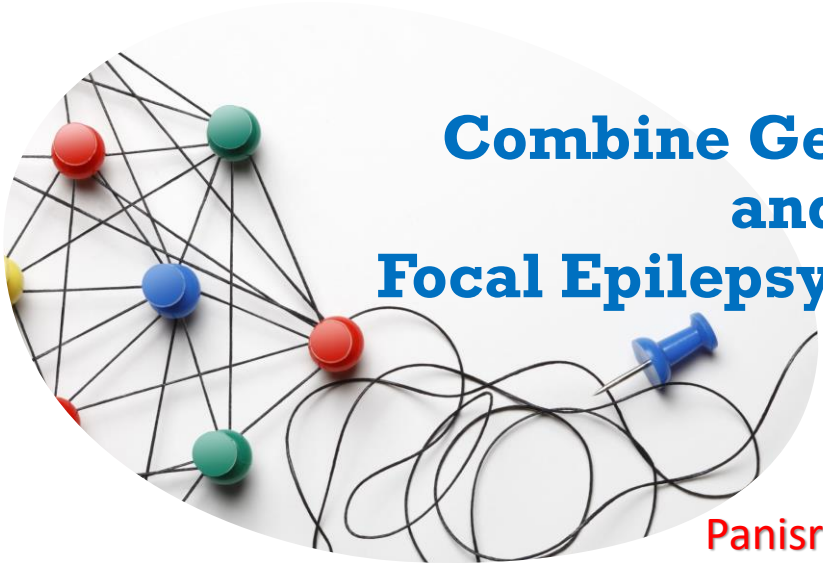


Combine Generalized and Focal Epilepsy Syndromes

Panisra Sudachan, M.D.
Pediatric Neurologist
Prasat Neurological Institute

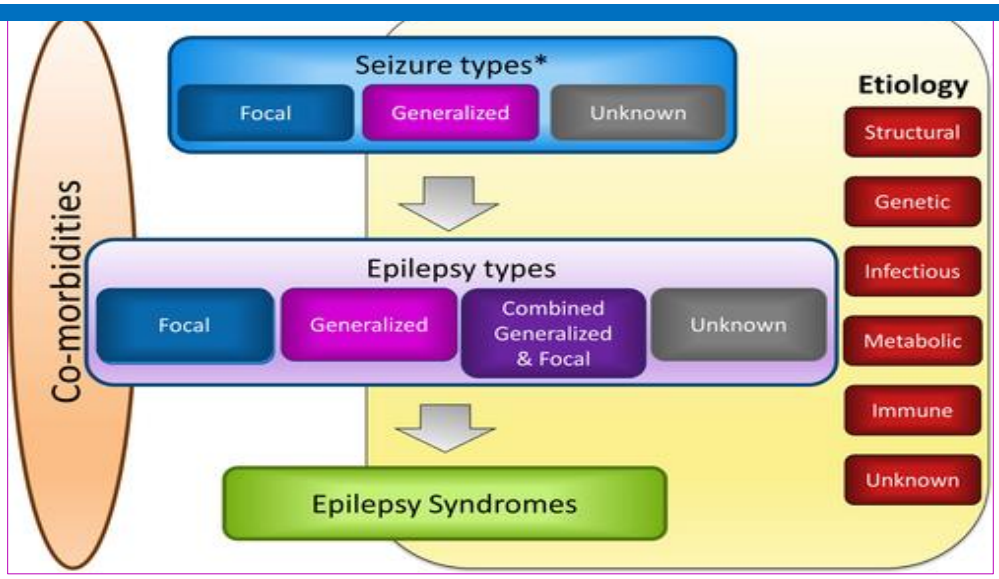
1

Outline of Topics

- What is combined generalized and focal epilepsy?
- Epilepsy syndromes in Combined generalized and focal epilepsy
- Dravet syndrome and Lennox Gastaut syndrome
- Current treatment in DS and LGS

2

What is Combined Generalized & Focal Epilepsy?



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ILAE International League Against Epilepsy

EpilepsyDiagnosis.org
Diagnostic Manual

> Combined Generalized and Focal

Log In For Videos

Choose a language

- Overview
  - Log In For Videos
  - Give Feedback
- Seizure Classification
  - Generalized onset seizure
  - Focal Onset Seizure
  - Unknown Onset Seizure
- Epilepsy Classification
  - Generalized Epilepsy
  - Focal Epilepsy
  - Generalized and Focal Epilepsy
  - Unknown Epilepsy
- Epilepsy Syndromes

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 following seizure types are therefore recognized for classifying focal seizures

- Aware or Impaired Awareness
  And
- Motor onset
- Non motor onset
  - Focal sensory seizure
  - Focal cognitive seizure
  - Focal emotional seizure
  - Focal autonomic seizure
  - Focal behavioural arrest seizure

