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Understanding Lennox-Gastaut Syndrome (LGS): Etiology, Presentations, Diagnosis, and Treatment Challenges

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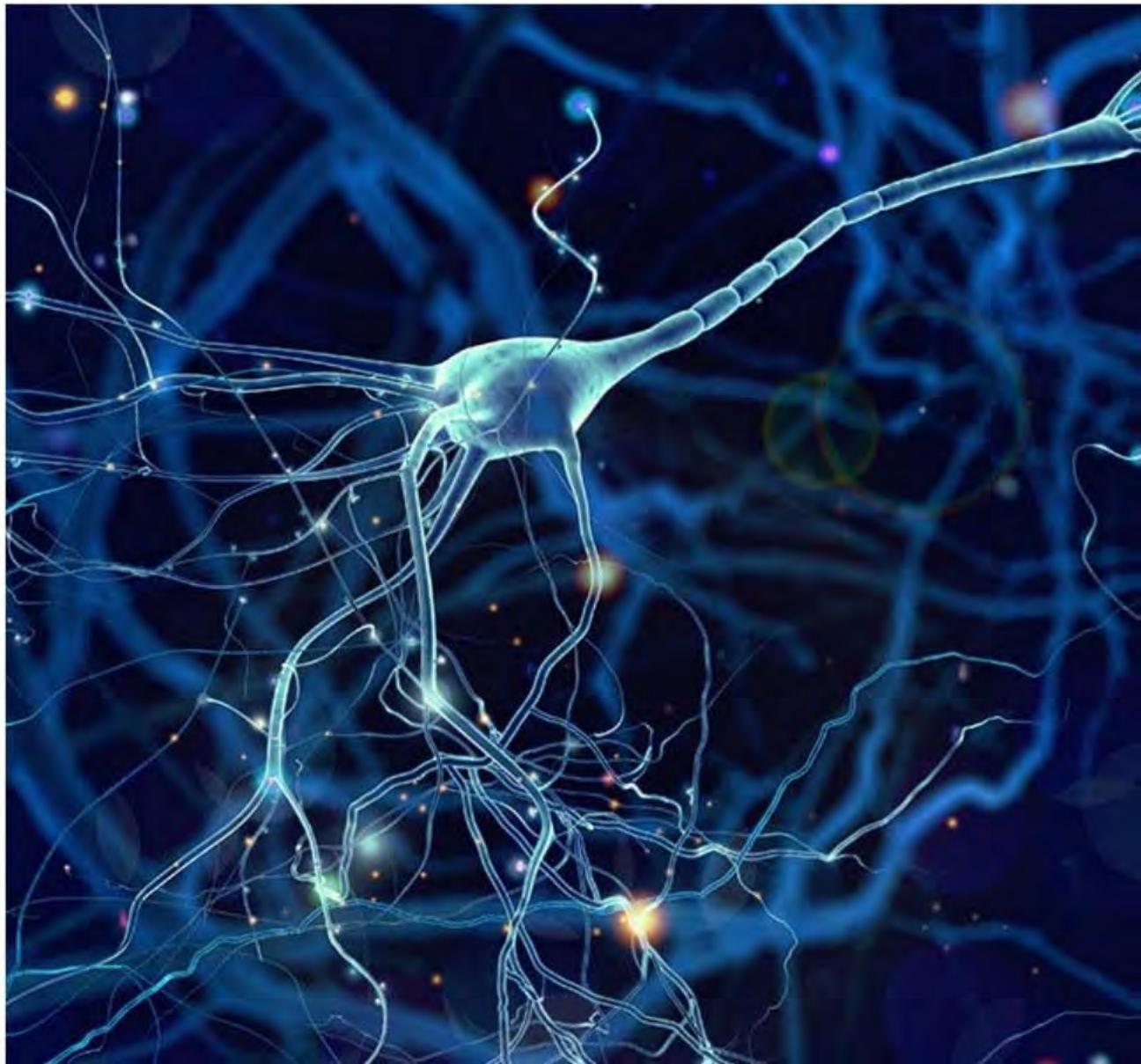


Case 1: Background

- Now 9y old girl
- Born to non-consanguineous parents; no relevant family history
- Born in good condition at term
- No concerns with motor development; speech delay needing speech therapy and slightly behind in cognitive development

Case 1: Epilepsy presentation

- First seizure at 4y of age: unwell with a febrile illness; had a seizure in bath with jerking of all 4 limbs
- Further tonic-clonic seizures resulting in hospitalization, commenced on levetiracetam and discharged
- Aggressive behaviour, hyperactivity and insomnia – levetiracetam switched to sodium valproate
- Further seizure after 4 weeks – given a short course of clobazam f/b carbamazepine
- Introduction of carbamazepine coincided with appearance of myoclonic jerks and absence episodes with eyelid flickering and loss of balance

Case 1: Epilepsy evolution

- When first seen at our service 3 months after seizure onset:
  - Nocturnal bilateral tonic-clonic seizures: most nights
  - Absence seizures: multiple daily
  - Epileptic spasms: multiple daily
  - Myoclonic seizures: few daily

