Combined Focal and Generalized Epilepsy Syndromes

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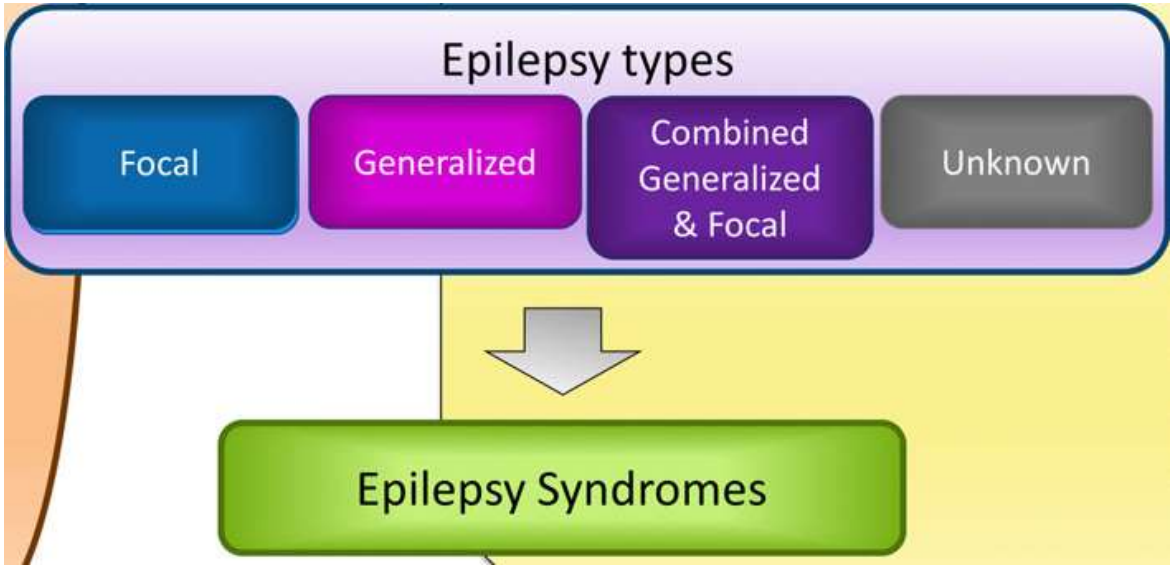
What is a combined focal and Generalized epilepsy syndromes?



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> Combined Generalized and Focal

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COMBINED GENERALIZED AND FOCAL EPILEPSY

Patients may have both generalized and focal seizure types, with interictal and/or ictal EEG findings that accompany both seizure types. Patients with Dravet syndrome and Lennox Gastaut syndrome may have generalized and focal epilepsy.

The diagnosis is made on **clinical grounds**, as there are patients who have **both generalized and focal seizures**, **supported by EEG findings**. Ictal recordings are helpful but not essential. The **interictal EEG** may show **both generalized spike-wave and focal epileptiform discharges**, but epileptiform activity is not required for the diagnosis.

ILAE 2017 Classification of Seizure Types Expanded Version[1]

Focal Onset

Aware | Impaired Awareness

Motor Onset
- automatisms
- atonic[2]
- clonic
- epileptic spasms[2]
- hyperkinetic
- myoclonic
- tonic

Non-Motor Onset
- autonomic
- behavior arrest
- cognitive
- emotional
- sensory

focal to bilateral tonic-clonic

Generalized Onset

Motor
- tonic-clonic
- clonic
- tonic
- myoclonic
- myoclonic-tonic-clonic
- myoclonic-atonic
- atonic
- epileptic spasms[2]

Non-Motor (absence)
- typical
- atypical
- myoclonic
- eyelid myoclonia

Unknown Onset

Motor
- tonic-clonic
- epileptic spasms

Non-Motor
- behavior arrest

Unclassified[3]

1 Definitions, other seizure types and descriptors are listed in the accompanying paper and glossary of terms.

2 These could be focal or generalized, with or without alteration of awareness

3 Due to inadequate information or inability to place in other categories

From *Fisher et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia doi: 10.1111/epi.13671*

Combined Focal and Generalized Epilepsy Syndromes

Common examples in which both types of seizures occur are :

- **Dravet syndromes**
- **Lennox Gastaut syndromes**

- **Febrile seizure plus, GEFS+**
- **Photosensitive OLE**
- **Myoclonic encephalopathy in non-progressive disorders**
- **EME**
- **EIEE (Ohtahara)**
- **West syndromes**
- **EE with CSWS**

Lennox-Gastaut syndrome :

Clinical presentation

- **History:**
  - Age onset from 1-7 years of age (peak 3-5)
  - Sex: both, 10-30% evolve from West syndrome or Otahara syndrome
  - Prenatal and perinatal history: may be normal
  - Development and cognitive-abnormal or normal and then **subsequently stagnation or regression** development after onset of seizures.
- **Physical examination:** may be normal or suggested structural brain abnormalities