Focal

Generalized onset seizures, are classified into

- Motor onset
  - Tonic-clonic and variants
  - Tonic
  - Atonic
  - Myoclonic
  - Myoclonic-atonic
  - Epileptic spasms
- Non motor onset
  - Typical Absence
  - Atypical Absence
  - Myoclonic absence
  - Absence with eyelid myoclonia

Generalized

4

Combined Generalized & Focal Epilepsy syndromes

- Dravet syndrome
- Lennox Gastaut syndrome

Others:

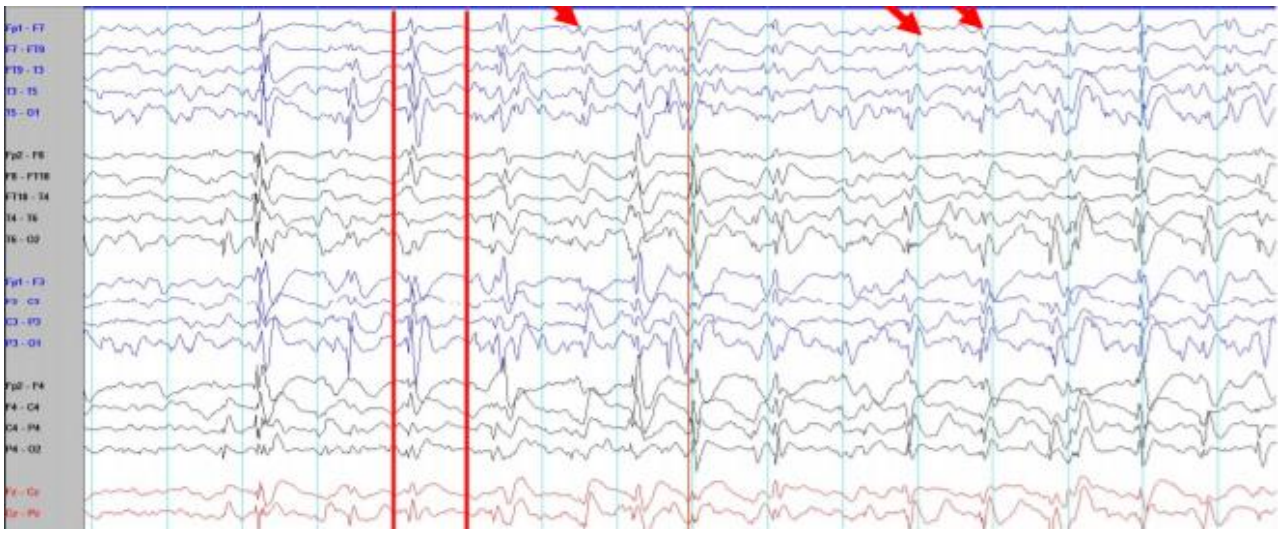
- Febrile seizure plus, GEFS+
- Photosensitive OLE
- Myoclonic encephalopathy in non-progressive disorders
- EME
- EIEE (Ohtahara)
- West syndrome
- EE with CSWS

5

เด็กหญิงอายุ 2 ปี ที่อยู่ จ.สระบุรี

CC: ชักเกร็งทั้งตัวมา 4 วัน PTA
PI: 4 วัน PTA มีอาการชักเกร็งทั้งตัวนาน 10 ถึง 15 วินาที หลังตื่นนอน 3-4 ครั้ง ห่างกันไม่นาน บางครั้งมีอาการผงกศีรษะ
5-6 เดือนก่อน มีอาการเหม่อนิ่ง ตาลอย บางครั้งตากลอกขึ้นด้านบน เรียกไม่รู้ตัว เป็นไม่นาน หลายครั้งต่อวัน
PH: พัฒนาการช้า
FH: ไม่มีประวัติโรคลมชักในครอบครัว
PE: Microcephaly, drooling, mental retardation
Minor dysmorphic facies
Spastic tone all limbs right>left, hyperreflexia