- Seizures improved after stopping carbamazepine and optimizing the dose of clobazam and sodium valproate

Case 1: Epilepsy evolution

- Over the next months, multiple hospital admissions with seizure clusters
- Concerns about non-convulsive status epilepticus (NCSE) and treated with oral steroids

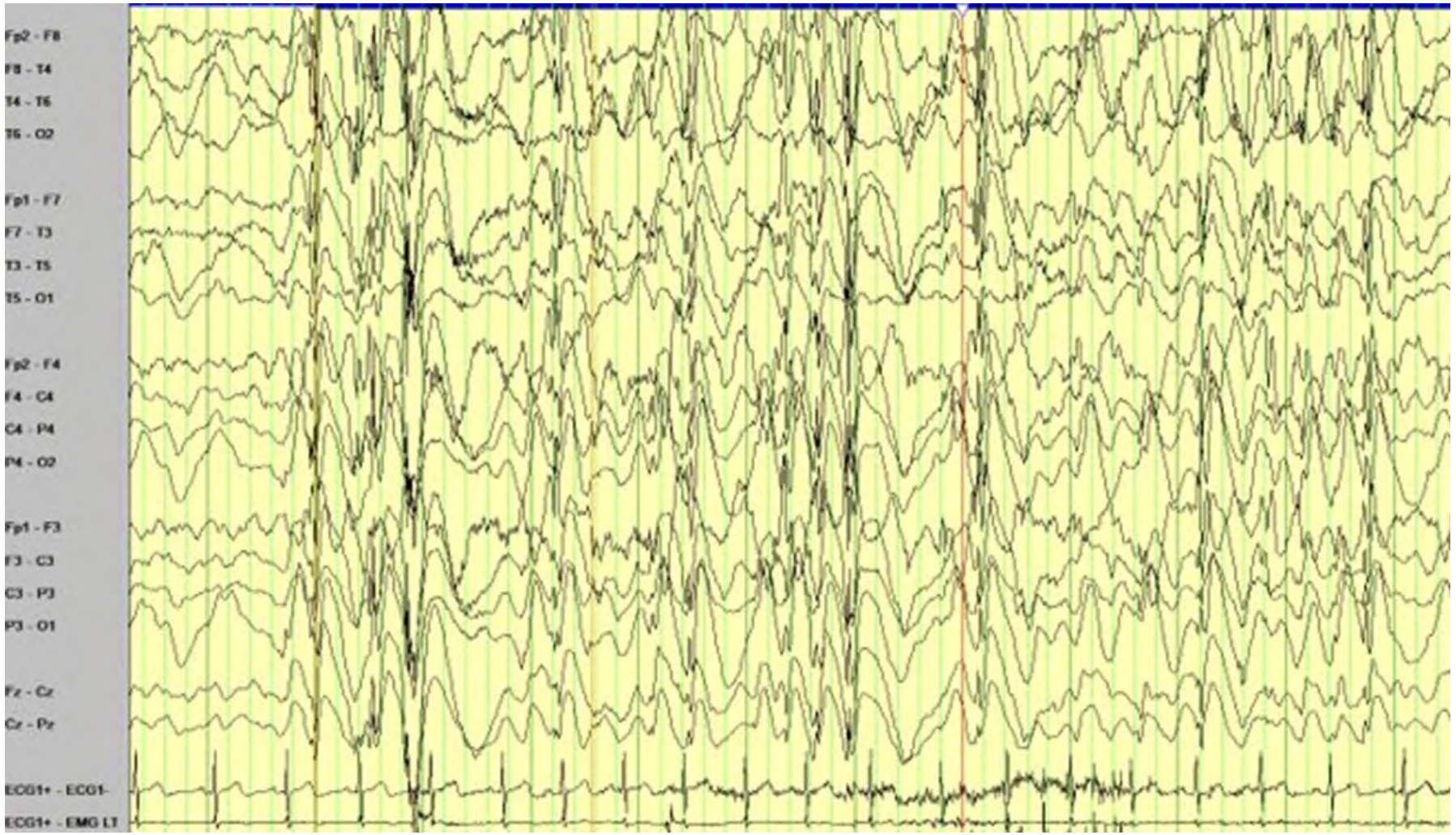
- In view of lack of response to medication, ketogenic diet was commenced
- Initial good response: nocturnal tonic seizures on most nights and multiple absence seizures daily

- Developmental plateau since increase in seizures and struggling in school; also has social communication difficulties, poor attention and difficult behaviour

Case 1: Investigations

- **MRI brain:**
  - No localizing or lateralizing epileptogenic lesion identified
  - Mild cerebral and cerebellar parenchymal volume loss
- **Video telemetry:**
  - Repetitive blinking, staring and sometimes behavioural pause and orofacial automatisms – EEG showing generalized spike/polyspike and wave epileptiform discharges at 1.5–2.5 Hz lasting up to 30 seconds
  - Brief tonic spasms with neck flexion and bilateral arm extension – EEG shows a burst of generalized polyspikes with brief hints of subsequent attenuation
  - Brief tonic seizure from sleep with bilateral arm extension and abduction – EEG shows generalized fast spiking
- Trio whole genome sequencing and neurometabolic work-up: non-diagnostic

