


Epilepsy Syndromes in Neonates/Infants/Children

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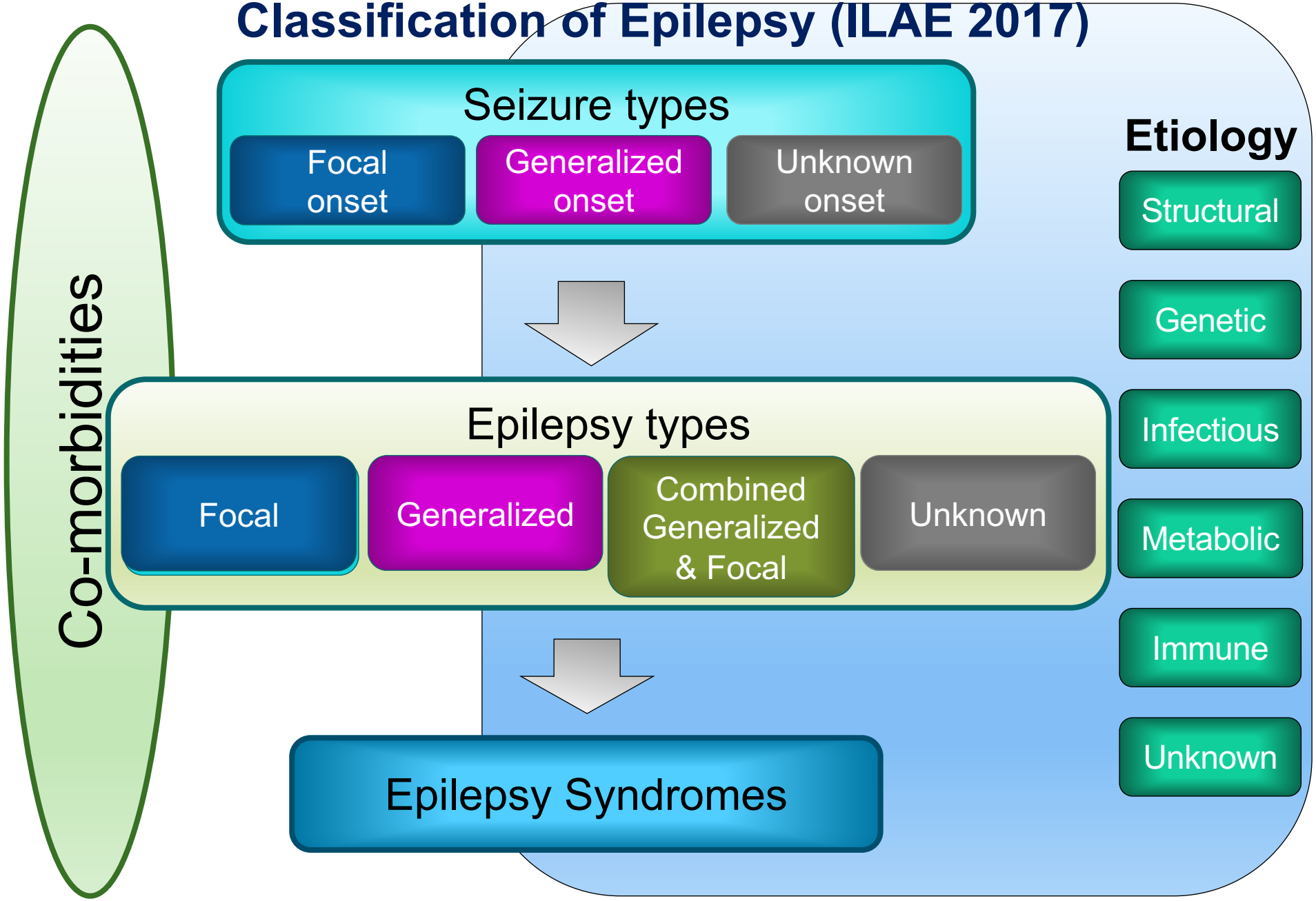
Outline

- Introduction to epilepsy syndromes (ILAE Task Force 2022)
- Epilepsy syndromes with onset in neonates/infants
- Epilepsy syndromes with onset in childhood

Classification of Epilepsy (ILAE 2017)

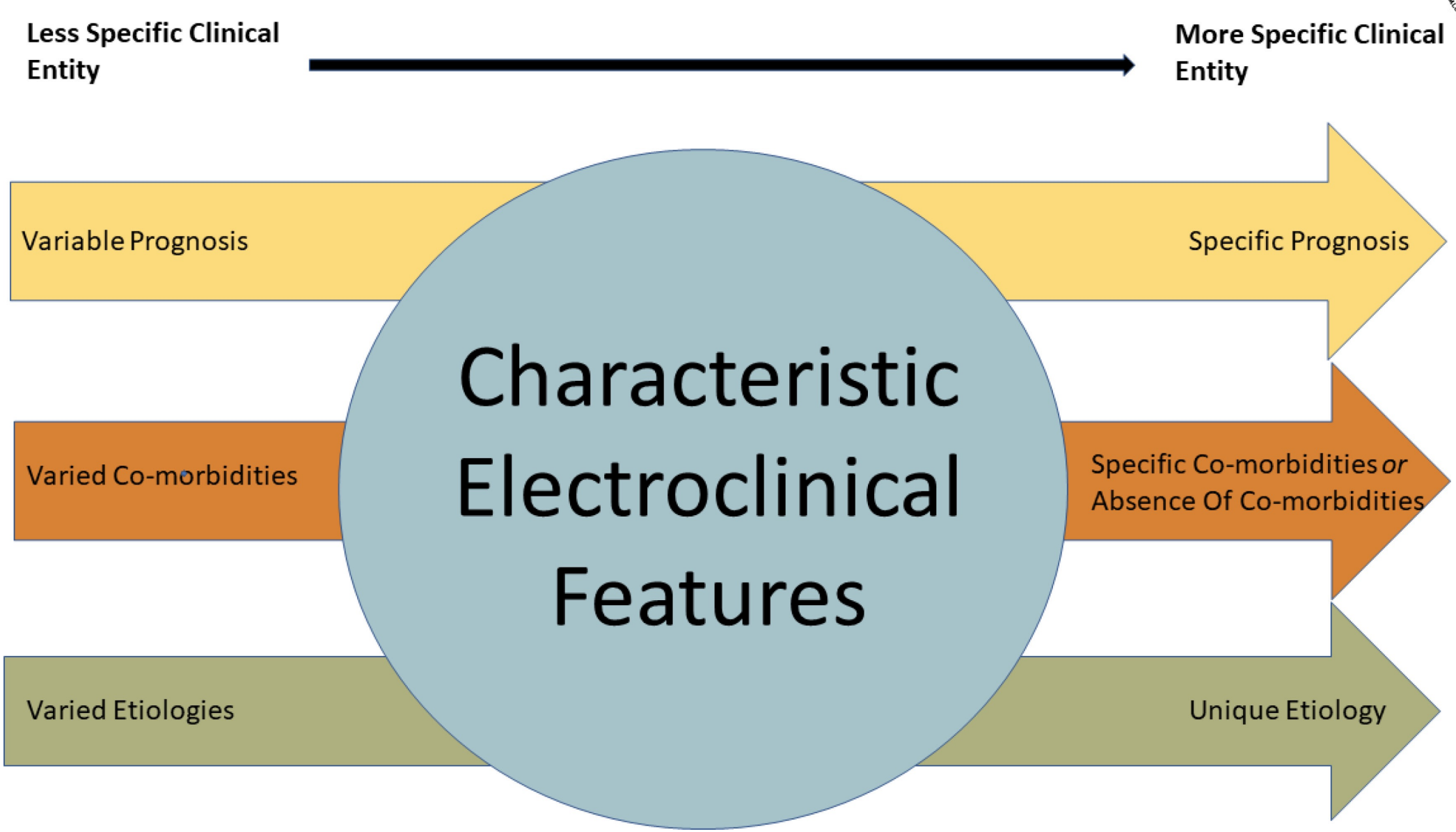


Epilepsy Syndrome

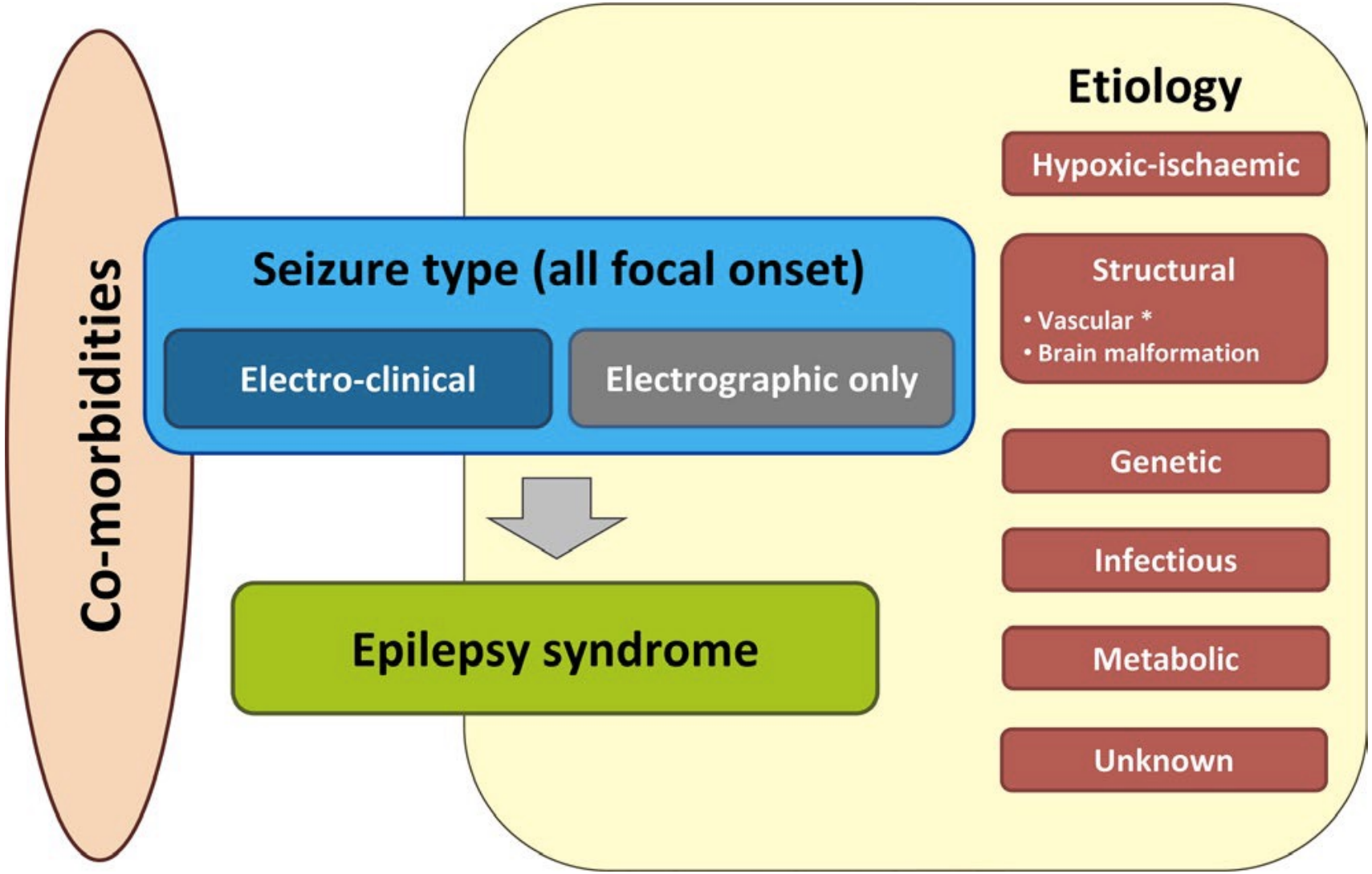
- A characteristic cluster of clinical and EEG features, often supported by specific etiological findings (structural, genetic, metabolic, immune, and infectious)