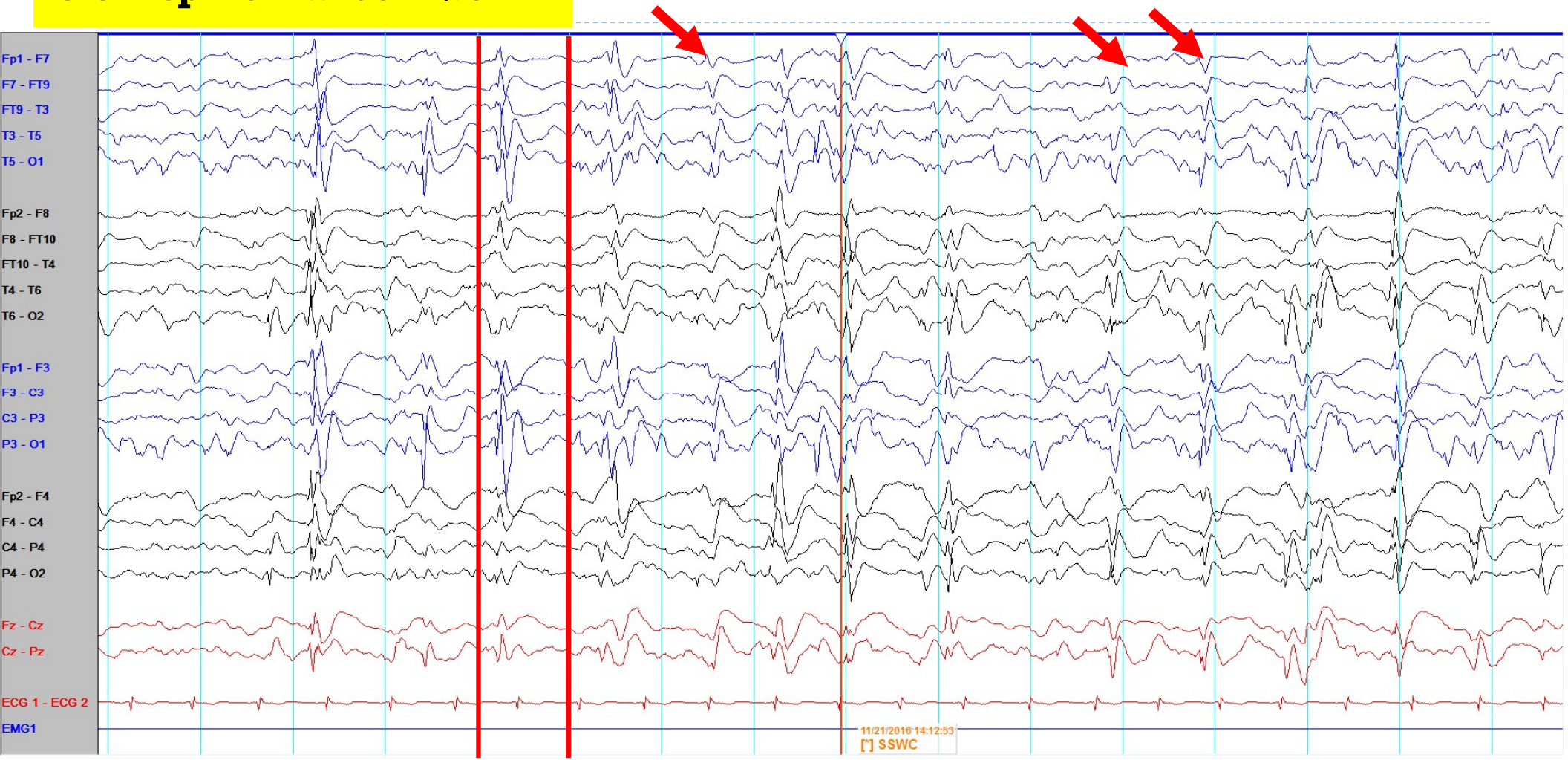
Lennox-Gastaut syndrome :

Seizure types

- **Tonic seizure** : mainly, from sleep (in slow wave sleep or wakening), truncal, brief, can occur in series
- May have: GTCs, atypical absence(2/3 of patients), atonic (50%of patient),myoclonic seizure, myoclonic-atonic, focal seizure or epileptic spasms
- **Caution** : myoclonic sz predominate=>Dravet syndrome, myoclonic-atonic sz=>epilepsy with myoclonic-atonic seizure