EEG showing slow spike-wave discharges with behavioural arrest and eyelid blinking



Case 1: Epilepsy evolution

- Over the years:
  - Bilateral tonic-clonic seizures
  - Tonic seizures
  - Epileptic spasms
  - Absence seizures
  - Myoclonic seizures
  - Atonic drops
  - Episodes of non-convulsive status epilepticus

- Unsuccessful therapies:
- Valproate, levetiracetam, ethosuximide, clobazam, carbamazepine, lamotrigine, topiramate, rufinamide, phenobarbital, felbamate, cannabidiol, ketogenic diet

Case 1: Current situation

- Current seizures:
  - Atonic drop seizures
  - Nocturnal tonic seizures
  - Epileptic spasms
  - Absence seizures
  - Bilateral tonic-clonic seizures

- Current development:
  - Moderate intellectual disability; needing additional support in school
  - Social communication difficulties
  - Behaviour that challenges

Case 1: Current situation

- Therapies under consideration:
  - Corpus callosotomy offered for drop seizures
  - Vagus nerve stimulation (VNS)
  - Deep brain stimulation (DBS) trial
  - Fenfluramine

LGS diagnosis in a nutshell

Mandatory

Tonic seizures (often more prominent in sleep)

≥1 additional seizure type, which may include:

- Atypical absences
- Atonic
- Myoclonic
- GTC
- Focal impaired awareness
- Epileptic spasms
- Non-convulsive status epilepticus (remains a risk at any age)

Generalized slow spike-and-wave complexes <2.5 Hz (or history of this finding on prior EEG)

Generalized paroxysmal fast activity in sleep (or history of this finding on prior EEG)

Alerts

Photoparoxysmal response at low frequencies (consider CLN2 disease)