- The diagnosis of a syndrome in an individual with epilepsy frequently carries prognostic and treatment implications

Epilepsy Syndrome: Electroclinical Features



Framework of Neonatal Seizures and Epilepsy Syndromes



Pressler RM, et al., ILAE classification 2021

Seizure Type Classification

- **Motor**
  - automatisms
  - clonic
  - epileptic spasms
  - myoclonic
  - tonic
- **Non-motor**
  - autonomic
  - behavior arrest
- **Sequential**
- **Unclassified**

Seizure type	Descriptors
Automatisms	Unilateral Bilateral asymmetric Bilateral symmetric
Clonic seizures	Focal Multifocal Bilateral
Epileptic spasms	Unilateral Bilateral asymmetric Bilateral symmetric
Myoclonic seizures	Focal Multifocal Bilateral asymmetric Bilateral symmetric
Tonic seizures	Focal Bilateral asymmetric Bilateral symmetric

A single predominant feature can be determined in the majority of cases.
Pragmatically, classify seizures according to the predominant clinical manifestations

Pressler RM, et al., ILAE classification 2021

Epilepsy Syndromes with Onset in Neonates and Infants

ILAE classification and definition of epilepsy syndromes with onset in neonates and infants: Position statement by the ILAE Task Force on Nosology and Definitions

Sameer M. Zuberi[1] | Elaine Wirrell[2] | Elissa Yozawitz[3] | Jo M. Wilmshurst[4] | Nicola Specchio[5] | Kate Riney[6,7] | Ronit Pressler[8,9] | Stephane Auvin[10] | Pauline Samia[11] | Edouard Hirsch[12] | Santiago Galicchio[13] | Chahnez Triki[14] | O. Carter Snead[15] | Samuel Wiebe[16] | J. Helen Cross[17,18] | Paolo Tinuper[19,20] | Ingrid E. Scheffer[21] | Emilio Perucca[22,23] | Solomon L. Moshé[24,25,26] | Rima Nabbout[27]

Zuberi SM, et al, ILAE 2022

Epilepsy Classification

- Focal epilepsies
- Generalized epilepsies
- Developmental and epileptic encephalopathy (DEE)

Epilepsy Syndromes with Onset in Neonates and Infants

Self-limited epilepsies

- Self-limited neonatal epilepsy (SeLNE)
- Self-limited familial neonatal-infantile epilepsy (SeLFNIE)
- Self-limited infantile epilepsy (SeLIE)
- Genetic epilepsy with febrile seizures plus (GEFS+)
- Myoclonic epilepsy in infancy (MEI)

Developmental and epileptic encephalopathies (DEE)

- Ealy infantile developmental and epileptic encephalopathy (EIDEE)
- Epilepsy in infancy with migrating focal seizures (EIMFS)
- Infantile epileptic spasms syndrome (IESS)
- Dravet syndrome (DS)

Etiology-specific syndromes

- *KCNQ2*-DEE
- Pyridoxine-dependent (*ALDH7A1*)-DEE (PD-DEE)
- Pyridox(am)ine 5'-Phosphate Deficiency (PNPO)-DEE (P5PD-DEE)
- *CDKL5*-DEE
- *PCDH19* clustering epilepsy
- Glucose Transporter 1 Deficiency Syndrome (GLUT1DS)
- Sturge Weber syndrome (SWS)
- Gelastic seizures with hypothalamic hamartoma (GS-HH)

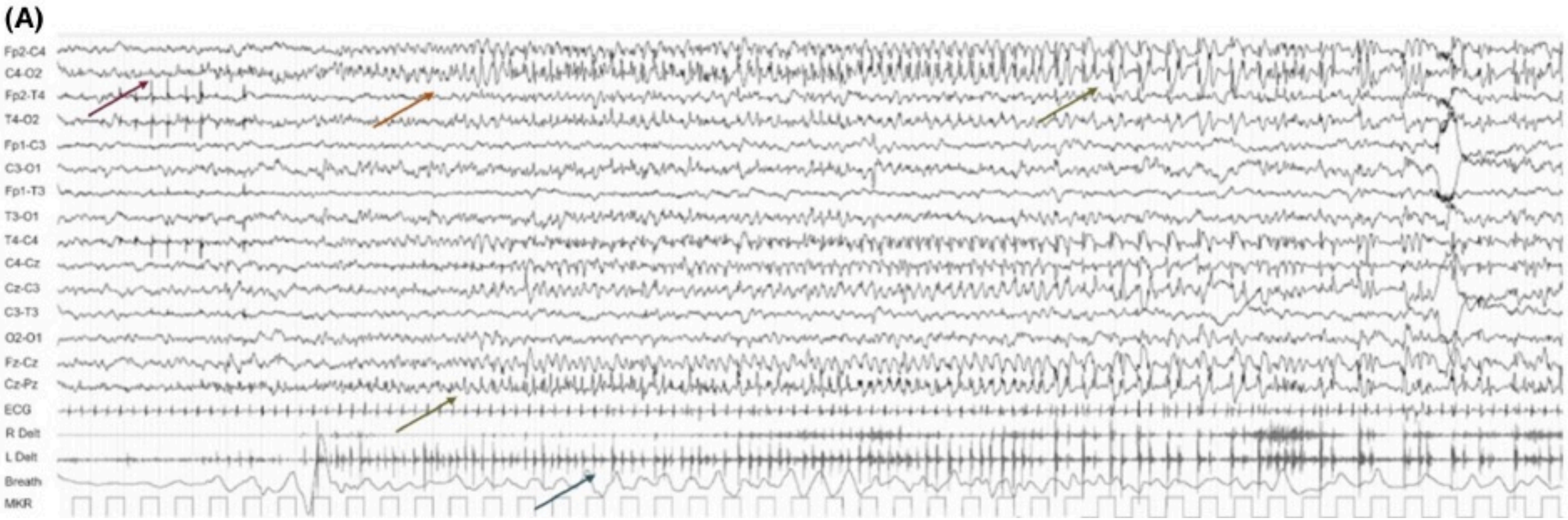
Zuberi SM, et al, ILAE 2022

Self-Limited Neonatal Epilepsy (SeLNE)

- Seizures occur between days of life 2-7
- Focal clonic or tonic seizurs may alternate sides
- May evolve to bilateral tonic or clonic seizures
- Normal clinical exam and head size
- EEG: normal background with or without spikes
- Ictal EEG: initial attenuation of EEG followed by repetitive spikes
- Neuroimaging: normal
- AD inheritance
- KCNQ2 (80%), KCNQ3, SCN2A mutation
- Seizures remit by 6 months of age (mostly by 6 weeks of age)

Zuberi SM, et al, ILAE 2022

Self-Limited Neonatal Epilepsy (SeLNE)



Zuberi SM, et al, ILAE 2022

Self-Limited Familial Neonatal-Infantile Epilepsy (SeLFNIE)

- Seizures occur from 1 day to 23 months of life
- Focal tonic seizures (head and eye deviation)
- Normal clinical exam, head size, and development
- EEG normal background with or without focal discharges
- Normal neuroimaging (if applicable)
- AD inheritance and a family history is required for diagnosis
- SCN2A (most common), KCNQ2 mutation
- Seizures cease by 12-24 months of life

Zuberi SM, et al, ILAE 2022

Self-Limited (Familial) Infantile Epilepsy (SeLIE)

- Formerly benign familial or non-familial infantile seizures
- Seizures occur 3 - 20 months of life (peak 6 months)
- Focal seizures are mandatory
- Normal clinical exam, head size, and development
- EEG normal background with or without midline spikes
- Normal neuroimaging (if applicable)
- De novo or familial inheritance
- PRRT2(most common), SCN8A mutation
- Seizures may be frequent at onset but usually remit within 1 year after onset

Zuberi SM, et al, ILAE 2022

Early-Infantile Developmental and Epileptic Encephalopathy (EIDEE)

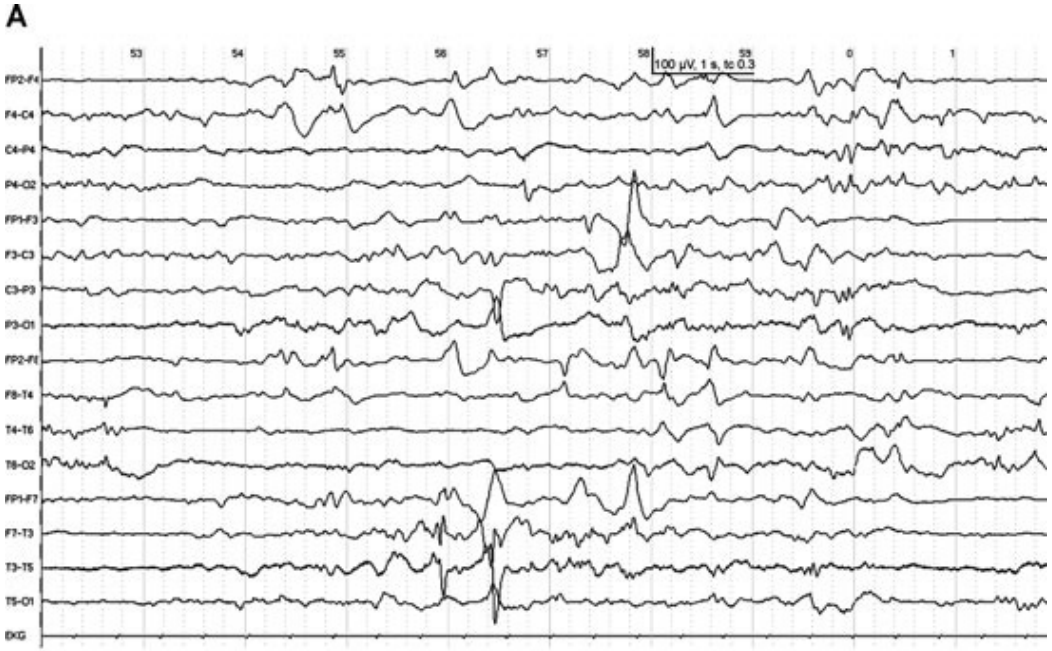
- Seizure onset within first 3 months of life
- Tonic and/or myoclonic seizures
- Frequent seizures and drug resistant
- Abnormal neurological exams
- EEG: burst suppression or multifocal discharges
- Various etiologies included genetic, metabolic, and structural
- Moderate to profound developmental impairment

Zuberi SM, et al, ILAE 2022

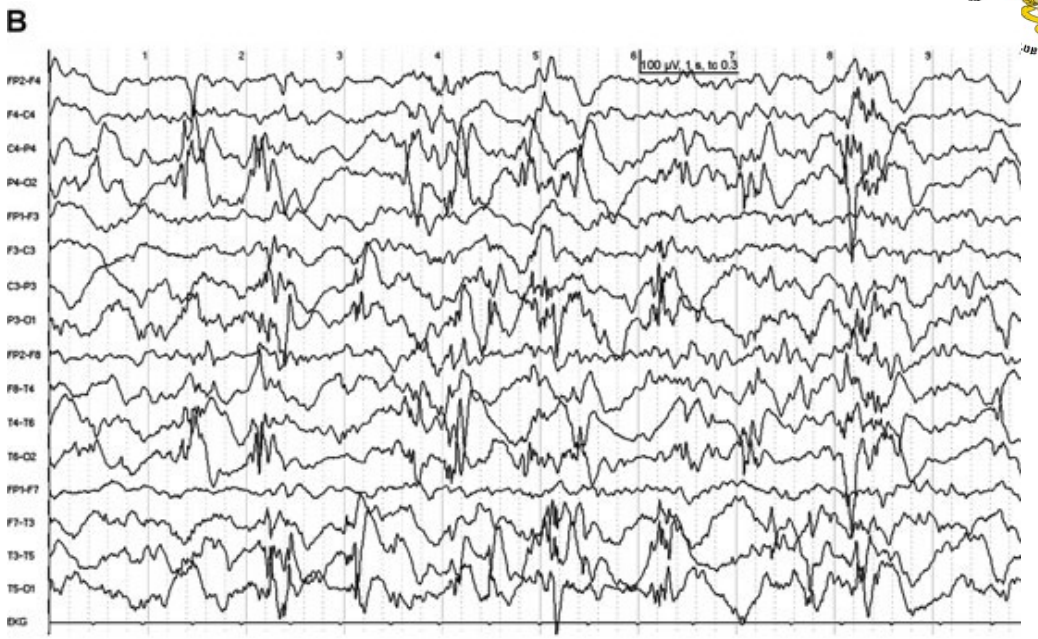
Infantile Epileptic Spasms Syndrome (IESS)