6



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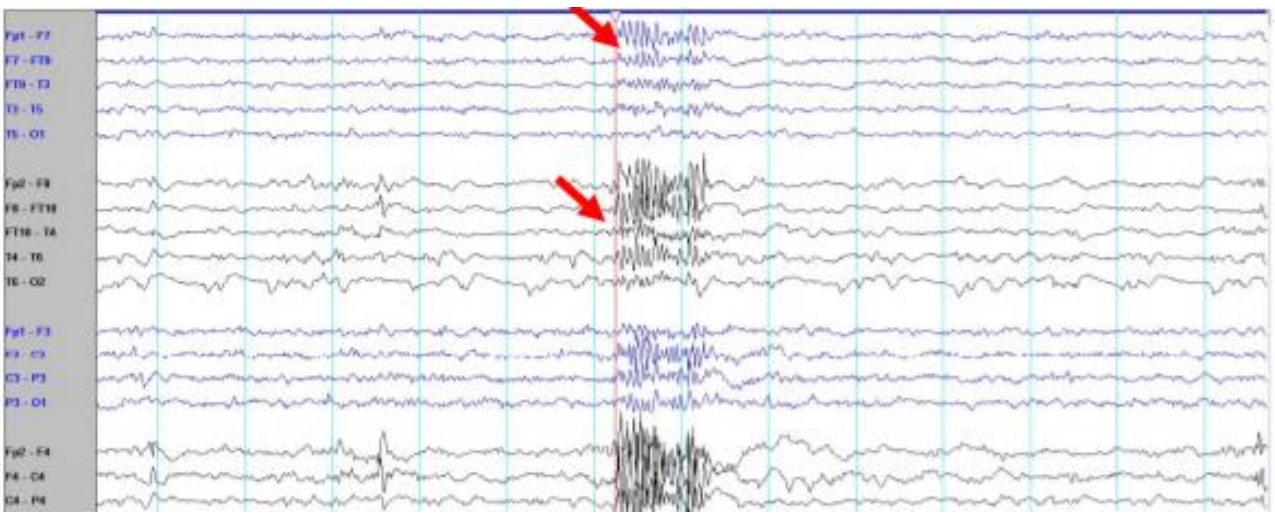

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What is likely diagnosis?

1. Dravet syndrome
2. West syndrome
3. Doose syndrome
4. Lennox Gastaut syndrome

9

Lennox Gastaut Syndrome

- Childhood-onset electroclinical syndrome and epileptic encephalopathy comprised by the **triad** of:

  1) polymorphic intractable seizures that are mainly **tonic, atonic** and **atypical absence seizures**

  2) **cognitive** and behavioral abnormalities

  3) electroencephalogram (EEG) with **paroxysms of fast activity** and **slow (<2.5 Hz) generalized spike wave discharges**

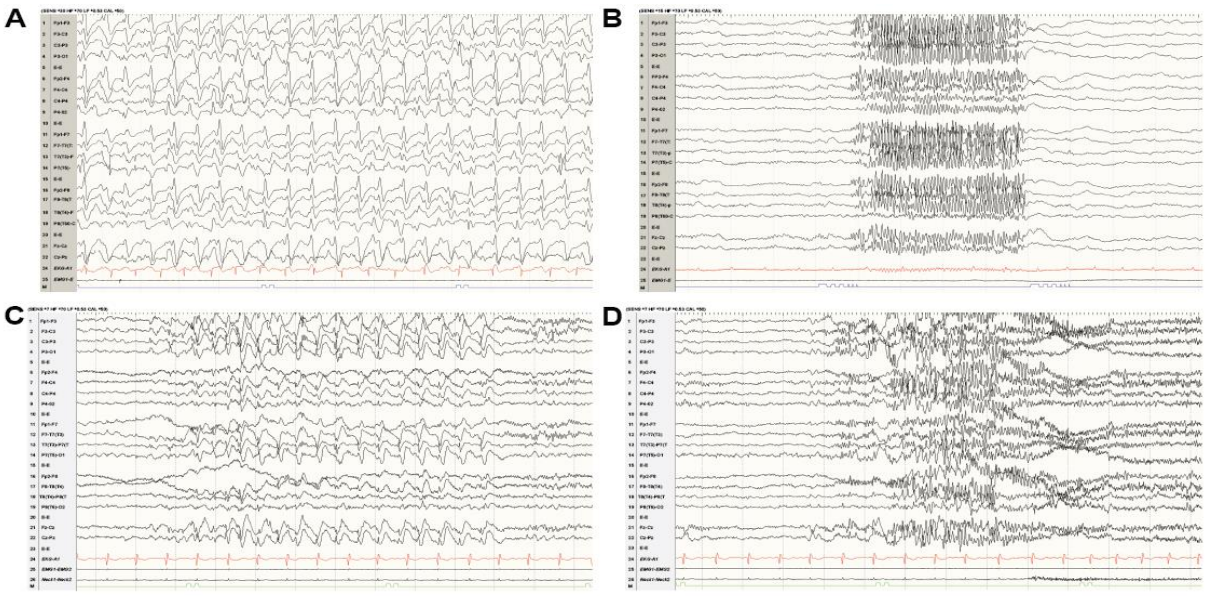
Ostendorf AP, Ng YT 2017

10

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

11



Ostendorf AP, Ng YT 2017

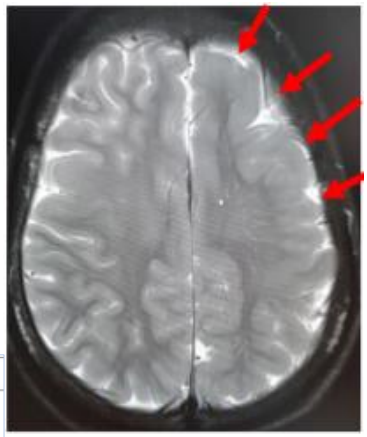
Figure 1 Electroencephalographic findings in Lennox-Gastaut syndrome.
Notes: Individuals with Lennox-Gastaut syndrome typically exhibit (**A**) generalized or diffuse slow spike and wave complexes and (**B**) generalized paroxysmal fast activity. (**C**) Lateralized predominance of epileptiform activity may be indicative of a focal lesion. (**D**) Generalized tonic seizures may arise from the background abnormalities.