Syndrome-in-evolution: ~50% of infants with a severe DEE evolve to LGS over time

>8 years old at onset

No developmental impairments

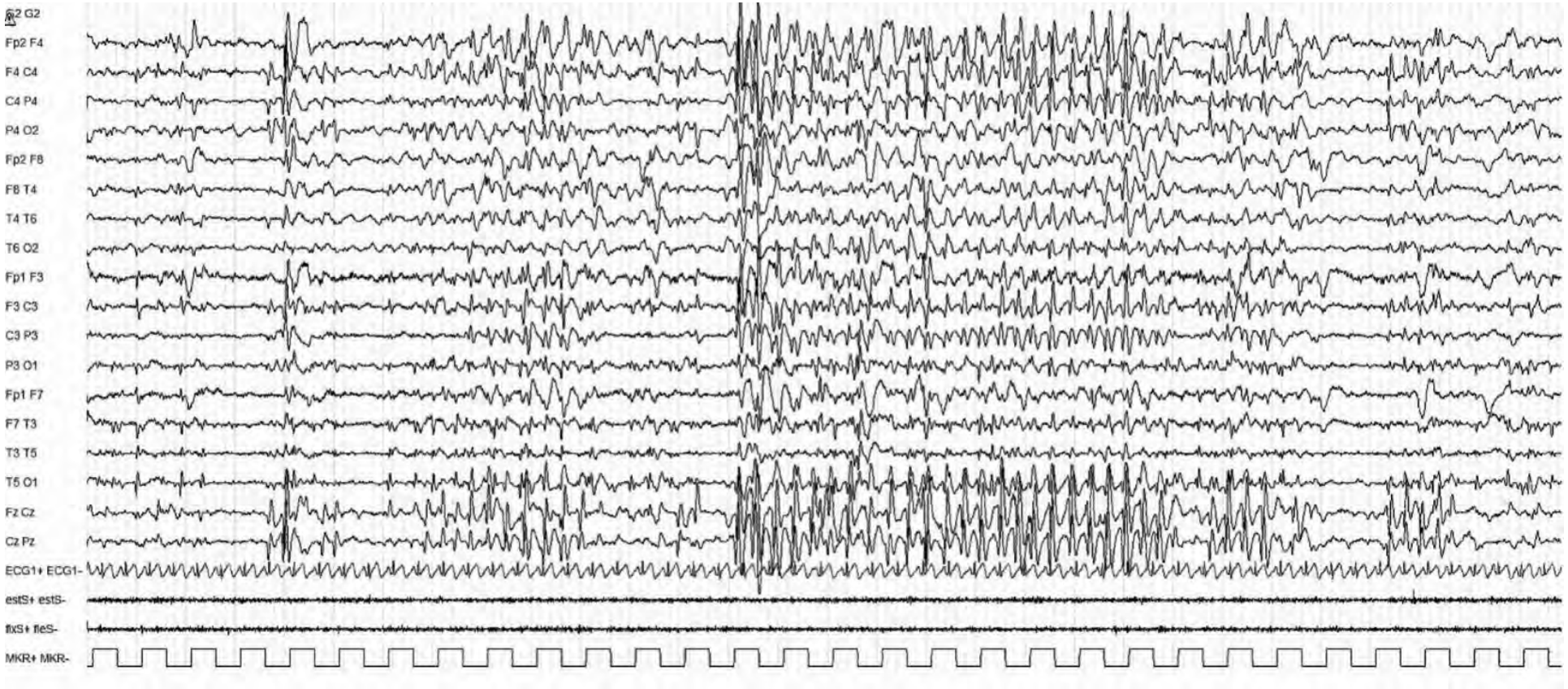
Exclusionary

Persistent focal abnormalities without generalized spike-and-wave pattern

Notes: Neuroimaging and genetic testing not required for diagnosis but helpful for evaluating etiology and guiding treatment.

Specchio, et al. *Epilepsia*. 2022;63(6):1398-1442. Berg AT, et al. *Epilepsia*. 2018;59(11):2096-2105. Smith KM, et al. *Neurol Clin Pract.* 2018;8(5):397-402.

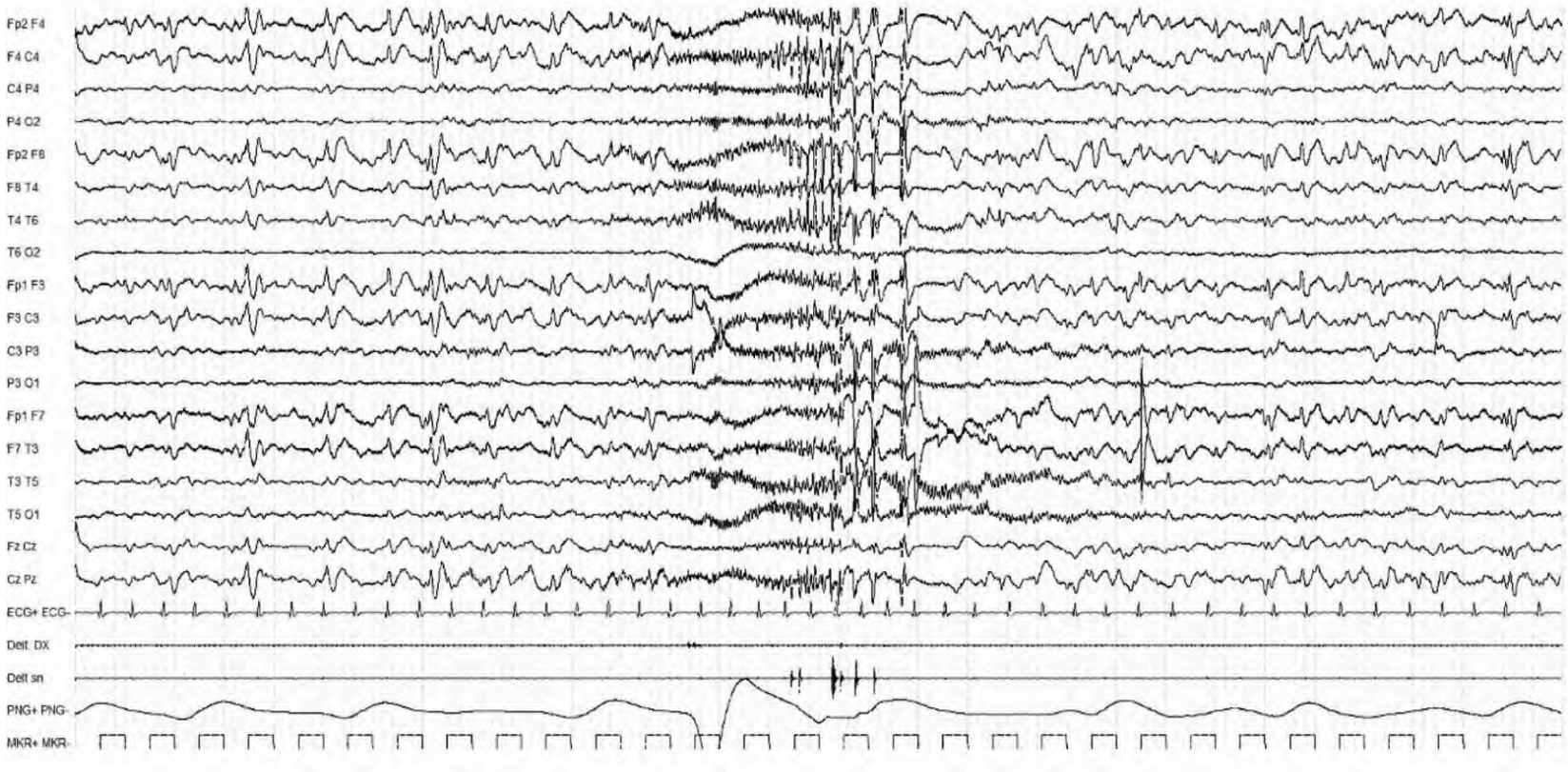
Lennox-Gastaut syndrome: Key EEG features



Interictal generalized slow spike-and-wave abnormalities at frequency of ≤2.5 Hz: may or may not be accompanied by atypical absence seizures

Adapted from Specchio, et al. *Epilepsia*. 2022;63(6):1398-1442.

