricht–Lundborg disease (ULD)
- Lafora disease
- Neuronal ceroid lipofuscinosis (NCL)
- Myoclonic epilepsy with ragged red fibers (MERRF)

Key characteristic of etiologies of PME

PME type	Age at onset	Progression	Diagnosis
ULD	7–13 years	Slow cognitive and motor deterioration with stabilization in adulthood	Cystatin B (*EMP1*) expansion variations account for ~90% of cases worldwide
LD	6–19 years	Early rapid cognitive, vision, and motor deterioration; fatal approximately a decade after onset; focal seizures with visual symptoms are an early feature	Laforin (*EMP2A*) pathogenic gene variant in 70%, malin (*EMP2B*) pathogenic gene variant in 27%, no pathogenic variant found in 3%; Lafora bodies are seen in sweat duct cells or other tissues
CLN2	2–4 years	Initial speech delay and seizures, subsequently deterioration in cognition and motor skills, and then vision loss emerges at 4–6 years of age	*CLN2/TPP1* pathogenic gene variants; TPP1 enzyme activity is reduced; EEG can show a photoparoxysmal response at low (1–3 Hz) frequency; curvilinear bodies profile of lipofuscin accumulation in tissues (e.g., skin) or lymphocytes
CLN3	4–10 years	Rapidly progressing vision loss, with macular degeneration, optic atrophy ± retinitis pigmentosa; survival: late teens—30 years	*CLN3* pathogenic gene variants; fingerprint profile of lipofuscin accumulation in tissue (e.g., skin) or lymphocytes; lymphocytes are vacuolated
Adult onset NCL (type A)	11–50 years	Slow development of dementia and ataxia; visual impairment is not expected	*CLN6* pathogenic gene variants (pathogenic variants in *CTSD*, *PPT1*, *CLN3*, *CLN5*, *CTSF*, and *GRN* also reported); mixed type inclusions (fingerprint, curvilinear, rectilinear) in tissue (e.g., skin) or lymphocytes

Abbreviations: TPP1, tripeptidyl-peptidase 1; PME, progressive myoclonus epilepsies; MRI, magnetic resonance imaging; ULD, Unverricht–Lundborg disease; LD, Lafora disease; CLN, ceroid lipofuscinosis; NCL, neuronal ceroid lipofuscinosis; EEG, electroencephalogram.

Epilepsia. 2022;63:1443–1474.

TREATMENT

- Pharmacotherapy: VPA, LEV, BZD, TPM, ZND, PER
- Dietary treatment; KD, modified atkins diet
- Neuromodulation: VNS, DBS, rTMS
- Immunomodulation
- Enzyme replacement therapy: cerliponase alpha (CLN2)
- Gene therapy

Thank you for your attention