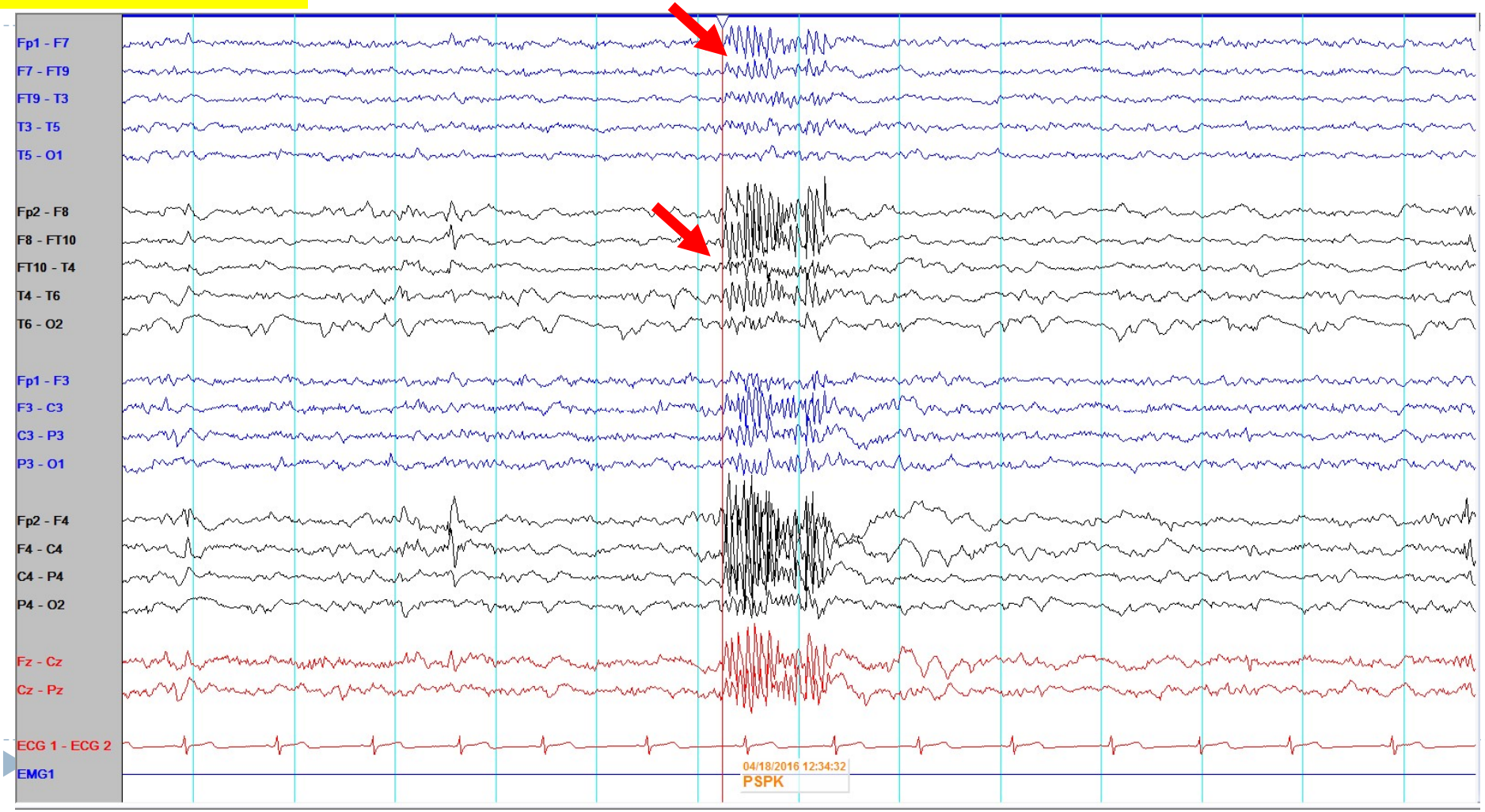
Lennox-Gastaut syndrome: EEG finding

Slow spike waves <2.5 Hz



Lennox-Gastaut syndrome: EEG finding

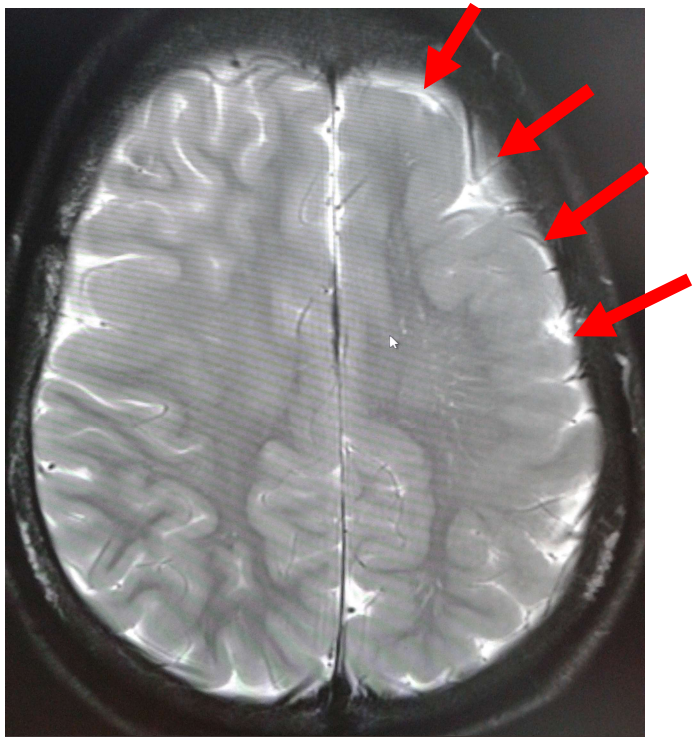
Fast activity



Lennox-Gastaut syndrome :

Etiology:

- **Structural brain abnormalities** (70% of cases)
- **Genetic etiologies** (de novo mutations): expected in many of currently unexplained cases



Prognosis:

- Poor prognosis, need multidisciplinary treatment

Dravet syndromes

Severe Myoclonic Epilepsy of Infancy (SMEI)

- **First described in 1978 as SMEI by Dr. Charlotte DRAVET**
- **In 2001, Change name to "DRAVET syndrome"=>persist to adult and not only myoclonic seizure**
- **Incidence: 1:20000-30000**
- **Epileptic Encephalopathy:** cognitive and behavioral impairments over those expected from the underlying etiology alone, and that suppression of epileptic activity might minimize this additional impairment.