Lennox-Gastaut syndrome: Key EEG features



Brief bursts of diffuse or bilateral fast (10 Hz or more) activity often seen during sleep

Adapted from Specchio, et al. *Epilepsia*. 2022;63(6):1398-1442.

Lennox-Gastaut syndrome: Epidemiology

- Relatively rare: 1%–2% of all persons with epilepsy
- Often evolves from another severe infantile epilepsy syndrome or aetiology: about 20% evolving from infantile epileptic spasms syndrome
- 3.6% of all children with epilepsy, and 19% of children with seizures starting in infancy, evolve to LGS
- Peak age at onset of 3–5y (typical age of onset 18m to 8y)
- Developmental impairment predates seizure onset in the majority; developmental stagnation or decline can occur with onset of frequent seizures

Specchio, et al. *Epilepsia*. 2022;63(6):1398-1442. Berg AT, et al. *Epilepsia*. 2018;59(11):2096-2105. Goldsmith IL, et al. *Epilepsia*. 2000; 41(4): 395–9.

Lennox-Gastaut syndrome: Diagnostic work-up

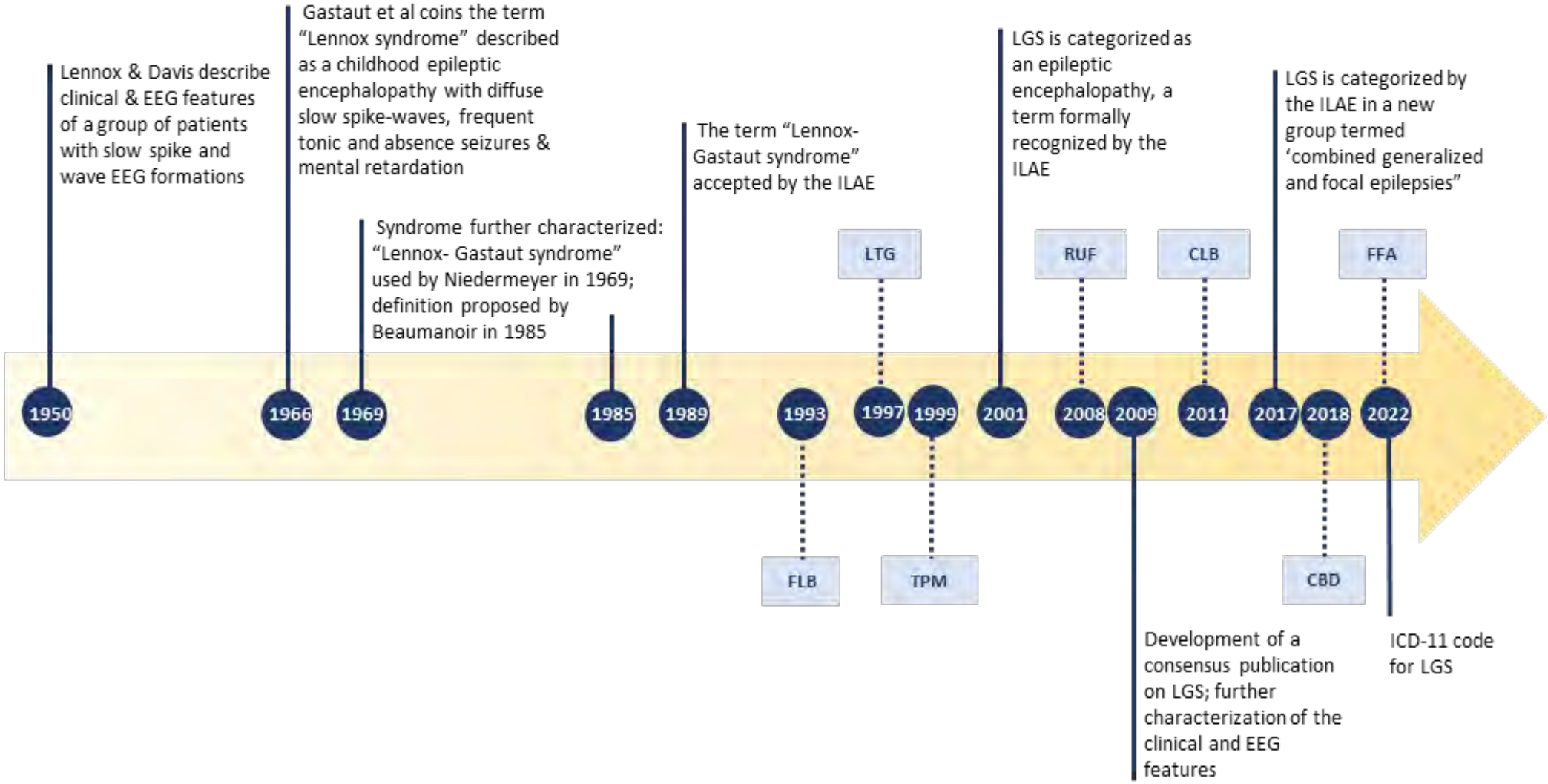
- **Brain imaging:** may reveal an aetiology
- **Genetics:** microarray and whole genome/exome sequencing
  - particularly important if normal brain MRI and suggestive clinical features or family history
  - also consider if structural brain disorder suggesting a genetic cause
- **Metabolic testing:** rare neurometabolic disorders

