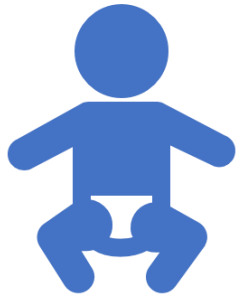


Childhood Epileptic Encephalopathies

- Seventh Annual Northern Ontario Paediatric Conference
- Sudbury, ON
- May 10, 2019

- Maria Zak, MN, NP-Paediatrics
- The Hospital for Sick Children

Faculty/Presenter Disclosure Slide 1

- **Speaker Name: Maria Zak**

- **Relationships with for-profit or not-for-profit organizations**
  - **Advisory Board Member: Novartis - Afinitor TSC Seizure National Advisory Board.**
  - **Speakers Bureau/Honoraria: Novartis - Afinitor TSC Seizure National Advisory Board.**
  - **Co-investigator on a prospective open-label study of a CBD/THC cannabis oil in Dravet Syndrome**
    - **CBD/THC cannabis oil supplied in kind by Tilray™**

Mitigating Potential Bias
Slide 3

- Provided with a speaker letter outlining the certification/accreditation requirements for their presentation (ie. Details regarding use of generic medication names, colour branding, incorporation of appropriate evidence, etc.).

- Learning objectives and focus of talk was decided upon in consultation with the planning committee and based on their needs assessment results.

- The presentation was sent to the planning committee for review prior to it’s delivery.

Objectives

- Identify 3 common childhood epileptic encephalopathies
- Describe the presenting features at the onset of 3 of the most commonly recognised pediatric epileptic encephalopathies – West syndrome (infantile spasms), Lennox-Gastaut syndrome, and Landau-Kleffner syndrome (continuous spike waves during sleep)
- Articulate the treatment options in managing seizures in children diagnosed with epileptic encephalopathy

Encephalopathy

What is an encephalopathy?

Encephalopathy Defined

en·ceph·a·lop·a·thy

/enˌsefəˈläpəTHē/

noun

1. a disease in which the functioning of the brain is affected by some agent or condition (such as viral infection or toxins in the blood):
   "a picture of how these encephalopathies are transmitted"

Powered by Oxford Dictionaries

Childhood Epileptic Encephalopathy – Quiz 1

Childhood epileptic encephalopathies:

a) Typically start early in life

b) Are associated with mild cognitive, behavioural, and motor delay

c) Can be treated effectively if caught early

d) All of the above

Case

Madeline is a 4 month old infant girl

Born at 39 weeks gestation

Birth weight 3800 grams

Apgar‘s 8 and 9

Fed well after birth

At 50th centile for height and weight on growth chart

Developmental milestones were normal

Presented to the ER after parents noted Madeline would have several very brief episodes where her head, body, and arms and legs would flex forward abruptly and she would cry

Case 1 (Cont'd)

These abrupt flexion episodes would occur every time Madeline would wake from sleep or a nap

The "jerks" where starting to happen one after the other

Otherwise happy, healthy baby

What is Wrong with Madeline?

Infantile Spasms

West W. On a particular form of infantile convulsions. Lancet. 1841;1:724–725.

- Commonly known as West syndrome
- In a letter to the editor of *The Lancet* in 1841, Dr. WJ West described the patient had "bobbings" that "cause a complete heaving of the head forward towards his knees, and then immediately relaxing into the upright position … these bowings and relaxings would be repeated alternately at intervals of a few seconds, and repeated from 10 to 20 or more times at each attack, which attack would not continue more than 2 or 3 minutes; he sometimes has 2, 3 or more attacks in the day." West also reported marked developmental delay and mental retardation in this child – his own son.