- Formerly as West syndrome
- Epileptic spasms (flexor, extensor, mixed)
- Spasms occur between 1-24 months of age
- Developmental slowing, arrest, or regression
- Interictal EEG: hysparrhythmia or multifocal spikes
- Ictal EEG shows electrodecremental response
- Various etiologies
- Carefully exam for tuberous sclerosis complex (TSC)
- Treatment: VGB for TSC, Steroid (ACTH or prednisolone) or combination therapy for non-TSC)

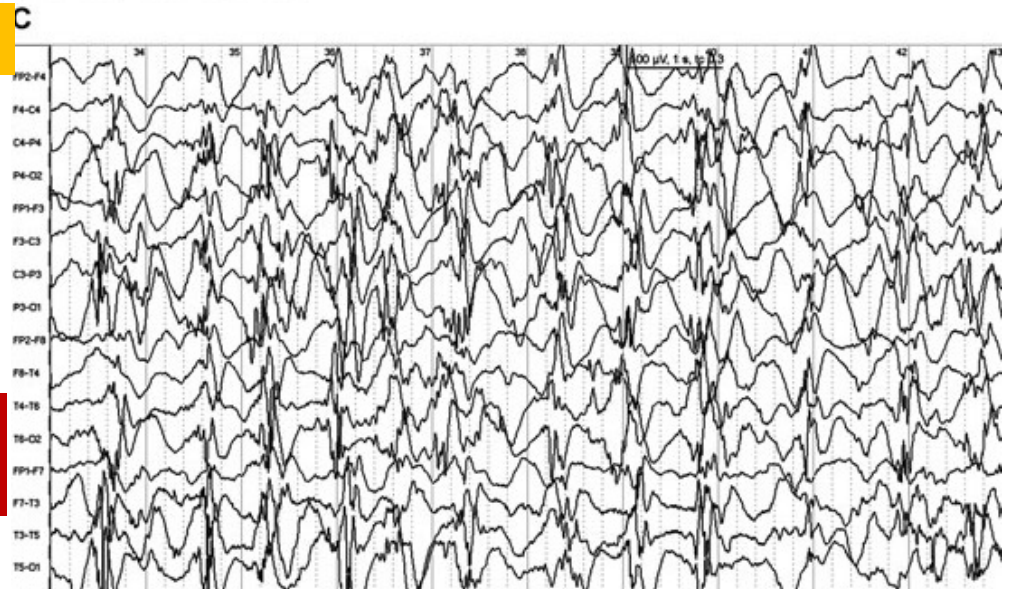
Evolution of Hysparrhythmia



Stage I: Multifocal spikes < 50%



Stage II: Bihemispheric sharp waves 50-90%

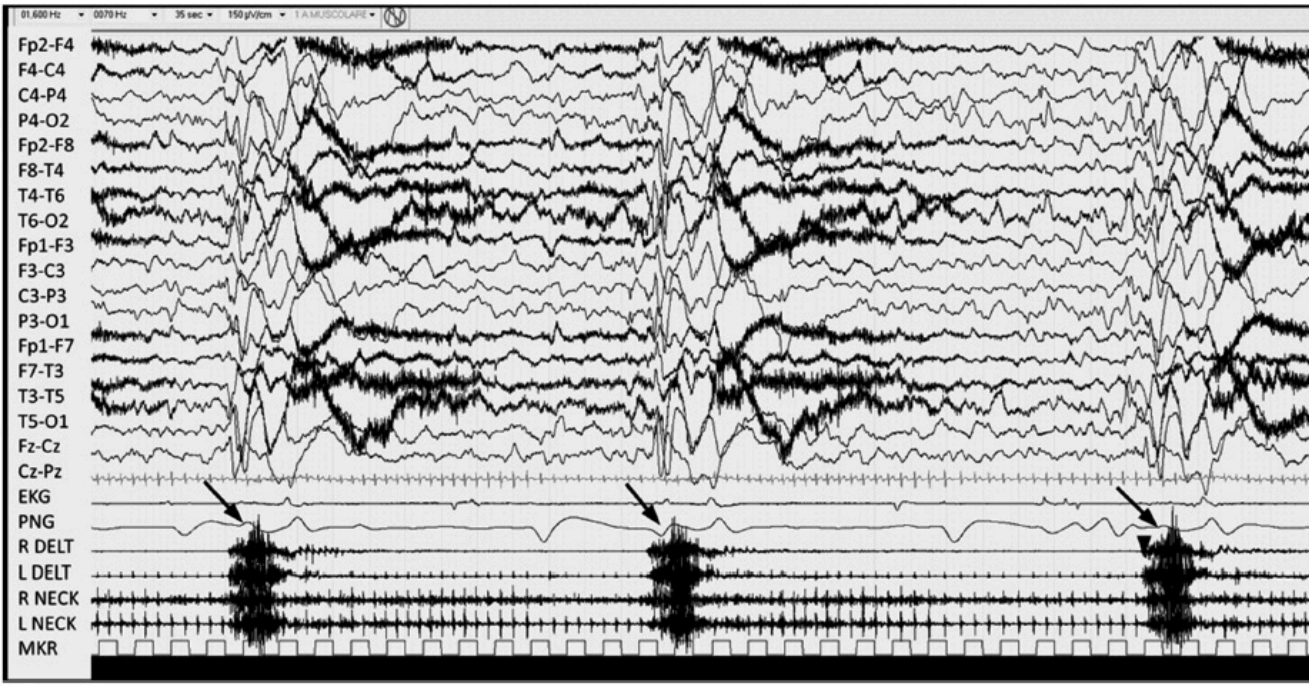


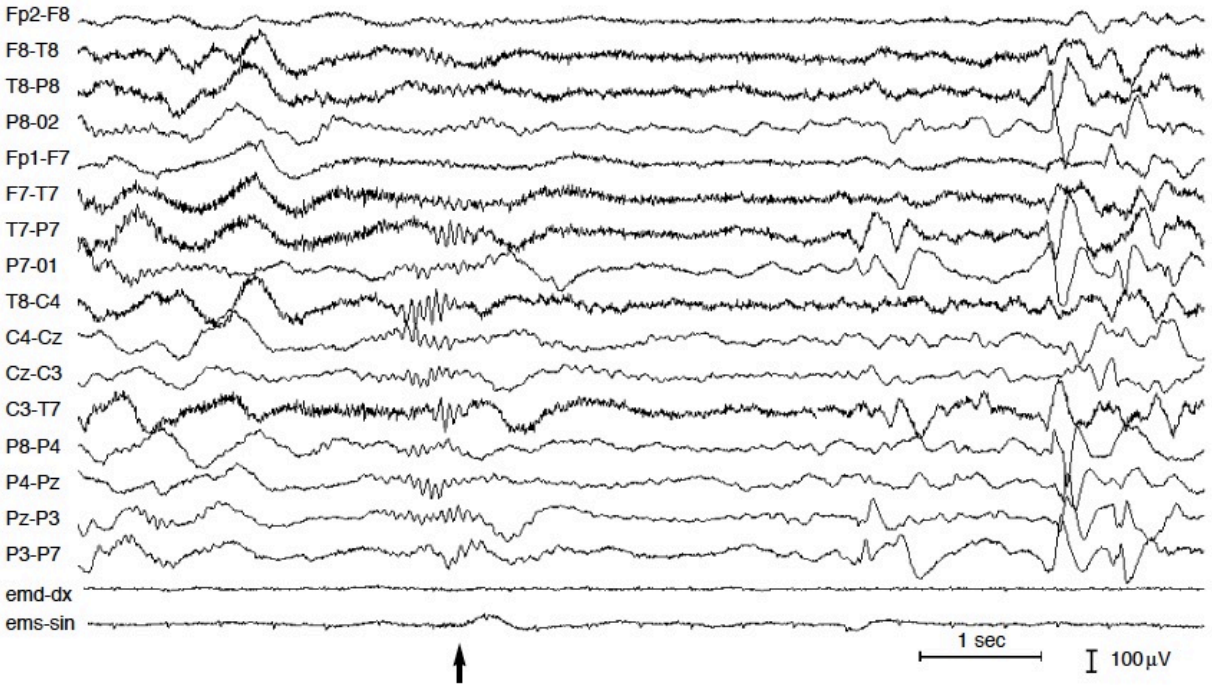
Stage III: Irregular bihemispheric sharp waves 90-100%

Poor interrater reliability;
K = 0.40

Philippi H, Epilepsia 2008,
Hussain S, Epilepsia 2015

Electrodecremental Response





Gaily E, Dev Med Child Neurol 2001

Evidence Based Treatment for Epileptic Spasms

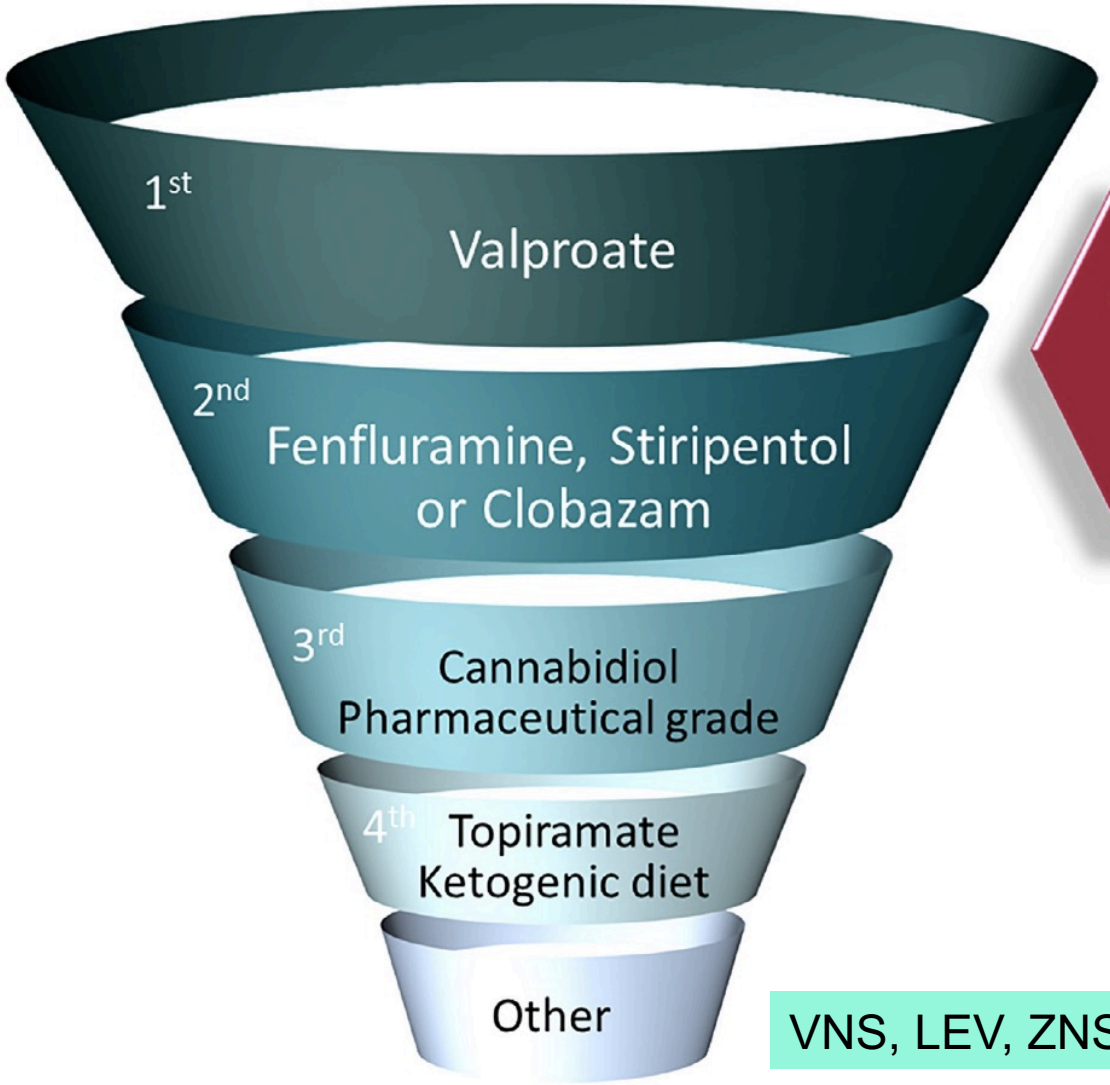
Study	Outcome Measure	Steroids	VGB
UKISS 2004 (non-TSC patients)	Spasm cessation on days 14	72% (40/55)	54% (28/52)
	Sustained spasms control with no relapse until 12-14 months of age	40% (22/55)	37% (19/52)
PERC 2016	Cessation of spasms within 2 wks of therapy, with EEG resolution sustained at 3 months	49% (74/151)	36% (17/47)
		Steroids alone	**Combined steroid and VGB**
ICISS 2017	Cessation of spasms between day 14-42	57%	72%