Lennox-Gastaut syndrome: Differential diagnosis

- **Epilepsy with myoclonic atonic seizures (EMAtS),** formerly known as Doose syndrome [normal development before seizure onset, myoclonic-atonic seizures are mandatory for diagnosis, typically >3 Hz generalized spike-and-wave pattern on EEG]
- **Dravet syndrome** [prolonged, hemiclonic seizures triggered by fever/illness in the first year of life, a pathogenic variant in *SCN1A* is present in more than 80%–85%]
- **DEE-SWAS or EE-SWAS** [associated with regression and marked activation of epileptiform abnormalities in sleep, with nearly continuous diffuse spike-and-wave complexes]
- **Ring (20) syndrome** [associated with refractory epilepsy, intellectual disability and behavioural abnormalities; tonic seizures usually during sleep; non-convulsive status epilepticus is frequent]
- **CLN2 disease** [typically begins in children with normal development or isolated speech delay; **progressive** motor and cognitive decline and ataxia following seizure onset; EEG shows characteristic photoparoxysmal response at 1–3 Hz]

EPILEPSIE ZENTRUM FRANKFURT RHEIN-MAIN

Lennox-Gastaut syndrome



Strzelczyk et al. Orphanet J Rare Dis . 2023 Mar 1;18(1):42.

Lennox-Gastaut syndrome

Triad of symptoms

Refractory seizures

- **Tonic**
- Atonic
- Atypical absence
- Myoclonic
- Partial
- Generalised tonic-clonic
- NCSE

EEG abnormalities

- Interictal pattern of diffuse SSW complexes at <3 Hz, while awake
- Paroxysmal fast rhythms (10–20 Hz) during sleep

Cognitive impairment

- Intellectual disability
- Impaired psychomotor ability
- Behavioural problems

Diagnostic challenges

- Features are not pathognomonic
  - Overlap with other DEEs
- Features evolve and change over time
- The triad of features not always present at outset
- Multiple aetiologies

- **Structural-Genetic-Metabolic**:
  - Brain damage
  - Congenital CNS infections
  - Brain malformation
  - Earlier onset DEE
  - TSC
  - Hereditary metabolic disorders
  - Other genetic causes
- **Unknown**
  - De novo mutation?
  - Autoimmune disorder?

Male born 1979 with Lennox-Gastaut syndrome

Medical history

- Accompanied by his mother, presented for the first time at our centre in 2003 (aged 24 years)
- Suffers from frequent focal-impaired awareness (onset at 2 years of age), tonic (falls, onset since childhood, but not exactly reported) and generalized tonic-clonic seizures (onset at 3.5 years), no febrile convulsions
- The medication had been changed several times over the years. A better seizure freedom could not be achieved. Under vagus nerve stimulation, some reduction in seizure duration was reported
- A detailed evaluation for metabolic disorder was unremarkable, recent genetic testing revealed no mutations, imaging shows no structural abnormalities, only cerebellar atrophy
- First milestones were fine, walking and speech development were normal until the age of 4 to 6 years. After that, a developmental decline became apparent. In addition, behavioural problems were reported

Patient case provided by speaker with permission. This case study is not necessarily representative of the study population.

Male born 1979 with Lennox-Gastaut syndrome (Nov 2021)

Medical history

- **Diagnosis at presentation:** Lennox-Gastaut syndrome
- **Previous ASM treatment:** levetiracetam* (seizure increase), oxcarbazepine*, phenytoin*, carbamazepine*, topiramate (speech problems), zonisamide* (kidney stones)
- **Current ASM treatment:**
  - Rufinamide: 600 mg – 0 – 600 mg
  - Valproate* ret: 1000 mg – 0 – 1300 mg
  - Lamotrigine 125 mg – 0 – 125 mg
  - Melperon drops PRN (for behavioural problems)