Clinical Presentation

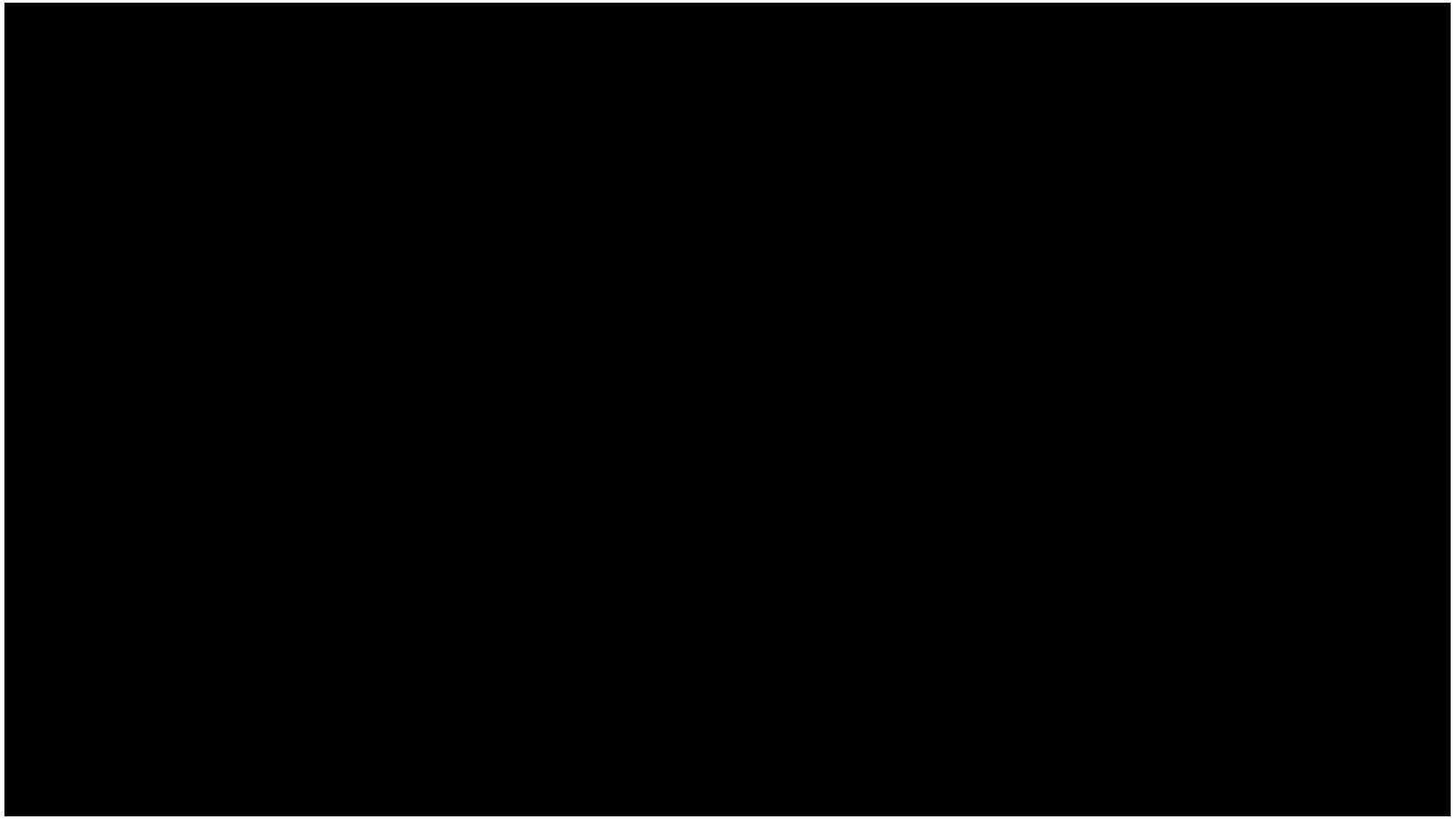
Bisulli F, Volpi L, Meletti S, Rubboli G, Franzoni E, Moscano M, d'Orsi G, Tassinari CA. Ictal pattern of EEG and muscular activation in symptomatic infantile spasms: A videopolygraphic and computer analysis. Epilepsia. 2002;43:1559–1563

Bisulli F, Volpi L, Meletti S, Rubboli G, Franzoni E, Moscano M, d'Orsi G, Tassinari CA. Ictal pattern of EEG and muscular activation in symptomatic infantile spasms: A videopolygraphic and computer analysis. Epilepsia. 2002;43:1559–1563

Lombroso C. A prospective study of infantile spasms: Clinical and therapeutic correlations. Epilepsia. 1983;24:135–158.