Dravet Syndrome

- Seizures present in 1-20 months of life
  - Recurrent hemiclonic seizures febrile or afebrile seizures
  - Prolonged seizures triggered by fever
- Normal growth and development as infants
- Drug resistant seizures evolved to myoclonic seizures, atypical absence, GTC, focal to bilateral GTC
- Initial EEG: normal prior to age 2 years
- EEG showed interictal discharges after 2 yo
- Developmental decline after 1-2 years of age, speech delay
- Genetic etiology: 70%-80% have **SCN1A** mutations

Zuberi SM, et al, ILAE 2022

Treatment Algorithm for Dravet Syndrome



AVOID
Carbamazepine,
Oxcarbazepine
Lamotrigine,
Phenytoin**

PHT may be helpful for SE

VNS, LEV, ZNS, CNZ

Wirrell EC, et al. Epilepsia 2022

GLUT1DS

- Cerebral “energy crisis”
- Symptoms develop in an age-specific pattern
- Infancy
  - Early onset absence epilepsy (< 4 oyo), Myoclonic-atonic seizures
  - Paroxysmal eye-head movement
- Movement disorders: paroxysmal or persistent
  - Ataxia, spastic, dystonia
- Acquired microcephaly and cogntive impairment
- LP shows hypoglycorrachia (< 40 mg/dL)
- SLC2A1 mutation or deletion/duplication
- Early ketogenic diet treatment: better intellectual outcomes

Klepper J, et al. Epilepsia Open 2020

Epilepsy Syndromes with Onset in Childhood

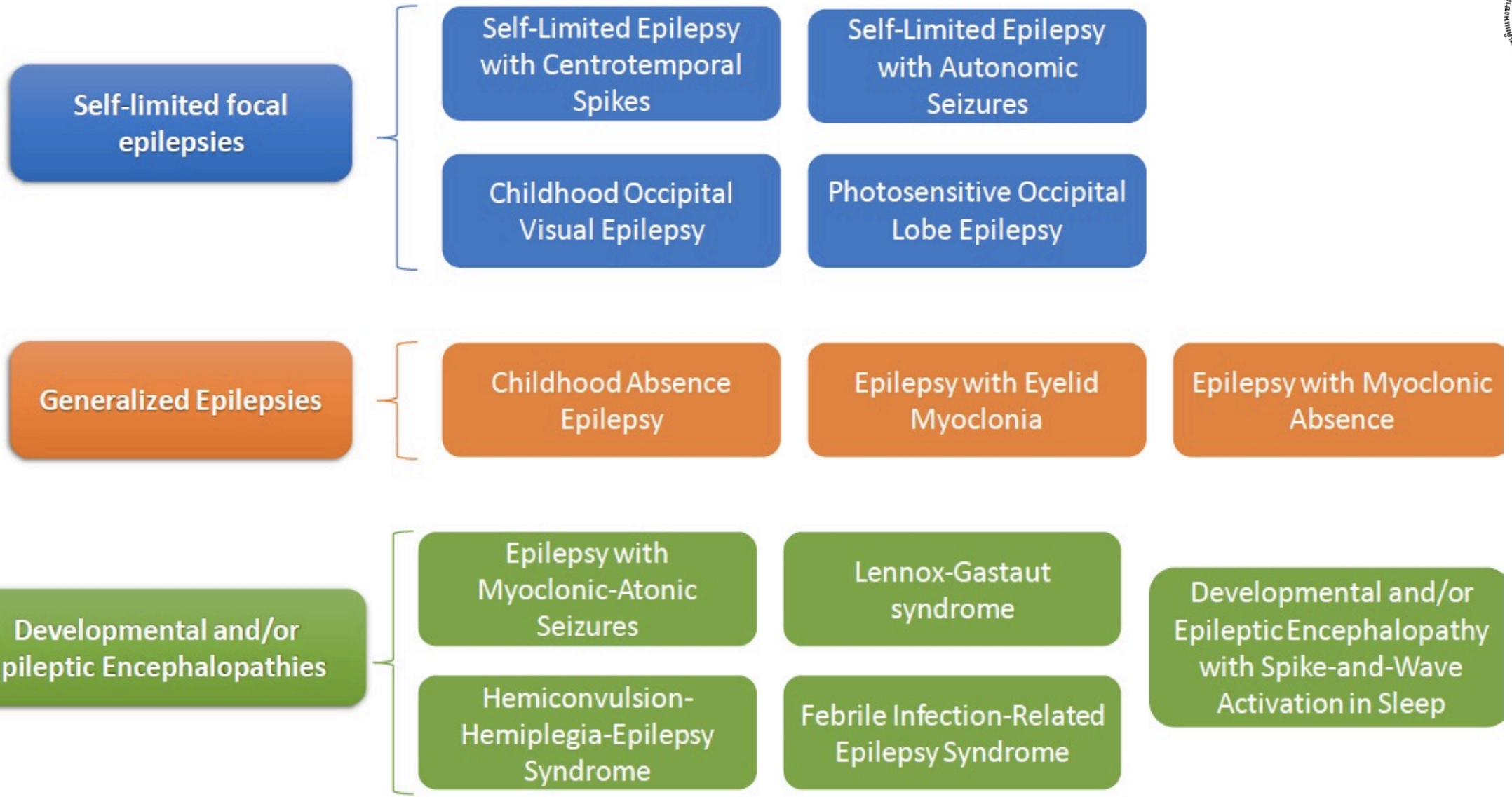
Epilepsia®

SPECIAL REPORT

International League Against Epilepsy classification and definition of epilepsy syndromes with onset in childhood: Position paper by the ILAE Task Force on Nosology and Definitions

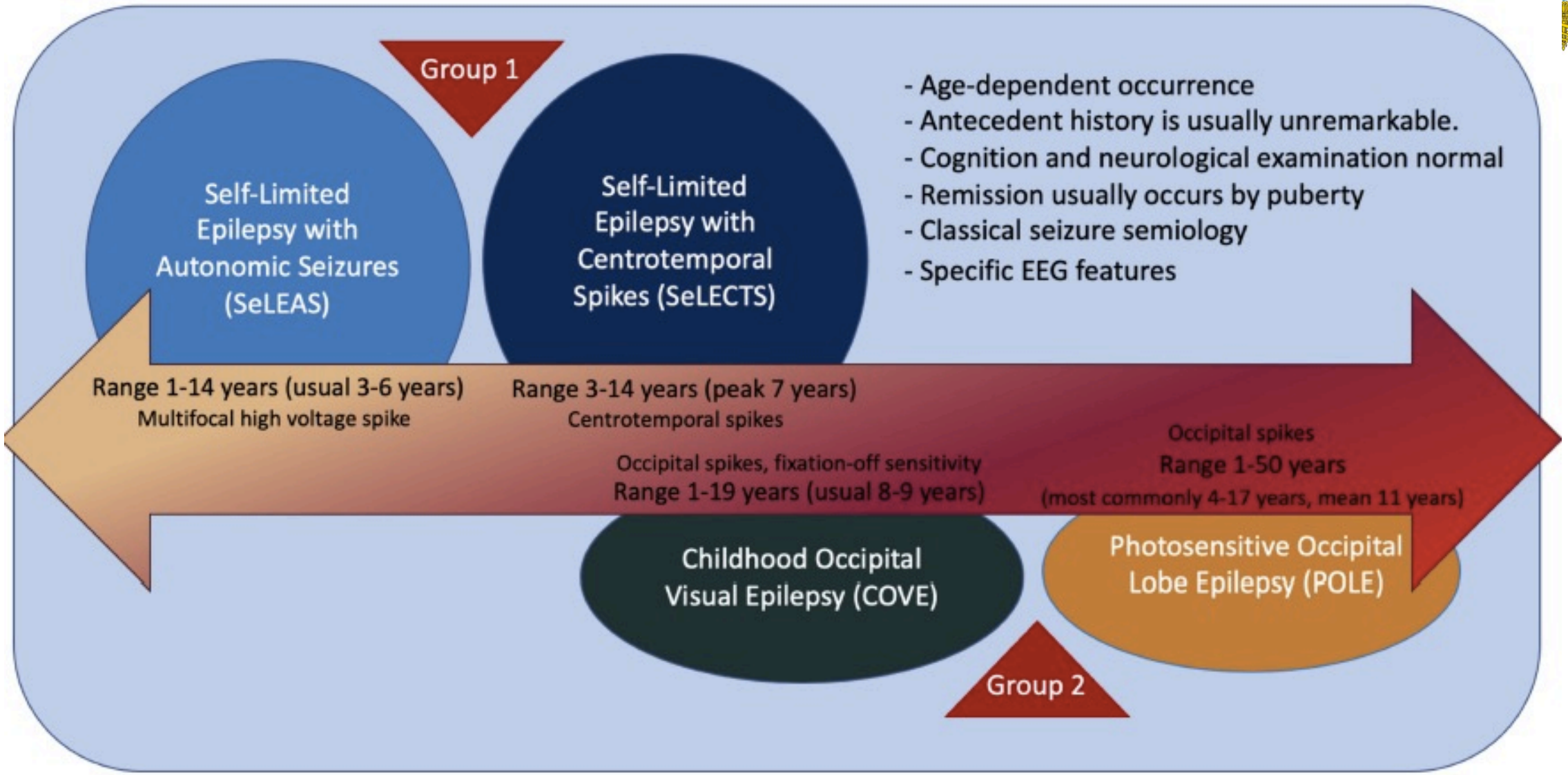
Nicola Specchio[1] | Elaine C. Wirrell[2] | Ingrid E. Scheffer[3] | Rima Nabbout[4] | Kate Riney[5,6] | Pauline Samia[7] | Marilisa Guerreiro[8] | Sam Gwer[9] | Sameer M. Zuberi[10] | Jo M. Wilmshurst[11] | Elissa Yozawitz[12] | Ronit Pressler[13] | Edouard Hirsch[14] | Sam Wiebe[15] | Helen J. Cross[16] | Emilio Perucca[17,18] | Solomon L. Moshé[19] | Paolo Tinuper[20,21] | Stéphane Auvin[22]