- **How to proceed with ASM therapy?**

*Not indicated for the treatment of seizures associated with Lennox-Gastaut Syndrome.
ASM, antiseizure medication; PRN, pro re nata, taken as needed.
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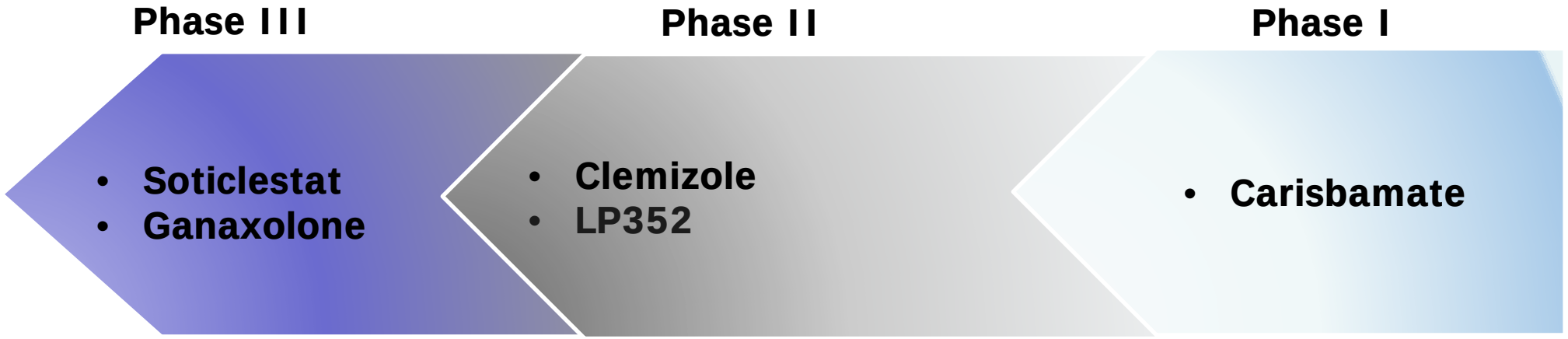
LGS treatment algorithm



modified from Strzelczyk A, Schubert-Bast S. CNS Drugs 2021

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  - Melperon drops PRN (for behavioural problems)

- **Our decision to add cannabidiol (Epidyolex) up to 600 mg (= 6 ml, 7.5 mg/kg bw)**
- **Reduction of valproate to 1000 mg – 0 – 1000 mg**

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Male born 1979 with Lennox-Gastaut syndrome (Sept 2022)

Medical history

- **Seizure: improved by 25% to 50%, mainly nocturnal seizures**
- **Improvement in behaviour, however sedated**
- **Current ASM treatment:**
  - Rufinamide: 600 mg – 0 – 800 mg
  - Valproate* ret: 500 mg – 300 mg – 1300 mg
  - Lamotrigine 100 mg – 0 – 100 mg
  - Cannabidiol 400 mg – 0 – 400 mg (= 10 mg/kg bw)
  - Melperon drops PRN (for behavioural problems)

- **What to do next?**

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  - Valproate* ret: 500 mg – 300 mg – 1000 mg
  - Lamotrigine 100 mg – 0 – 100 mg
  - Cannabidiol 400 mg – 0 – 400 mg (= 10 mg/kg bw)
  - Melperon drops PRN (for behavioural problems)

- **What to do next?**
- **Increase in cannabidiol (Epidyolex) to 1000 mg (= 10 ml, 12.5 mg/kg bw)**

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Male born 1979 with Lennox-Gastaut syndrome (May 2023)

Medical history

- **Seizure: mainly nocturnal seizures persist**
- **Further improvement in behaviour, still sedated**
- **Current ASM treatment:**
  - Rufinamide: 600 mg – 0 – 800 mg
  - Valproate* ret: 500 mg – 0 – 1000 mg
  - Lamotrigine 100 mg – 0 – 100 mg
  - Cannabidiol 500 mg – 0 – 500 mg (= 12.5 mg/kg bw)
  - Melperon drops PRN (for behavioural problems)

- **What to do next?**
- **Introduction of fenfluramine (Fintepla) to 13.2 mg (= 6 ml, 0.165 mg/kg bw)**

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Male born 1979 with Lennox-Gastaut syndrome (Oct 2023)

Medical history

- **Seizure: mainly nocturnal seizures persist, those reduced by 50%**
- **Current ASM treatment:**
  - Rufinamide: 600 mg – 0 – 800 mg
  - Valproate* ret: 500 mg – 300 – 1000 mg
  - Lamotrigine 100 mg – 0 – 100 mg
  - Cannabidiol 500 mg – 0 – 500 mg (= 12.5 mg / kg bw)
  - Fenfluramine 6.6 mg – 0 – 6.6 mg (= 6 ml / 0.165 mg/kg bw)

- **Next steps:**
- **Increase of fenfluramine to 17.6 mg (8 ml / 0.22 mg/kg bw), withdrawal of rufinamide**