Dravet syndromes :Clinical presentation

Severe Myoclonic Epilepsy of Infancy (SMEI)

- **History:**
  - Age onset around 6 months of age (most:onset <15 mo, minority: <2 yrs)
  - First seizure: 60% of cases associated with a **fever** (sensitivity of seizures to fever may persist throughout life), may be trigger by **immunization** (non-specific, first seizure)
  - Sex: both, Antecedent, birth and neonatal history: normal
  - Development: typically normal in the first year of life, with **plateauing or regression in later** years.
- **Physical examination:** Head size & N/S :initially normal, over time **ataxia and pyramidal signs** may develop.

Dravet syndromes :

Seizure types

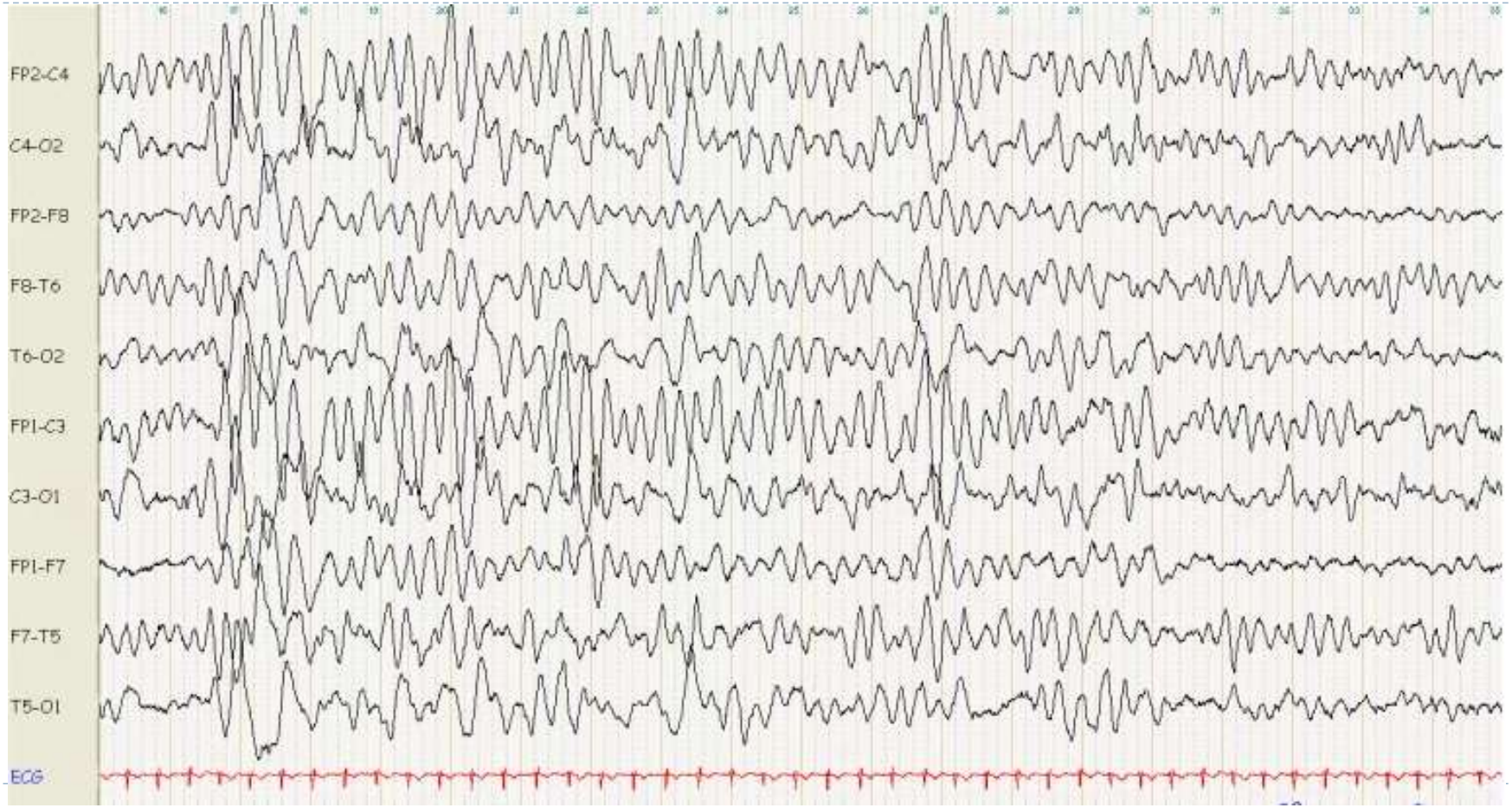
- **Hemiclonic seizures** : common, different side of body in different seizures
- **Focal and generalized** seizure types : clonic-tonic-clonic sequence to tonic-clonic
- May have: Atypical absence, Myoclonic, Atonic, Non-tonic-clonic status epilepticus
- **Caution** : Tonic seizures and Epileptic spasms are not expected, =>consider other epilepsy syndromes.