- Age of onset:
  - 2-12 months (peak time of presentation 6 months)
- Semiology of seizures:
  - Typical presentation - clusters of flexion jerks of neck, trunk, and extremities lasting 1–2 seconds
  - May also present as extension of upper and lower extremities or both
  - Can be as subtle as a brief head drop
  - Often misdiagnosed as a Moro reflex or simple startle reflex
  - May remain unappreciated for weeks or months.
  - Spasms may present as a single jerk event
  - Clusters or spasms are more common and often occur on awakening in the morning or after a nap
  - Other seizure types may arise concurrently or sequentially with infantile spasms

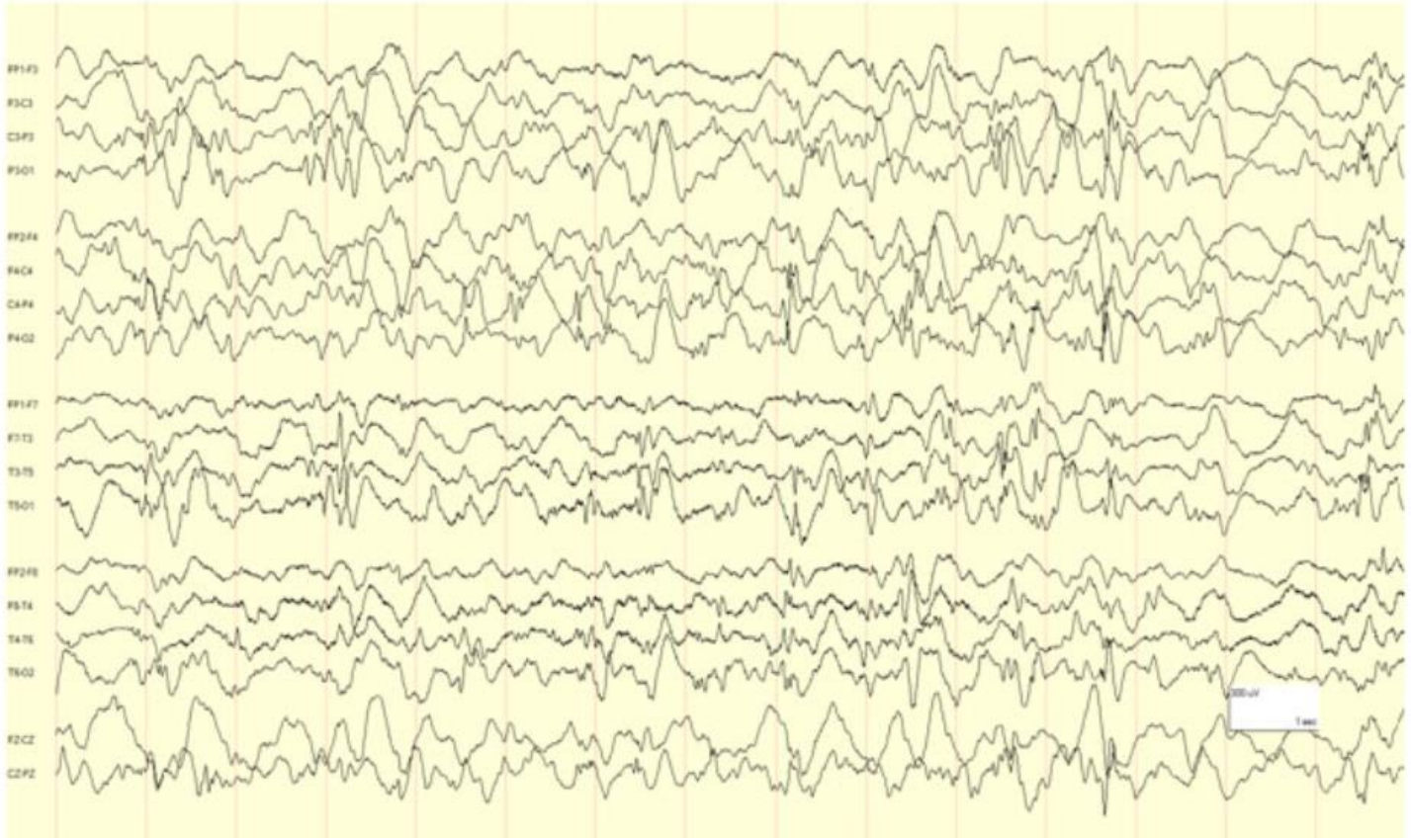
West Syndrome (Infantile Spasms)