Specchio N, et al, ILAE 2022



Specchio N, et al, ILAE 2022

Self-Limited Focal Epilepsies



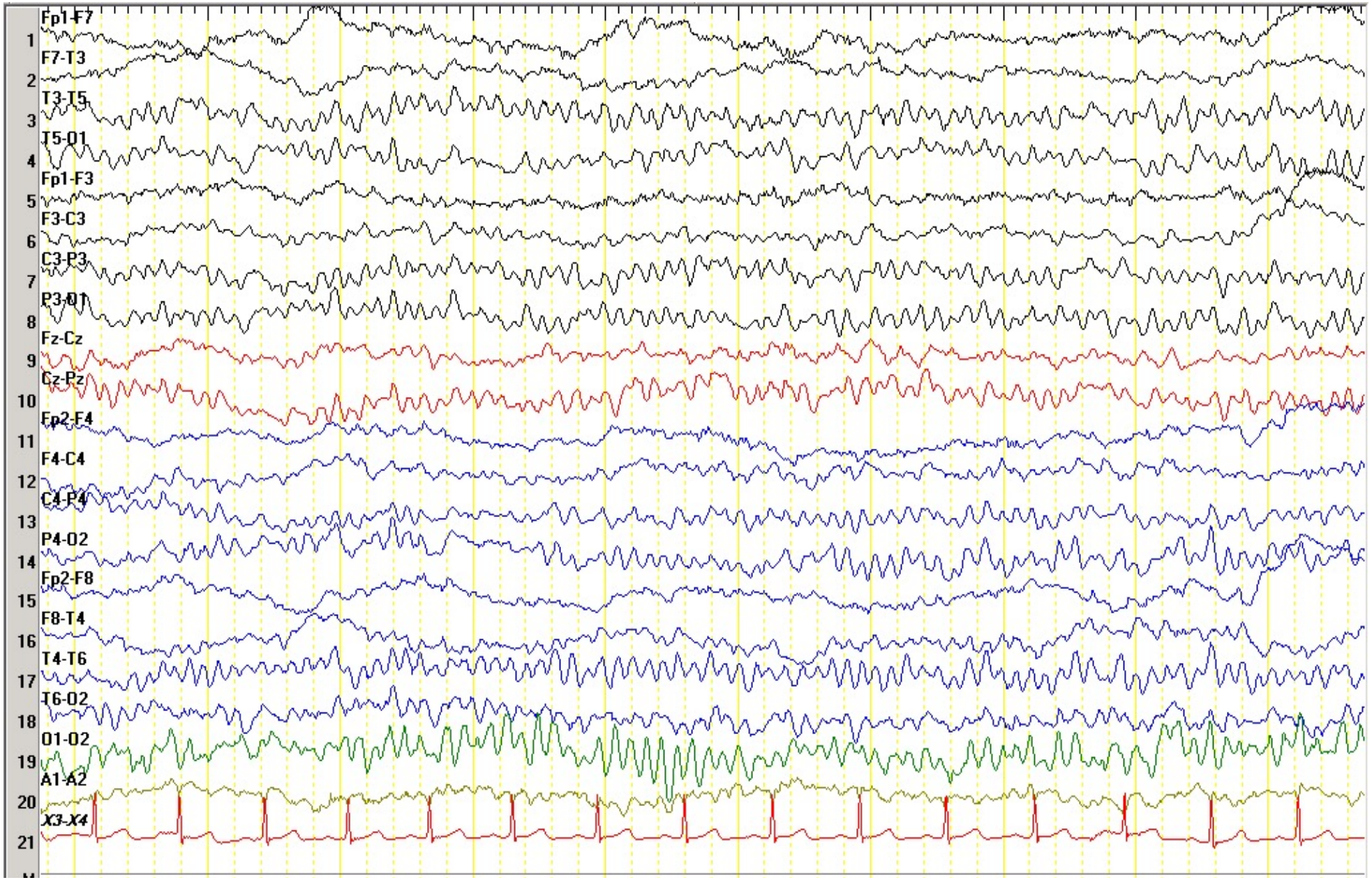
Specchio N, et al, ILAE 2022

Self-Limited Epilepsy with Centrotemporal Spikes (SeLECTs)

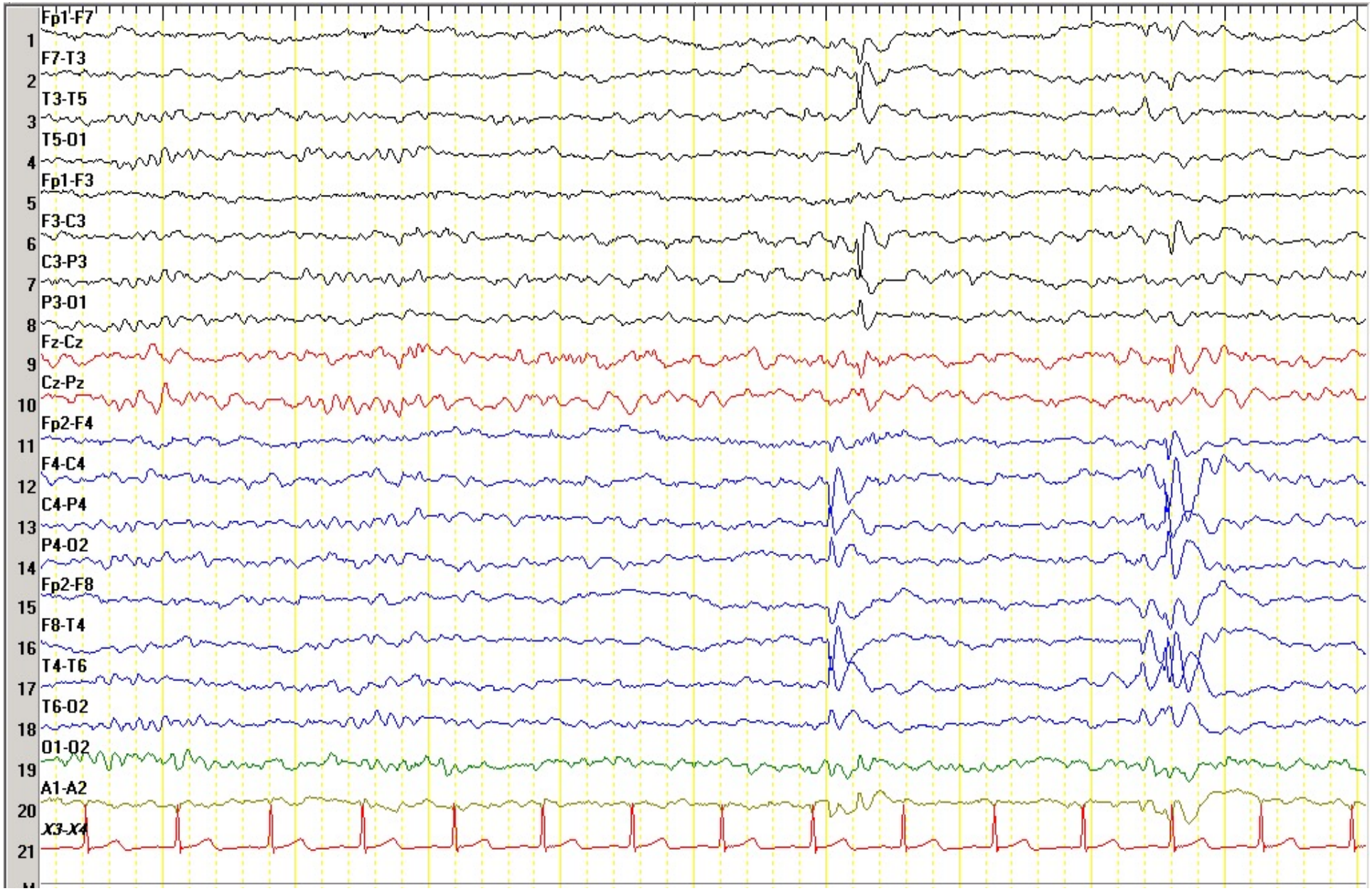
- Formerly BECTs, benign rolandic epilepsy (BRE)
- Most common idiopathic focal epilepsy
- Seizure: brief, focal clonic or tonic seizures of the throat/tongue
- May evolve to a focal to bilateral GTC seizures
- Age at onset: 3-13 years, peak 9-10
- EEG: normal background with centrotemporal spikes activate in drowsiness and sleep are mandatory
- Mild cognitive impairment, LD but no regression
- Treat VS not to treat
- Seizures respond well with ASMs and resolve by puberty