Dravet syndromes : EEG findings

- **Background:** normal in first year of life=>diffuse slowing
- **Interictal**: Generalized spike and waves and multifocal discharges are seen by 2-5 years of age
- **Activation:**
  - Photosensitivity; generalized spike and waves; atypical absence/myoclonic seizures (infancy, all ages)
  - Sleep deprivation and sleep : enhanced EEG abnormalities
- **Ictal EEG**: varies according to seizure types
- **Caution**: diffuse electrodecremental patterns/paroxysmal fast activity: not seen

Dravet syndromes : Onset 9 m

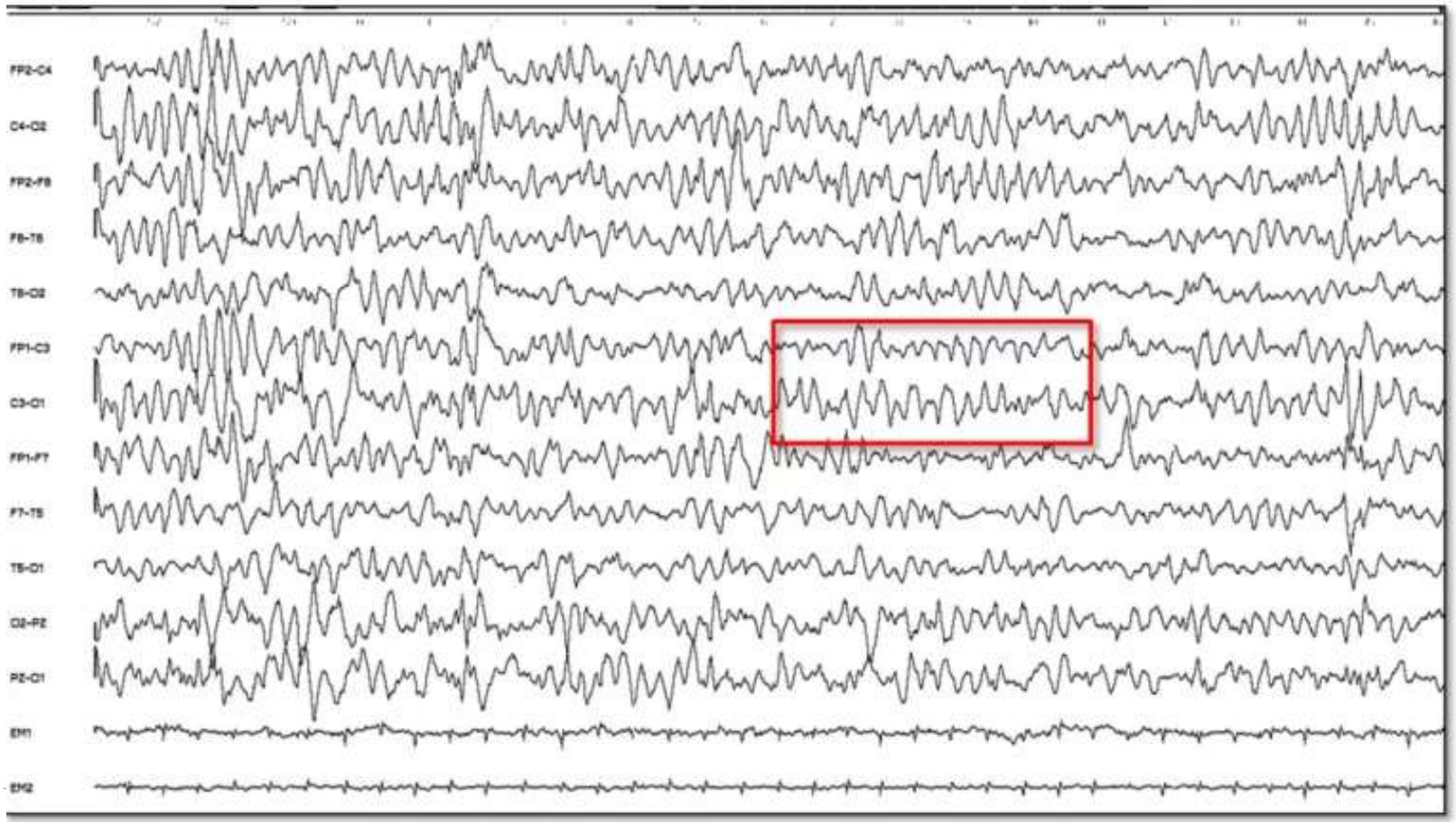
rhythmic theta activity 4-5Hz may be present on centro-parietal areas and **vertex**