Developmental Presentation

- Development prior to seizure onset may be normal or abnormal
- Development may plateau
- Often see regression with onset of spasms
- Outcome varies with etiology
- 80% of children with a confirmed etiology will have developmental delay

Lancet Neurol 2016; 15: 304-16.



EEG Presentation

- https://www.epilepsydiagnosis.org/syndrome/west-syndrome-eeg.html

Ictal EEG Findings

- Highly disorganized background
- High voltage irregular slow waves intermixed with multifocal spikes and polyspikes – hypsarrhythmia
- 1/3 of cases of infantile spasms have asymmetry can other patterns of modified hypsarrhythmia

- https://www.epilepsydiagnosis.org/syndrome/west-syndrome-eeg.htmlps://www.

Etiologies

https://www.epilepsydiagnosis.org/syndrome/west-syndrome-overview.html

Lancet Neurol 2016;15:304-16.

- Structural brain abnormalities:
  - developmental abnormalities
  - pre- or peri-natal acquired brain injuries (e.g. hypoxic-ischemic encephalopathy, cerebrovascular accidents, intracranial infection).
  - Aicardi syndrome, lissencephaly, tuberous sclerosis common causes
- Chromosomal disorders:
  - Down syndrome
  - Miller-Dieker syndrome
- Gene abnormalities
  - ARX, CKDL5, SPTAN1, STXBP1, CDKL5, FOXG1 (duplications), SCN1A, PTEN, GRIN2A among many others
- Metabolic etiologies - rare

Treatment of West Syndrome

Vigabatrin (VGB) – GABA analogue

Irreversibly binds to GABA-Transaminase (enzyme involved in removal of GABA from neuronal synapse)