12

Lennox-Gastaut Syndrome

❖Etiology

- **Structural brain abnormalities (70 -80%)**
  - hypoxic–ischemic encephalopathy, meningoencephalitis, neurocutaneous disorders and brain malformations, including hypothalamic hamartomas and metabolic syndromes, account for ~70%–80% of all cases.
- **Genetic etiologies (de novo mutations):**
  - De novo mutations in *ALG13* and *GABRB3* have been described as causative in individuals with LGS.[17] Other genes implicated include *CHD2, DNM1, CACNA1A, CHD2, FLNA, GABRA1, GRIN1, GRIN2A, GRIN2B, HDAC3, HNRNPU, IQSEC2, mTOR, NEDD4L* and *SCN8A, STXBP1* and *SYNGAP1*



Gene	Association
SCN1A	GEFS+/Dravet syndrome/other phenotypes
SLC2A1	GLUT1-deficiency syndrome
STXBP1	Infantile spasms/West syndrome, Lennox–Gastaut syndrome
DNM1	Infantile spasms/West syndrome, Lennox–Gastaut syndrome
GABRB3	Infantile spasms/West syndrome, Lennox–Gastaut syndrome

GEFS+, generalized epilepsy with febrile seizures plus; GLUT1, gluc type 1; LGS, Lennox–Gastaut syndrome.

Cross et al. Frontiers in Neurology | www.frontiersin.org
September 2017 | Volume 8 | Article 505

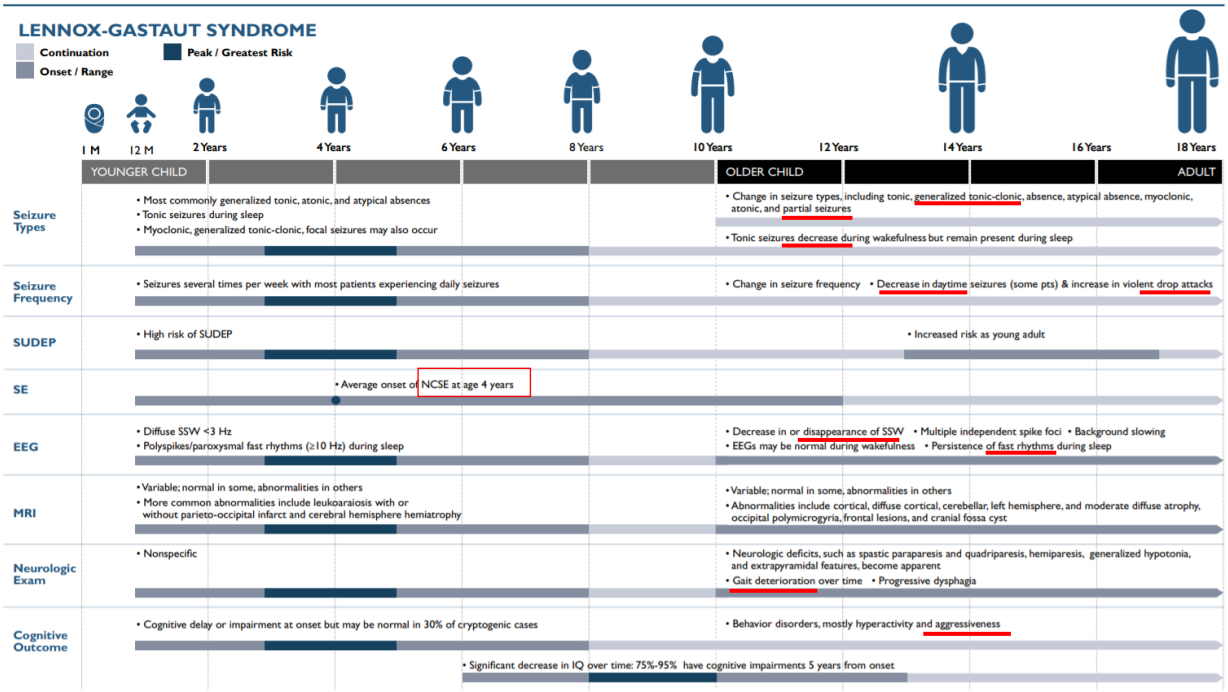
13

Lennox Gastaut Syndrome

- **Prognosis :**poor; intractable and not response to AEDs (>90%), < 10% seizure freedom as adult
  - pre-existing West syndrome -
  - early age of onset
  - symptomatic causes
  - abnormal neuroimaging
  - more frequent seizures or status epilepticus or focal/multifocal EEG abnormalities
- **Risk factors for SUDEP** (sudden unexplained death in epilepsy):
  - frequent generalized tonic-clonic seizures
  - early age of epilepsy
  - long duration of epilepsy
  - intellectual disability
- **Early death occurs in up to 15% of individuals with LGS**