https://pro.dravet-syndrome.us/diagnosis/

Dravet syndromes : Worsening 3 yrs

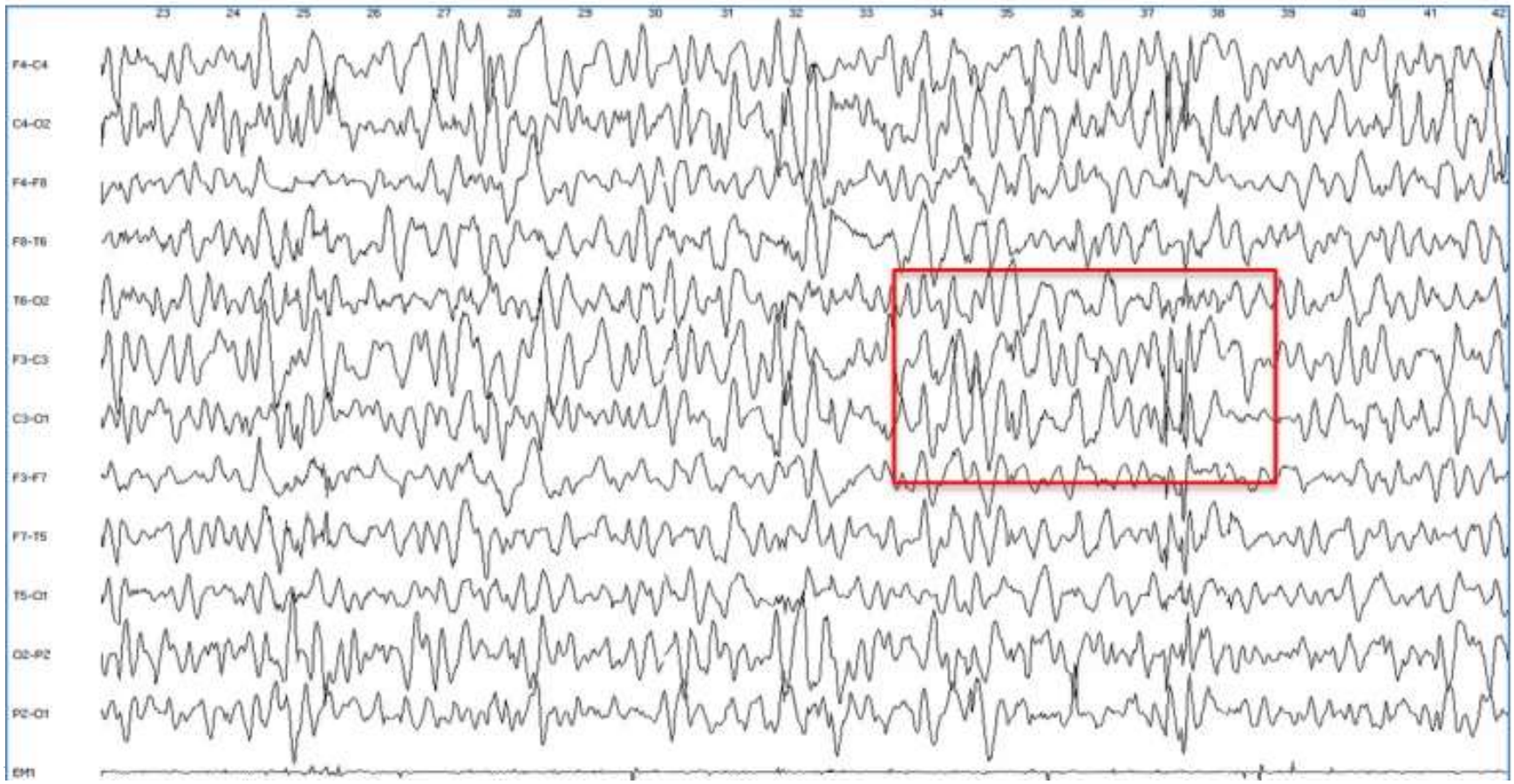
Background slowing, with 4Hz theta rhythms mostly on central areas.