Specchio N, et al, ILAE 2022

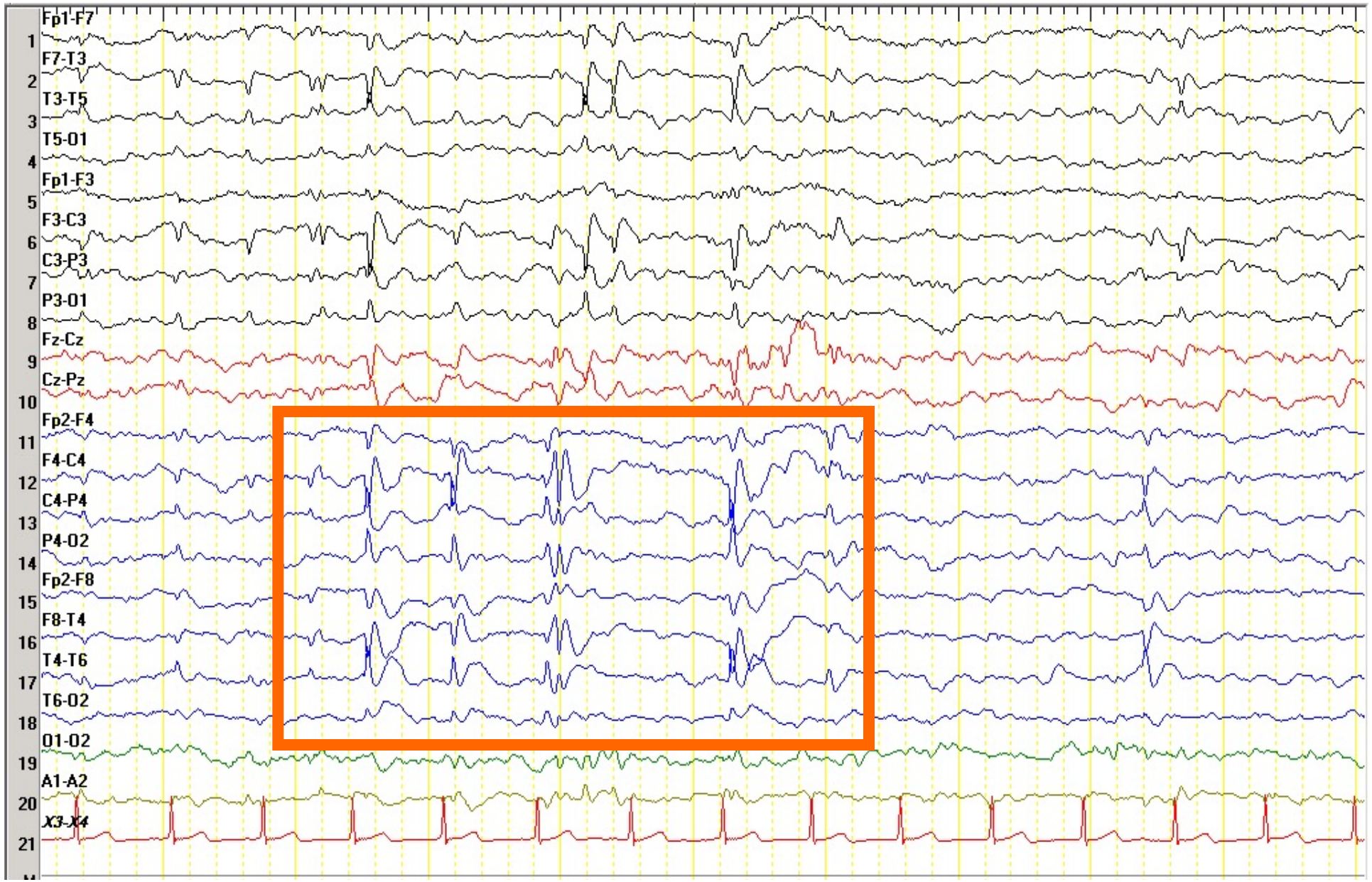
Normal Awake Recording



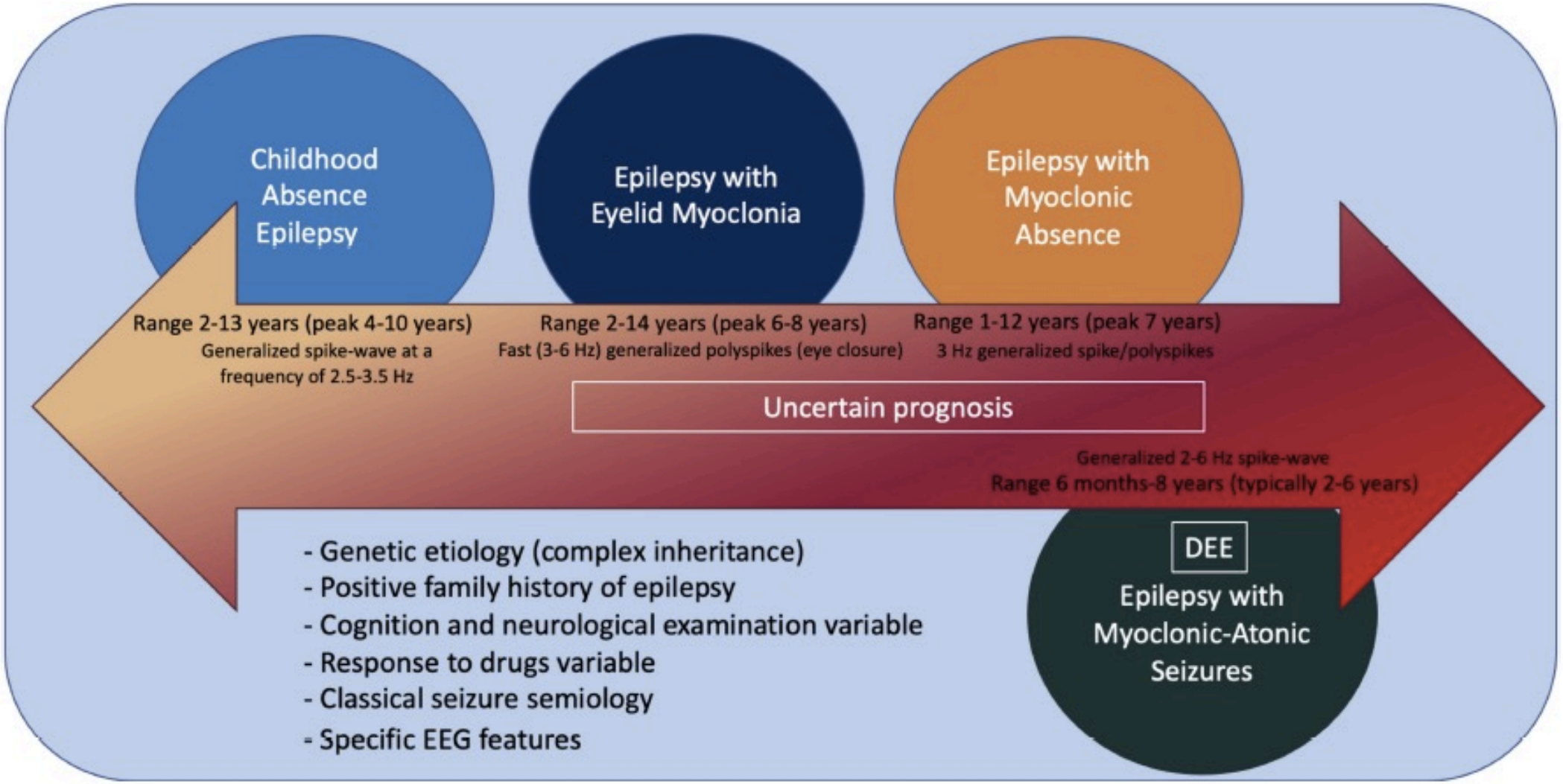
Drowsiness, Centrotemporal spikes



Sleep, Centrotemporal spikes



Genetic Generalized Epilepsies



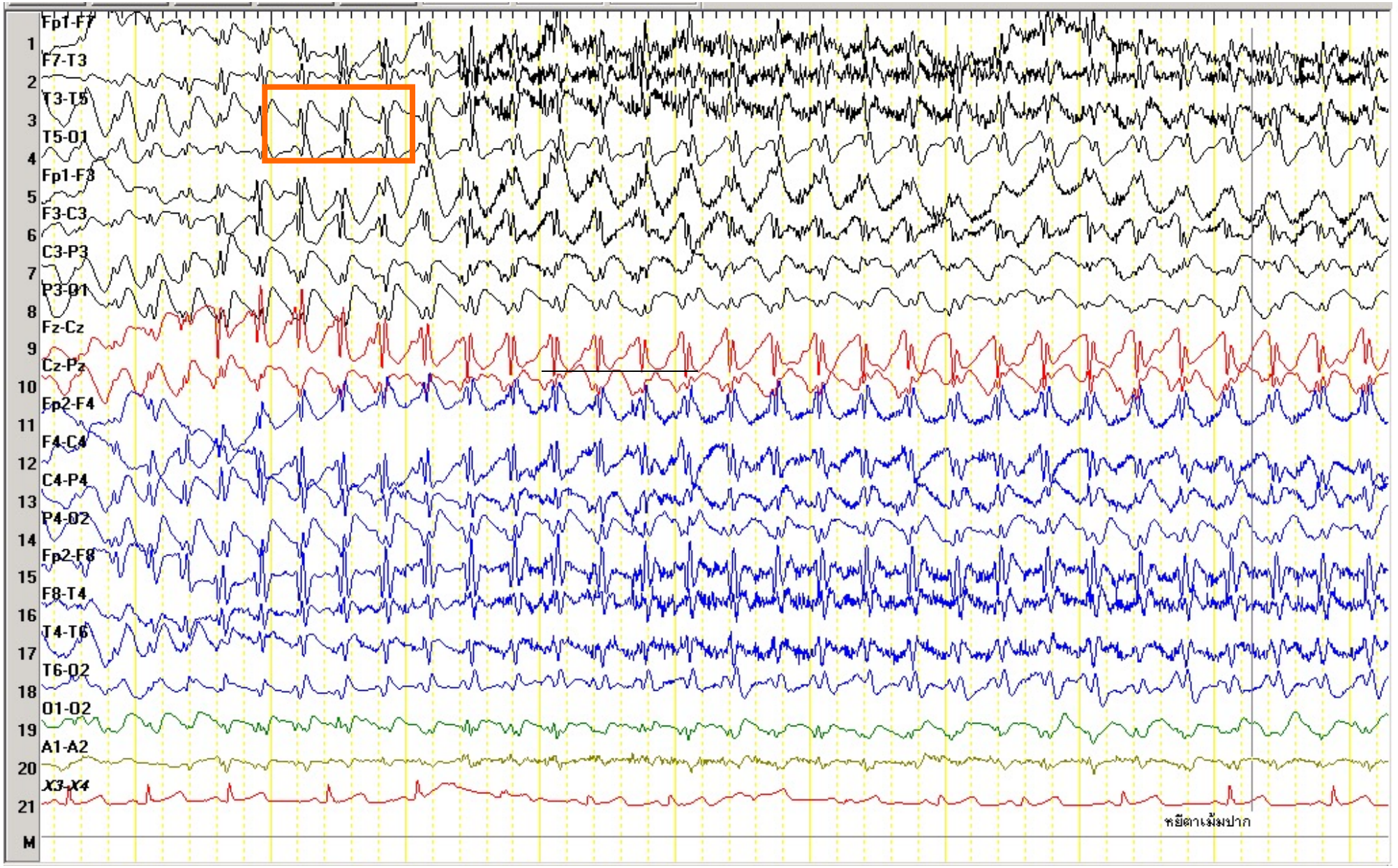
Specchio N, et al, ILAE 2022

Absence Epilepsy

- Childhood absence epilepsy (CAE)
  - Onset 4-10 years
  - Absence seizures occur daily but GTC seizure rarely occur
- Juvenile absence epilepsy (JAE)
  - Onset 9-13 years
  - GTC seizures commonly occur (80%) but absence seizures occur less than daily
- Induced by hyperventilation
- EEG:
  - CAE: 2.5-4 Hz generalized spike-wave (GSW)
  - JAE: 3-5.5 Hz irregular generalized spike-wave
- If no GSW is seen within hyperventilation for 3 min in an untreated patient, CAE or JAE can be excluded
- Treatment: valproate, ethosuximide, lamotrigine

Specchio N, et al, ILAE 2022

Generalized 3 Hz spike-waves complexes

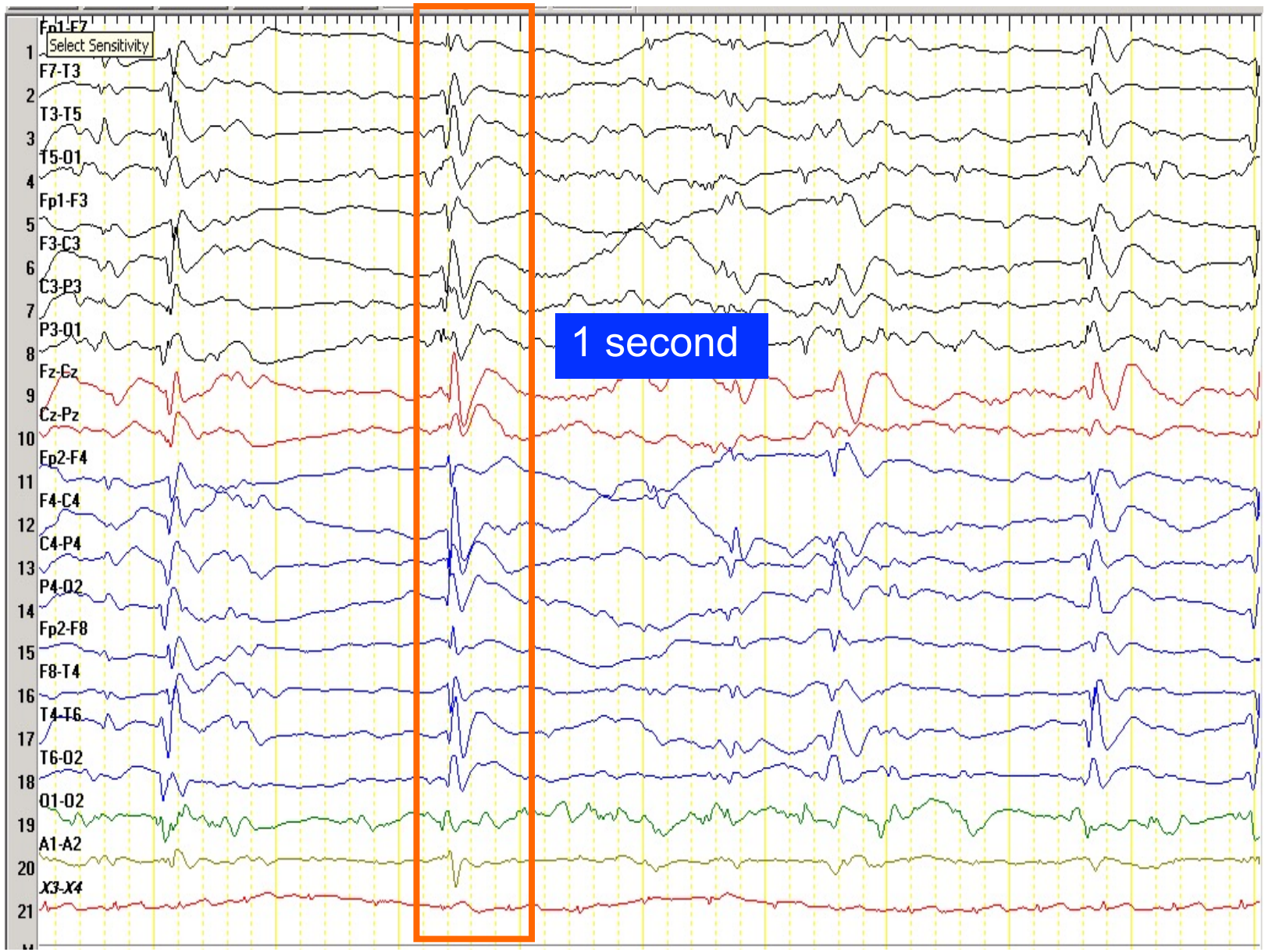


Lennox-Gastaut Syndrome (LGS)