Ostendorf AP, Ng YT 2017

14



15

NICE National Institute for Health and Care Excellence

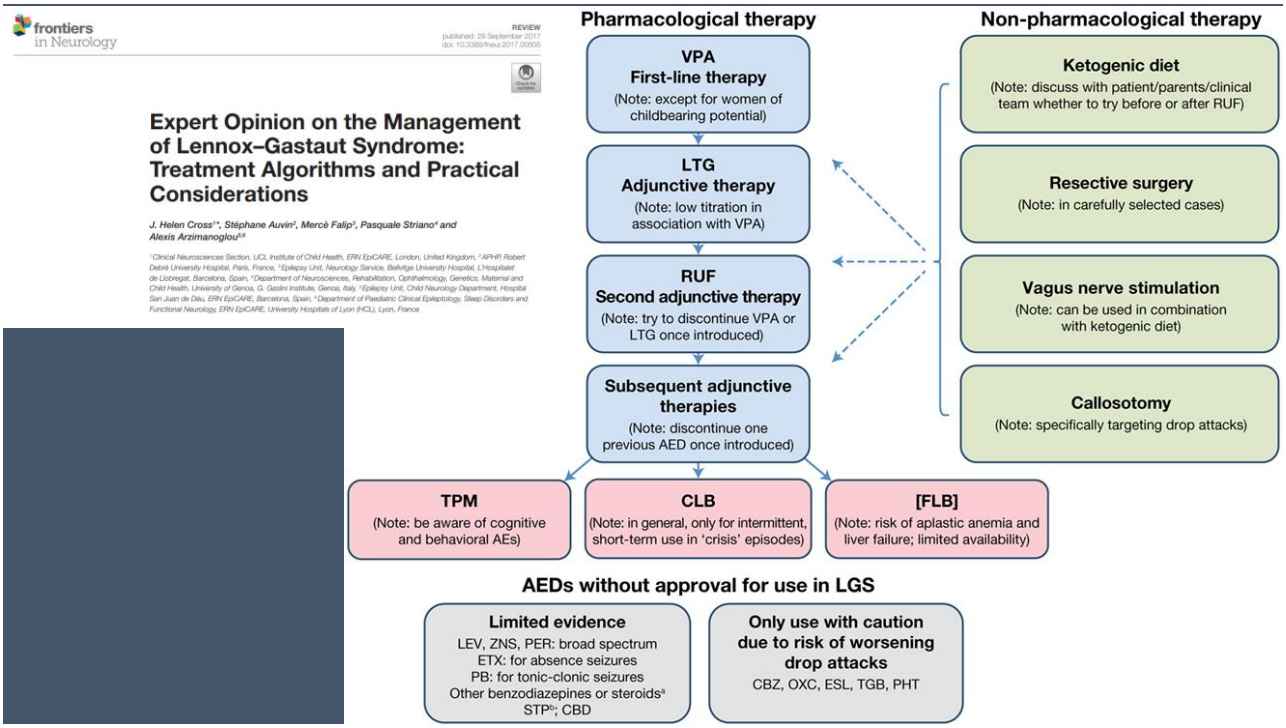
UPDATE : FEB2020

NICE guideline

Treatment : NICE guideline

- **Pharmacological treatment**
  - Antiepileptic drugs (AEDs), CBD
- **Non- pharmacological treatment**
  - Ketogenic diet
  - Surgery : Corpus callosotomy
  - VNS

16



17

เด็กหญิงอายุ 2 ปี 1 เดือน ลูกครึ่งญี่ปุ่น

CC: ชักเกร็งกระตุกทั้งตัวมา 30 นาที PTA
PI: 30 นาที PTA ขณะนั่งเล่นมีอาการตาลอยนิ่ง หน้าคล้ำเล็กน้อย เรียกไม่รู้ตัว จากนั้นกระตุกแขนขาทั้งตัวนาน 5 ถึง 10 นาที มาถึง รพ. หยุดชัก หลับไปจากนั้นสับสนเล็กน้อย ร้องไห้เสียงดัง วัดไม่มีไข้ หรืออาการอื่น
PH: มีประวัติไข้ชักมา 5 ครั้งตั้งแต่อายุ 6 เดือน
- แรกเกิดปกติดี พัฒนาการปกติยกเว้นยังไม่พูดแต่ทำตามสั่งได้
FH: มารดาและพี่ชายมีประวัติไข้ชักตอนเด็ก
PE: Alert, responsive, no dysmorphic facies
N/S: intacted

18

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

19

What is likely diagnosis?