https://pro.dravet-syndrome.us/diagnosis/

Dravet syndromes : Worsening 4 yrs

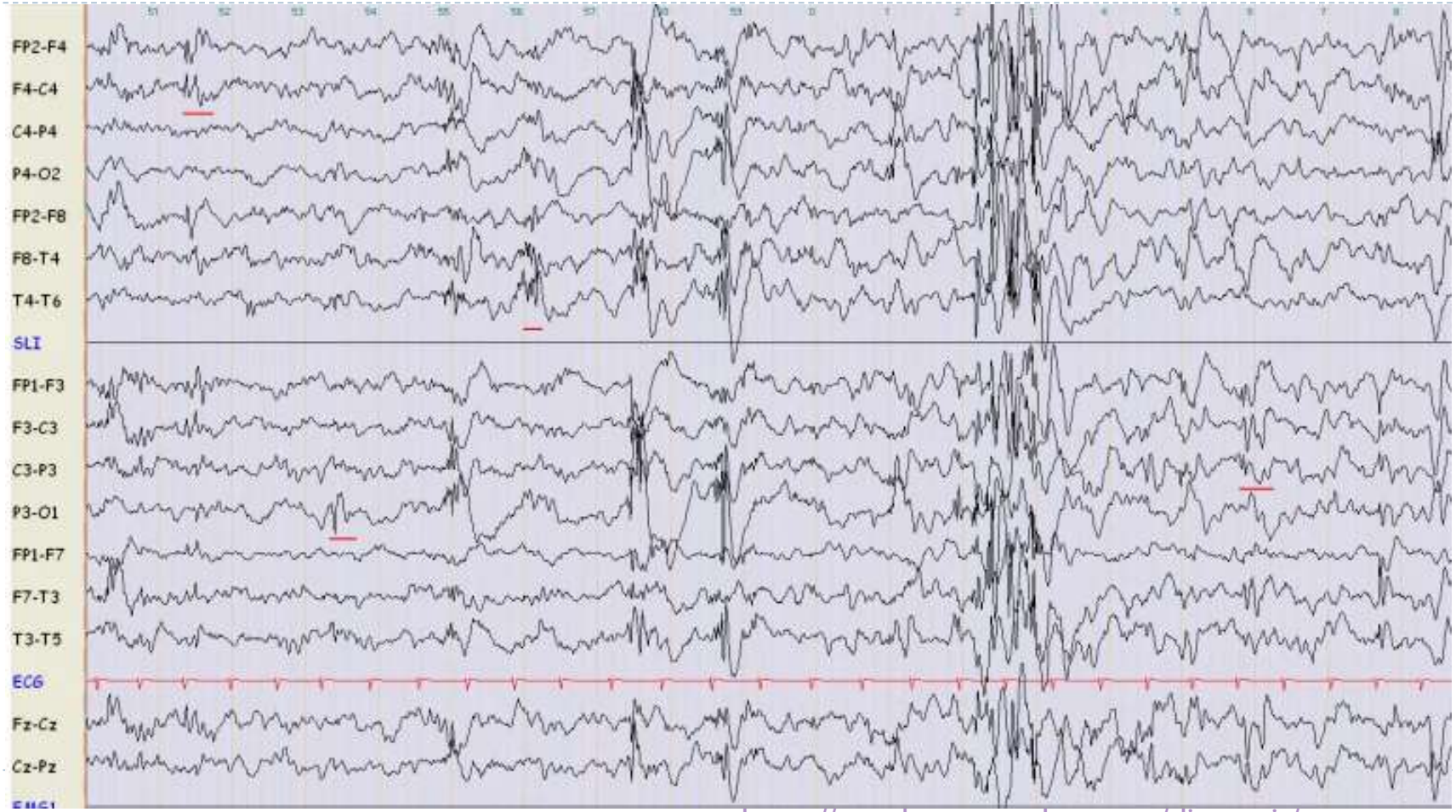
Slowing of background activity and rare bilateral central spikes.



https://pro.dravet-syndrome.us/diagnosis/

Dravet syndromes : Worsening 5 yrs

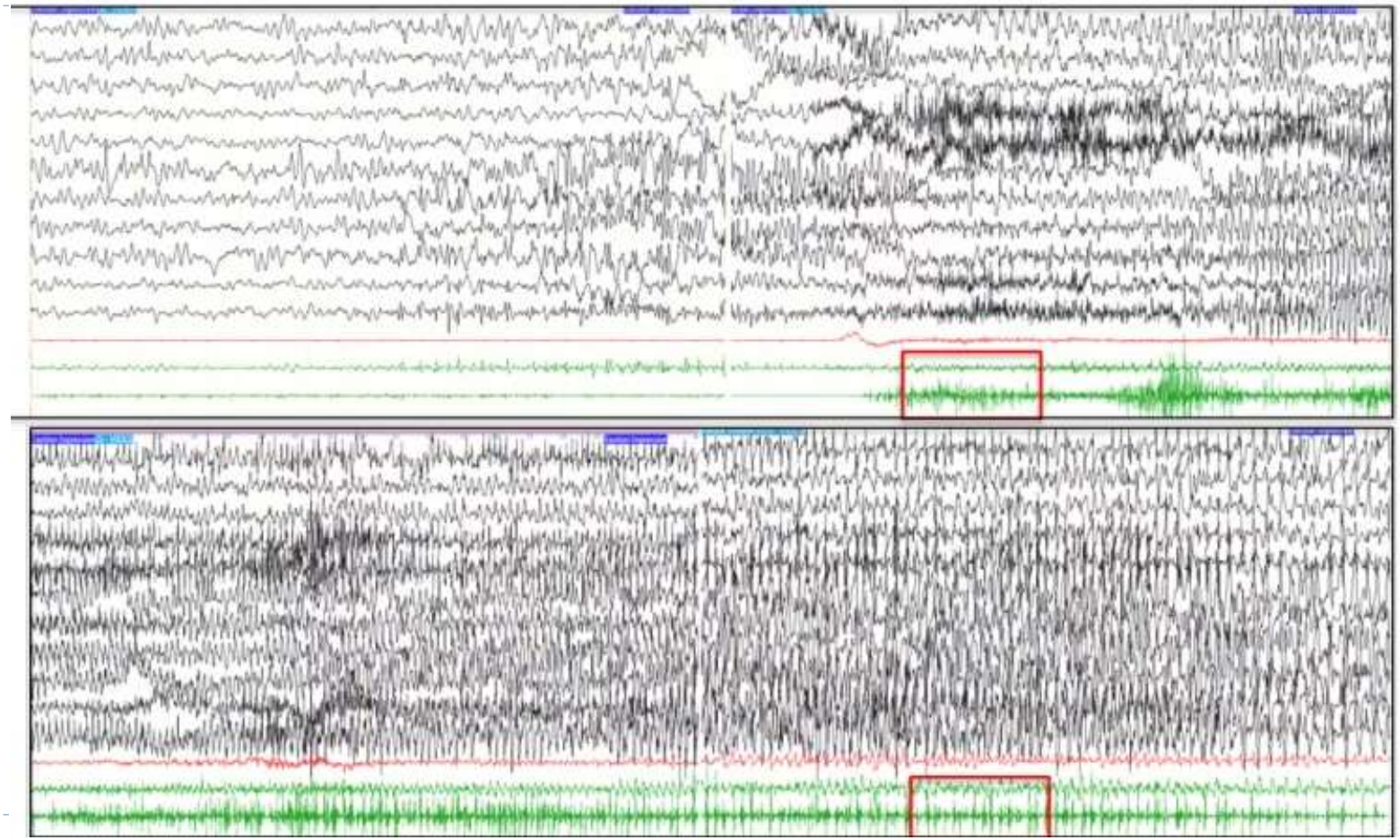
Burst of generalised spike-waves associated with independent multifocal spikes over the frontal-central and parieto-occipital areas.