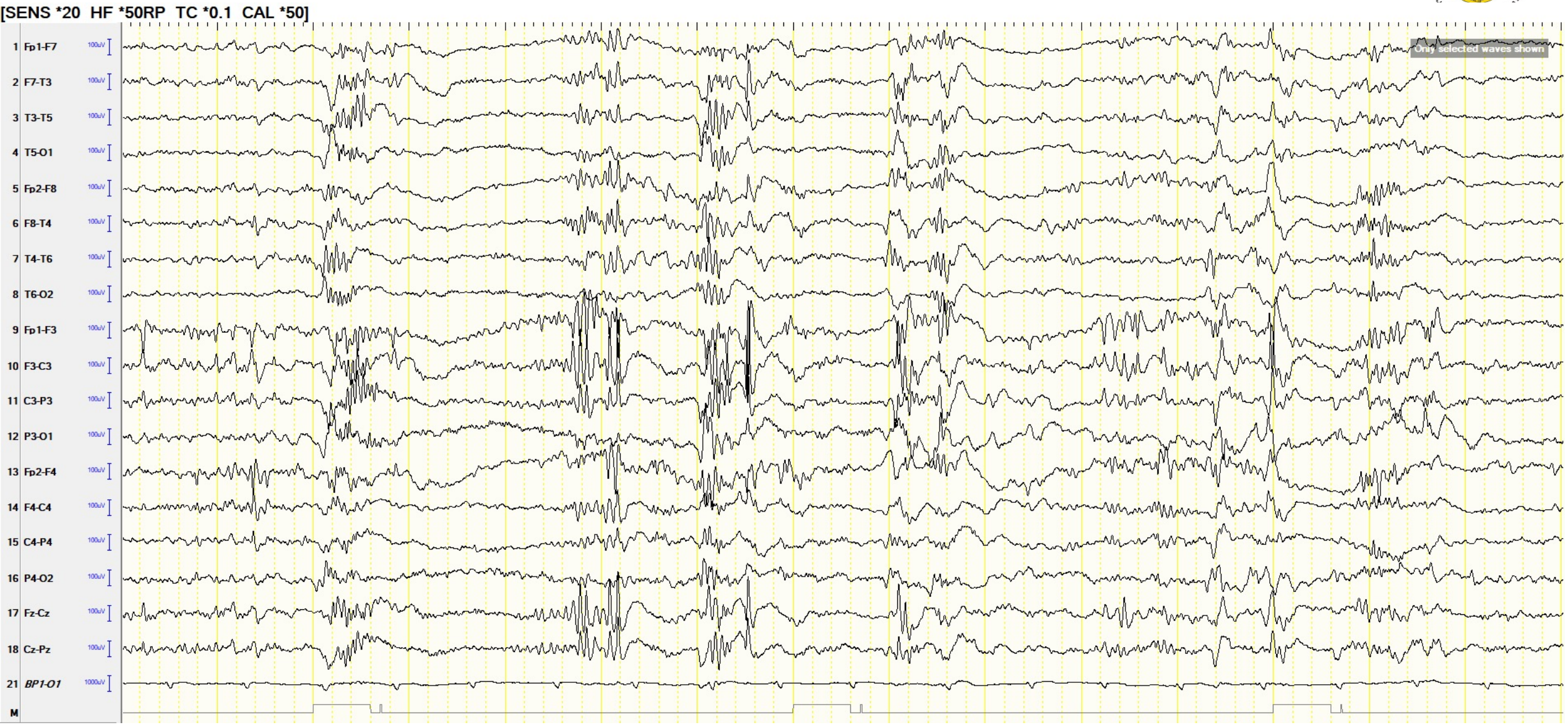
- DEE with wide range of etiologies
- Multiple types of DRE with onset <18 yo
- Seizures begin between 18 mo – 8 yo (peak 3-5 yo)
- Tonic seizure is mandatory
- Other seizures include atypical absence, atonic, myoclonic, etc
- Cognitive and behavioral impairment
- EEG showed generalized ≤ 2.5 Hz slow spike-wave and generalized PFA

Zuberi SM, et al, ILAE 2022

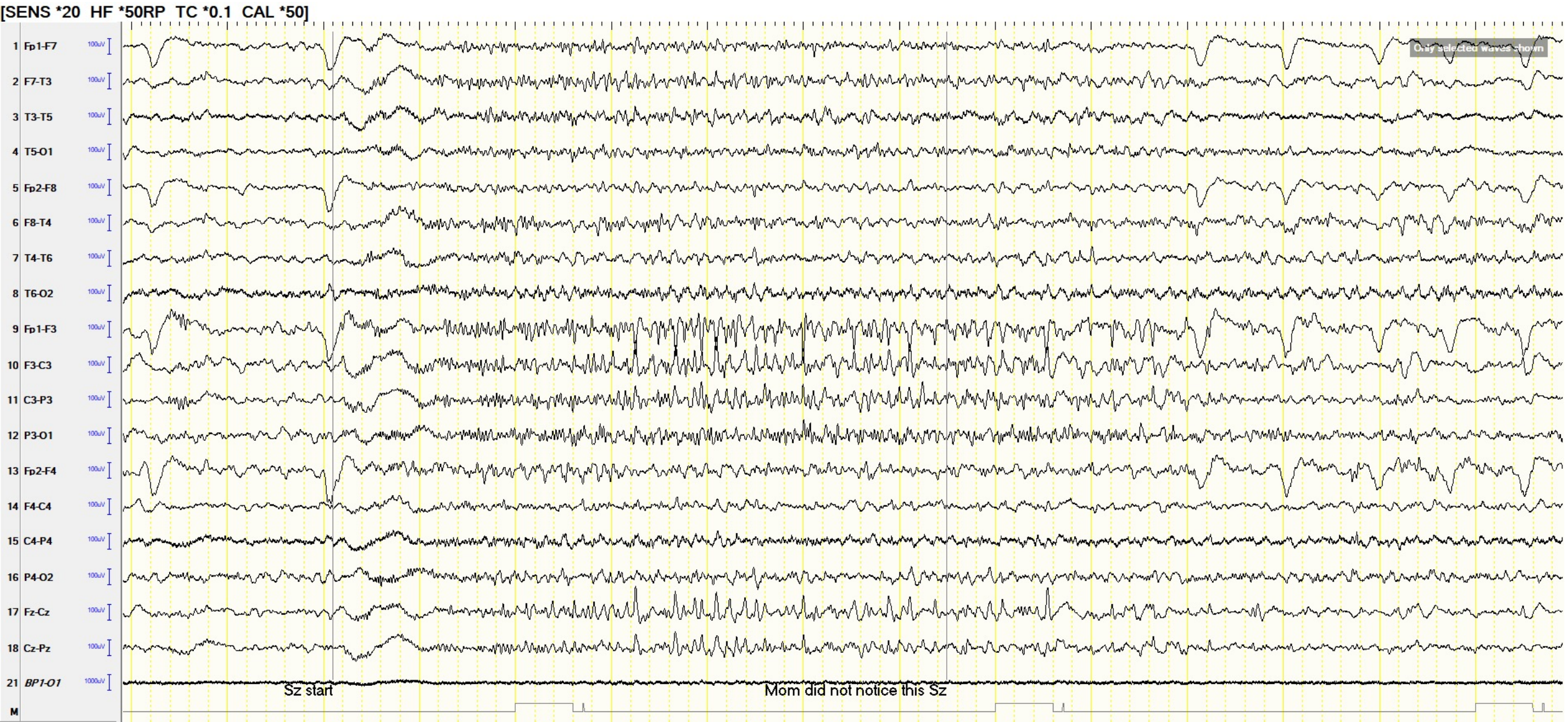
Generalized 1.5-2.5 Hz Slow spike-wave



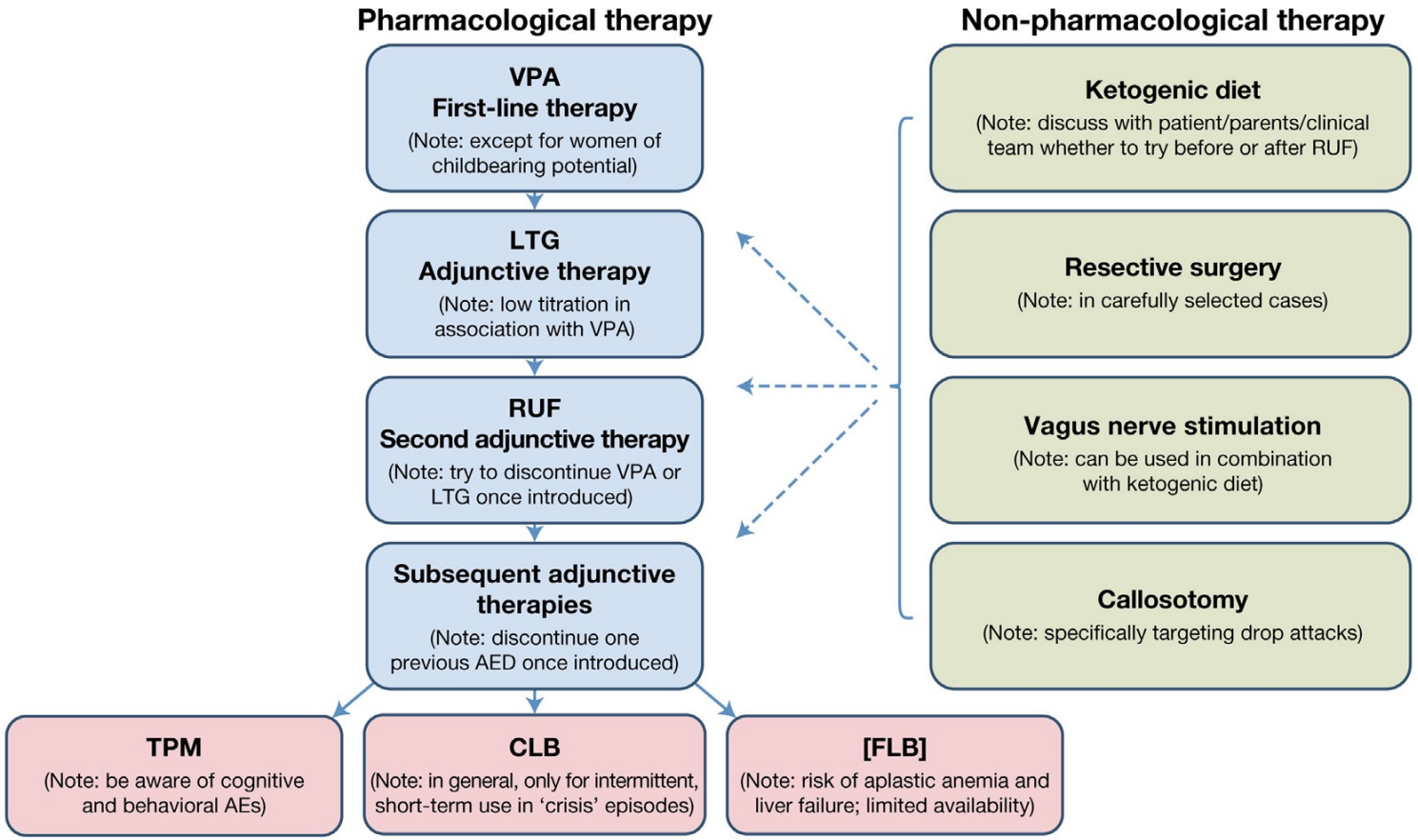
Paroxysmal Fast Activity (PFA)