1. Dravet syndrome
2. West syndrome
3. Doose syndrome
4. Lennox Gastaut syndrome

20

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.

21

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.

22

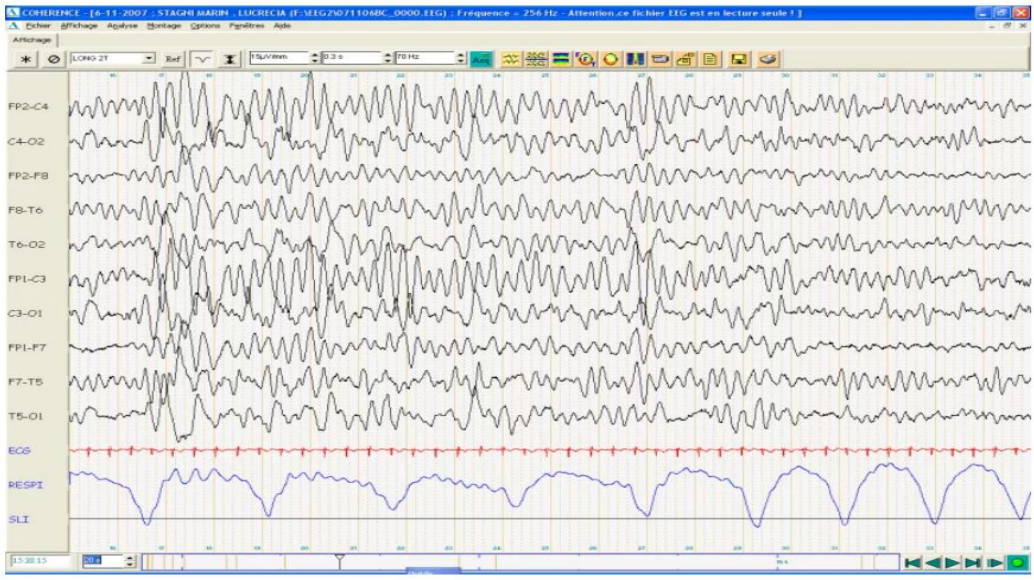
Dravet syndromes : EEG findings

- **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

23

Onset phase

Recording in a 9-months-old patient :



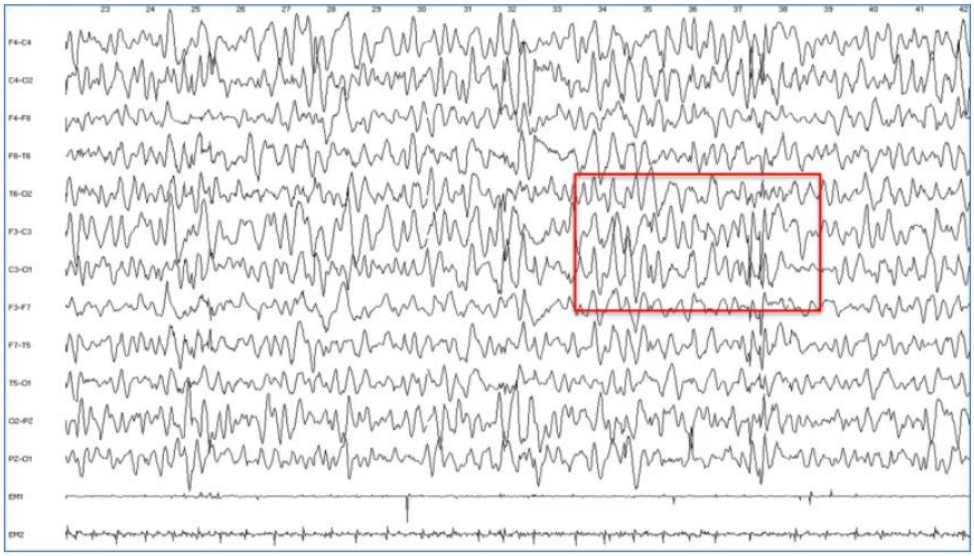
Normal symmetrical background activity when drowsy.

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

24

Worsening phase

Recording in an awake 4-year-old patient :



Slowing of background activity and rare bilateral central spikes.