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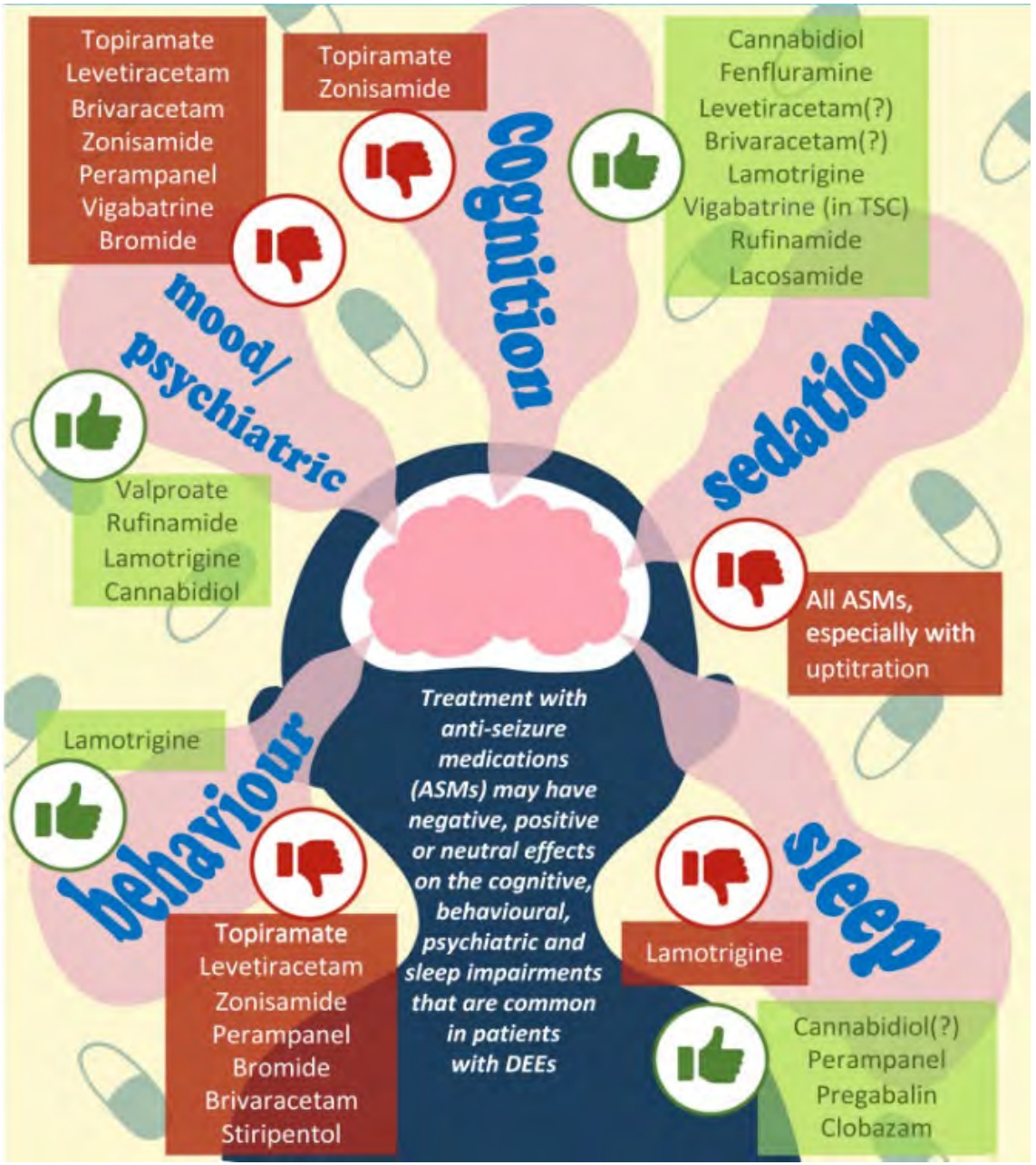
Psychobehavioural and cognitive adverse events of ASMs in DEE

DEE	Classification of evidence		Caution
	Class I-II	Class III-IV	
DS	Valproate Topiramate Stiripentol* Clobazam Cannabidiol* Fenfluramine*	Bromide Levetiracetam Zonisamide Ethosuximide Perampanel Brivaracetam	Predominant sodium channel blockers Gabapentinoids Tiagabine Vigabatrin
LGS	Valproate Topiramate* Lamotrigine* Rufinamide* Clobazam* Cannabidiol* Fenfluramine*	Felbamate* Levetiracetam Zonisamide Ethosuximide Perampanel Brivaracetam	Carbamazepine Oxcarbazepine Gabapentinoids Phenytoin
Notes	*Carries approved indication for specified condition		



Strzelczyk A, Schubert-Bast S. *CNS Drugs*. 2022;36(10):1079-1111. Wirrell EC, et al. *Epilepsia*. 2022;63(7):1761-1777. Strzelczyk A, Schubert-Bast S. *CNS Drugs*. 2022;36:217–237. Northrup H, et al. *Pediatr Neurol.* 2021;123:50-66. Montouris G, et al. *Epilepsy Behav.* 2020;110:107146. Strzelczyk A, Schubert-Bast S. *CNS Drugs*. 2021;35(1):61-83.

Take-home messages

- Lennox-Gastaut syndrome is a DEE syndrome-in-evolution
- Characteristic clinical and EEG features may not be present early in the course of LGS
- Do remember the mandatory clinical and EEG criteria for LGS diagnosis
- Psychiatric and behavioural comorbidities are important both in children and adults
- LGS can be difficult to diagnose in adults due to evolution of EEG changes
- Prompt diagnosis is important for prognosis and targeted interventions could improve the quality of life of individuals with LGS