https://pro.dravet-syndrome.us/diagnosis/

Dravet syndromes : Ictal

Bilateral tonic-clonic seizure



https://pro.dravet-syndrome.us/diagnosis/

Dravet syndromes :

- **Imaging** : usually normal at onset, 10% abnormalities (later); generalized atrophy or hippocampal sclerosis

- **Genetics** : - 75% SCN1A (95% de novo, 5% inherited)
  - minority of females: mutation of PCDH 19 gene
  - 30-50% FH of febrile seizures
  - some of them: GEFS+

Differential diagnosis

Clinical Feature	Dravet syndrome	Febrile seizures	Focal epilepsy	Doose syndrome (MAE)	Lennox-Gastaut syndrome
Onset <1 year	+	+/–	+/–	–	–
Fever-sensitive seizures	+	+	+/–	+/–	–
Hemiconvulsion	+	–	+	–	–
Generalised convulsion	+	+/–	–	+	+/–
Partial seizures	+	+/–	+	–	+/–
Myoclonic seizures	+/–	–	–	+	+/–
Tonic seizures	–	+/–	–	–	+
Atypical absences	+/–	–	–	+	+
Generalised epileptiform discharges	+/–	–	–	+	+
Multifocal epileptiform discharges	+/–	–	–	–	–
Focal epileptiform discharges	–	+	+	–	–
Photosensitivity	+	–	–	–	–
Abnormal cognitive development	+	–	+/–	+	+
Abnormal brain MRI	–	–	+	+/–	+/–
SCN1A mutation	+/–	+/–	–	–	–

https://pro.dravet-syndrome.us/diagnosis/

Dravet syndrome	Lennox-Gastaut syndrome
Onset < 1 year	Onset > 1 year (between 2 and 8)
Sensitivity to fever	No sensitivity to fever
GTCS. No tonic seizures	Tonic seizures +++
Atypical absences, myoclonic, focal seizures	Atypical absences, focal seizures, myoclonic seizures (rare)
EEG: generalised/multifocal spikes	EEG: diffuse slow spike-waves, rapid diffuse rhythms(sleep)
For 75%: SCN1A mutation	No SCN1A mutation

https://pro.dravet-syndrome.us/diagnosis/

Treatment: NICE 2017

Epilepsy syndrome	First-line AEDs	Adjunctive AEDs	Other AEDs that may be considered on referral to tertiary care	Do not offer AEDs (may worsen seizures)
Dravet syndrome	Discuss with, or refer to, a tertiary paediatric epilepsy specialist Sodium valproate[b] Topiramate[a]	Clobazam[a] Stiripentol		Carbamazepine Gabapentin Lamotrigine Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin
Lennox–Gastaut syndrome	Discuss with, or refer to, a tertiary paediatric epilepsy specialist Sodium valproate[b]	Lamotrigine	Felbamate[a] Rufinamide Topiramate	Carbamazepine Gabapentin Oxcarbazepine Pregabalin Tiagabine Vigabatrin

SUMMARY

- The new group "Combined Generalized and Focal Epilepsies" : both generalized and focal seizures and EEG support diagnosis
- Common example:

Dravet syndrome and Lennox-Gastaut syndrome

- Considered an **'epileptic encephalopathy'**
- Difficult or intractable to treatment, need multidisciplinary treatment