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

25

Worsening phase

Recording in an awake 5-year-old patient :

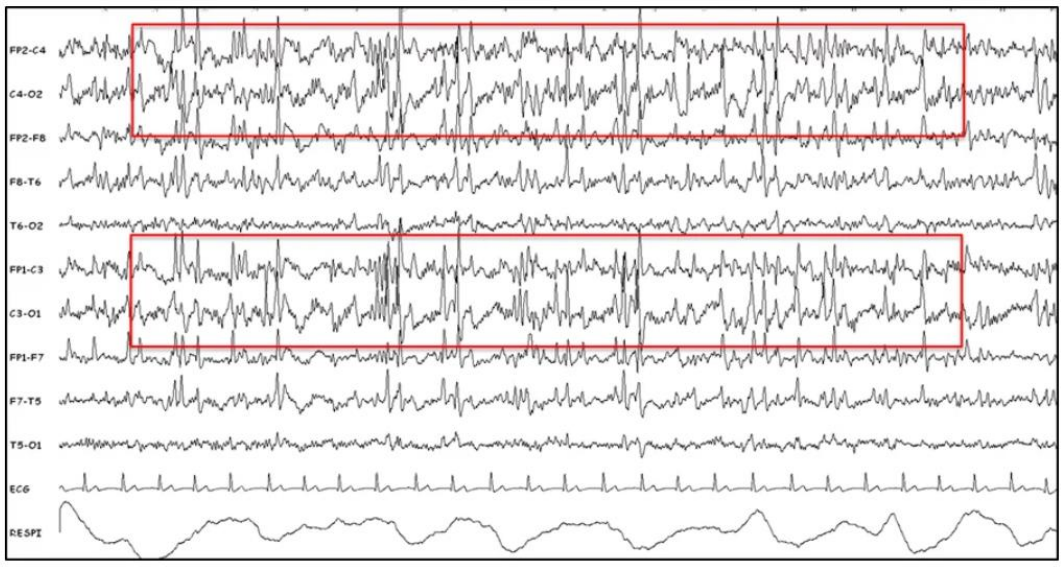
https://pro.dravet-syndrome.us/

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

26

Stabilisation phase

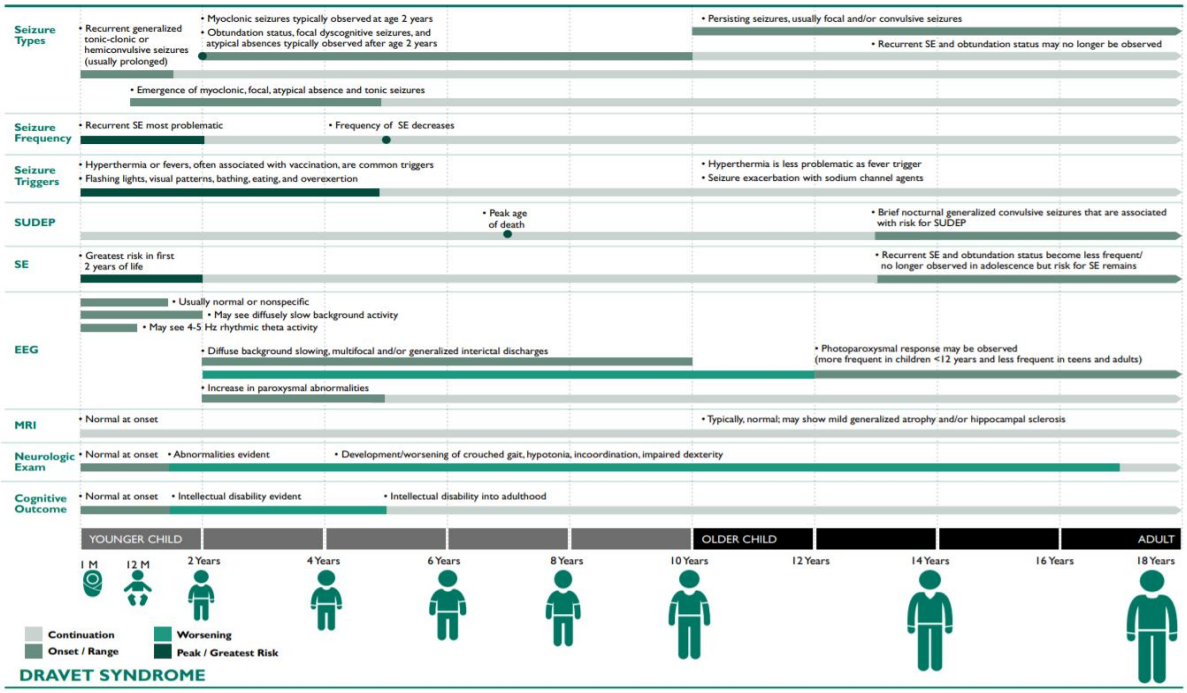
Recording in an asleep 10-year-old patient



Rare sleep spindles and subcontinuous biphasic spikes on both central regions, symmetrical or not.