Tonic Seizure

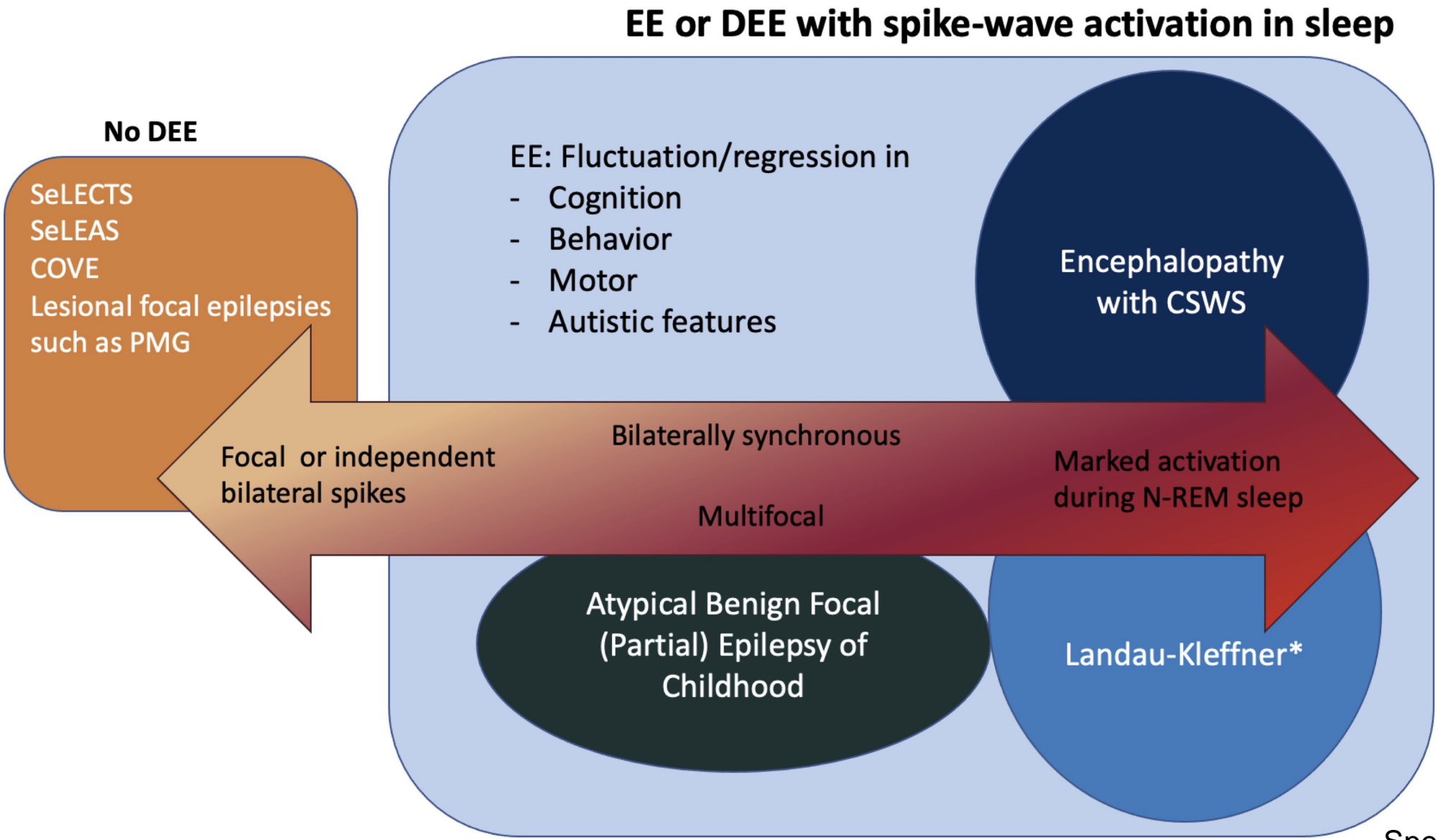


Treatment Algorithm for a Newly Diagnosed LGS



Cross JH, et al, Frontiers in Neurology 2017

DEE- or EE- with spike and wave activation in sleep (SWAS)



Specchio N, et al, ILAE 2022

DEE or EE-SWAS

- Formerly as Landau-Kleffner syndrome (LKS), CSWS, or ESES
- Cognitive, language, behavioral, or motor regression or plateauing temporally related to SWAS on EEG
- EE-SWAS: pre-existing normal development with and an activation of 1.5-2 Hz spike and wave complexes in NREM sleep
- DEE-SWAS: pre-existing neurodevelopmental disorders and a documented persisting worsening of various combinations of development

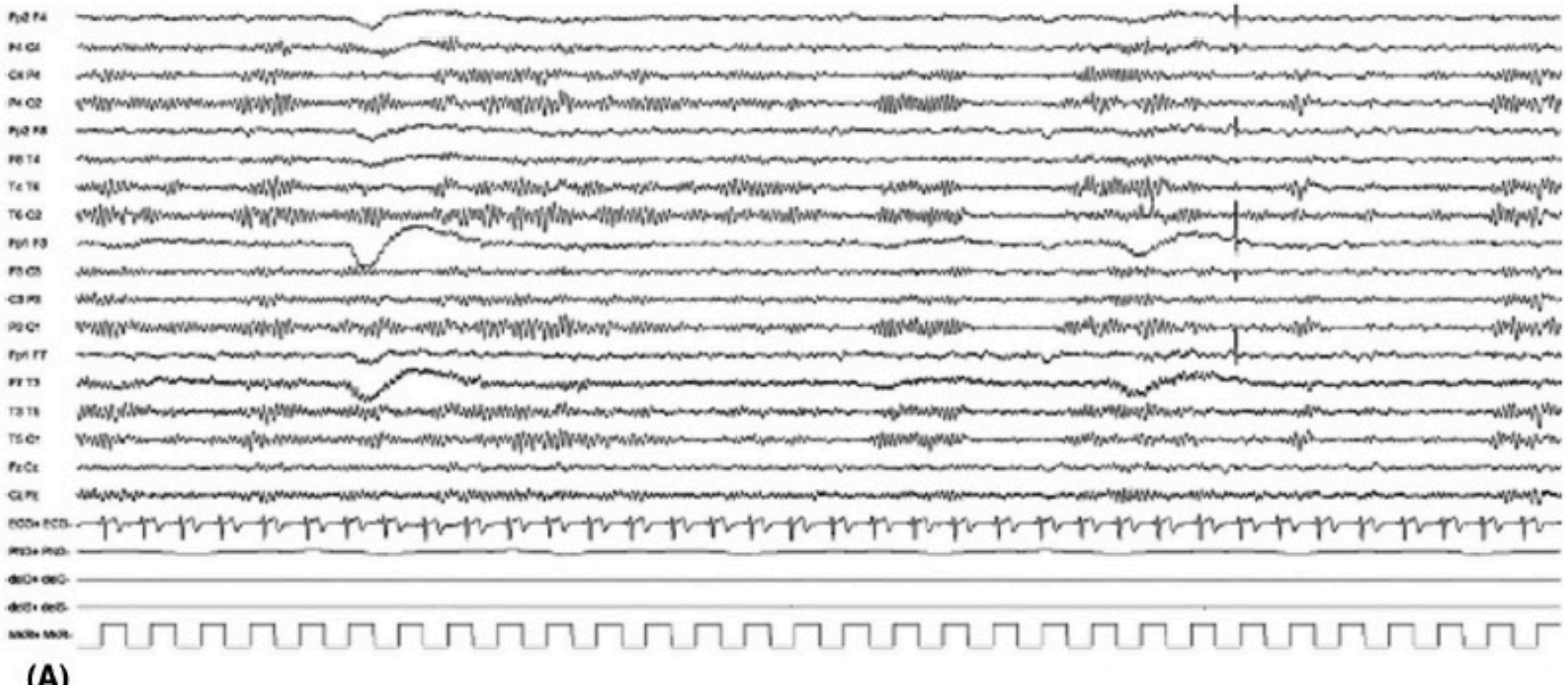
Zuberi SM, et al, ILAE 2022

DEE or EE-SWAS

- Seizure onset: 2-12 yo (peak 4-5 yo)
- Regresison in cognitve, behavioral, or psyhciatric functioning is the cardinal symptoms
- Sleep EEG is mandatory
- EEG shows spike-and-wave activation in sleep
- Thalamic injury in early life and bilateral perisylvian polymicrogyria are risk factors
- Duration and etiology are the most important predictors of outcome
- Poor outcomes are associated with younger onset or present > 2 y
- Treatment: steroids, clobazam

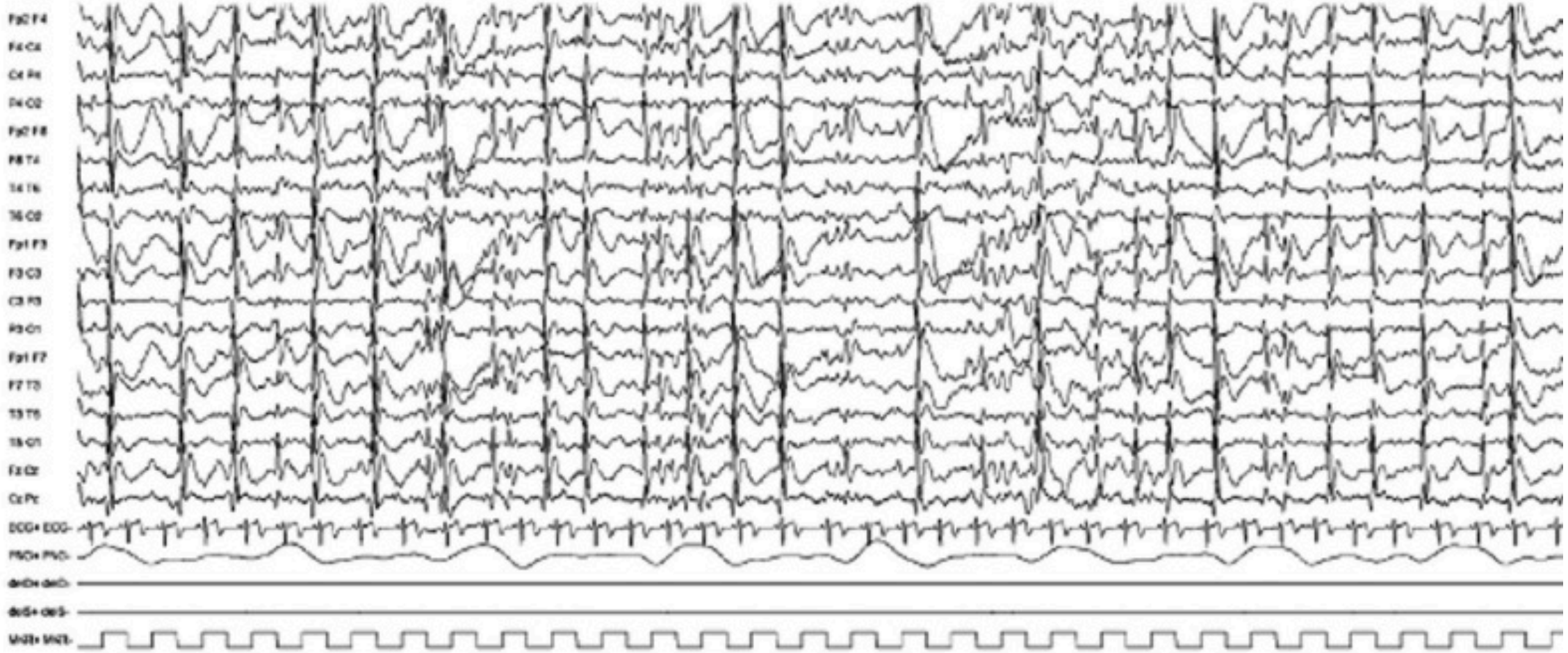
Zuberi SM, et al, ILAE 2022

DEE or EE-SWAS: Awake EEG



(A)

DEE or EE-SWAS: Sleep EEG



(B)

Conclusions

- Each syndrome has mandatory seizure types, EEG features, age at onset, and findings from key investigations
- Syndromes can be divided into self-limited focal epilepsies, generalized epilepsies, and DEE
- Precise identification of an epileptic syndrome can provide useful information on prognosis and management