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

27



EEG, electroencephalogram; IQ, intelligence quotient; MRI, magnetic resonance imaging; N/A, not applicable; NCSE, non-convulsive status epilepticus; pts, patients; SE, status epilepticus; SSW, slow spike-wave; SUDEP, sudden unexpected death in epilepsy.
Figure 1 adapted from multiple publications.[1,13,16,20,21,26,30,31,33,34,37,42]

28

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+

29

A predictive DS risk factor test

First phase calculation

If the calculated clinical risk score is ≥6 then genetic testing should be considered.

Clinical score	Risk score
Onset ≤7 months	2
Total number of seizures ≥5	3
Hemiconvulsions	3
Focal seizures	1
Prolonged seizures	3
Hot-water induced seizures*	2

*In countries where hot baths are not usual, this item can be replaced by febrile seizures

Second Phase: Calculation of genetic score

Type of genetic mutation	Genetic score
SCN1A missence mutation	1
SCN1A truncated mutation	2

Overall results:

If the total calculated risk score is ≥7 then a diagnosis of Dravet syndrome should be strongly suspected.

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

30

Dravet syndrome v.s Febrile seizures

Dravet syndrome	Febrile seizures
Onset before the age of 1 year	Onset usually after the age of 1 year
Febrile and afebrile seizures	Only febrile seizures
Other seizure types appear	Only brief seizures
Later cognitive decline	Normal cognitive outcome/No epilepsy
For 75%: *SCN1A* mutation	*SCN1A* mutation (possible GEFS+ spectrum)

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

31

Dravet syndrome v.s LGS

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/

32

Current and potential future treatment pathway in DS

- AEDs to **avoid** (exacerbate seizures)
  - Carbamazepine
  - Oxcarbazepine
  - Lamotrigine
  - Phenytoin
  - Vigabatrin
  - Gabapentin
  - Pregabalin
  - Tiagabine

First-line
- VPA[a] or CLB[a]
- If first choice is not effective, add the other

Second-line
- STP adjunctive therapy[a,c]

or
- Topiramate[a]

or
- Ketogenic diet[a,d]

Third-line
- Addition of an AED
- Bromide[c,e]
- Clonazepam[a]
  - Levetiracetam[a]
  - Zonisamide[a]
  - Ethosuximide[b] (for atypical absence sz)
  - Phenobarbital[b]
  - Rufinamide or acetazolamide[c]

or
- Consider VNS[b]

New therapies
- Cannabidiol as adjunctive therapy for patients ≥ 2 years (in conjunction with clobazam in the EU)[c]
- Fenfluramine in patients ≥2 years (approved in the US ; subject to approval in the EU)

Adam Strzelczyk [a,b] and Susanne Schubert-Bast [a]

EXPERT REVIEW OF NEUROTHERAPEUTICS
2020, VOL. 20, NO. 10, 1065–1079

33

Pilot studies	Phase I	Phase II	Market Approval
Lorcaserin • Modulates serotonin (5-HT) signaling	**Clemizole** • Modulates serotonin (5-HT) signaling	**Ataluren (Translarna®)** • Enables ribosomal readthrough of mRNA containing a premature stop codon, resulting in production of a full-length protein	**Stiripentol (Diacomit®)[a]** • Multiple mechanisms including enhancement of inhibitory, GABAergic neurotransmission
		Verapamil • Inhibits the P-glycoprotein, a drug efflux transporter located at the blood brain barrier, which may limit the ability of CNS drugs to enter the brain	**Cannabidiol (Epidiolex®)[b]** • Potential multiple mechanisms including reducing neuronal hyperexcitability through the transient receptor potential vanilloid 1, antagonism of the G-protein coupled receptor 55, and modulation of adenosine reuptake
		Soticlestat (TAK-935/ OV935) • Highly selective first-in-class inhibitor of the enzyme cholesterol 24-hydroxylase (CH24H), a brain-specific enzyme responsible for cholesterol catabolism	**Fenfluramine (Fintepla®)[c]** • Selective serotonin releasing agent; stimulates multiple 5-HT receptor sub-types through the release of serotonin • May also act on other receptors

[a] Approved in EU (2007), Canada (2012), and Japan (2012) ***in conjunction with CLB and VPA as adjunctive therapy of refractory generalized tonic-clonic seizures in patients with DS whose seizures are not adequately controlled with CLB and VPA***
Approved in the USA (2018) ***for the treatment of seizures associated with DS in patients 2 years of age and older taking CLB***.

[b] Approved in the USA (2018) ***for the treatment of seizures associated with LGS or DS in patients 2 years of age***
Approved in EU (2019, Epidyolex®) ***for use as adjunctive therapy of seizures associated with LGS or DS, in conjunction with CLB, for patients 2 years of age and older***

[c] Approved in the USA (June 2020) ***for the treatment of seizures associated with DS in patients 2 years of age and older***; awaiting approval in the EU

. Pharmacologic agents approved or in development for Dravet syndrome.

34

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

35

36