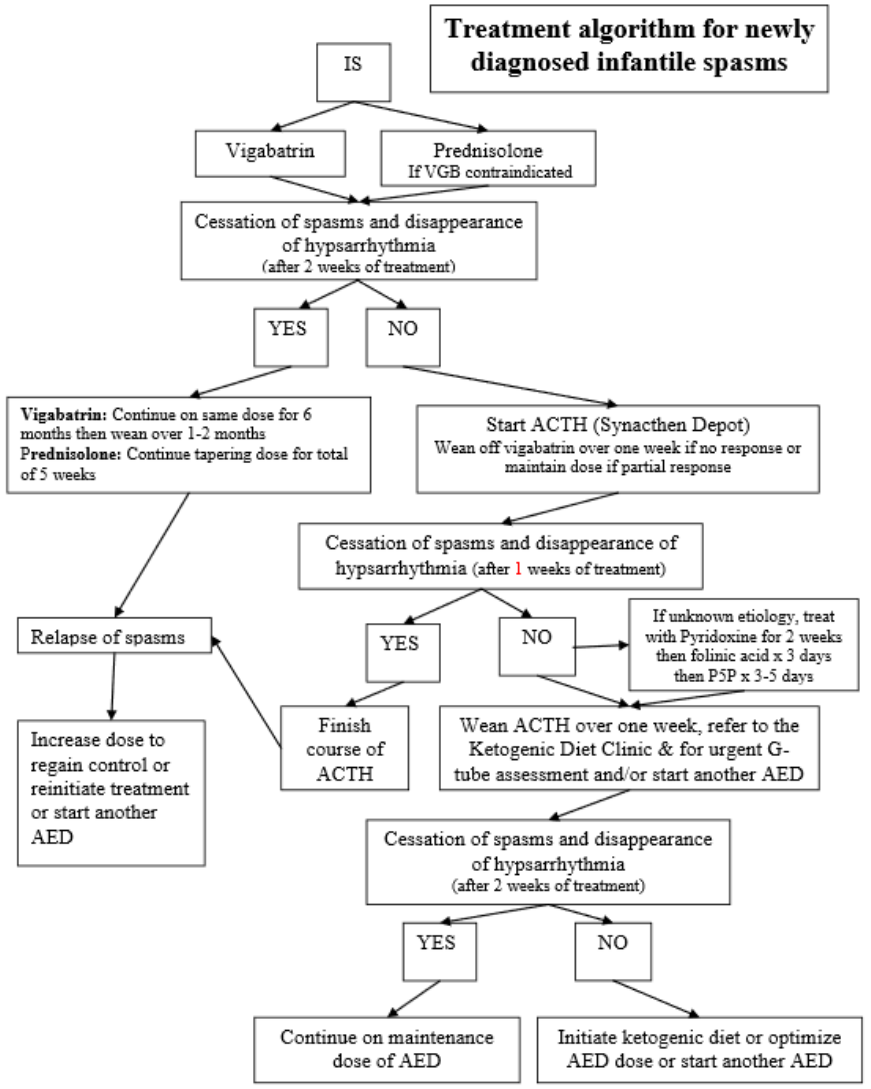
Inhibition → accumulation and prolonged effect of GABA neurotransmitter at postsynaptic receptors → decrease in neuronal excitability

Starting dose 50 mg/kg/d and rapidly titrated to 150 mg/kg/d if spasms continue

Electroretinogram (ERG) recommended – check for retinal toxicity as VGB can cause progressive and permanent bilateral concentric visual field constriction due to retinal toxicity

Semin Pediatr Neurol 2016, 23:167-179

SickKids Infantile Spasms Protocol, 2018



Childhood Epileptic Encephalopathy – Quiz 2

- The cause of epileptic encephalopathies was unknown until:

a) 1960
b) 1970
c) 1980
d) 2001

Lennox-Gastaut Syndrome – Quiz 3

The most common seizure type(s) see in Lennox-Gastaut Syndrome include:

a) Atonic

b) Tonic

c) Atypical absence

d) All of the above

e) None of the above

Lennox-Gastuat Syndrome – Quiz 4

Symptomatic causes of Lennox-Gastaut Syndrome include:

a) Cortical dysplasia

b) Tuberous sclerosis

c) Perinatal hypoxia

d) Congenital infections

e) All of the above

f) Only (a) and (d)

Lennox-Gastaut Syndrome (LGS)

Semin Pediatr Neurol 23: 180-186, 2016

- Electroclinical syndrome
- Multiple etiologies
- May evolve from West syndrome
- May be de novo in early childhood
- Multiple seizure types seen but the most typical seizures seen are:
  - Tonic
  - Atonic
  - Atypical absence
  - Myoclonic seizures

Lennox-Gastaut Syndrome – Presentation

https://rarediseases.org/rare-diseases/lennox-gastaut-syndrome/

Lancet Neurol 2016; 15: 304-16

- Onset usually between 2 – 7 year of age
- Peak onset between 3 to 5 years
- Accounts for 1 – 4 percent of all childhood epilepsies
- Affects males slightly more often than females
- Seizures at onset include:
  - Tonic with or without atypical absence seizures
  - Absence
  - Atonic
  - Myoclonic
  - Generalized tonic-clonic
  - Spasms
  - Focal seizures
  - Episodes of tonic or non-convulsive status epilepticus

Lennox-Gastaut - Development

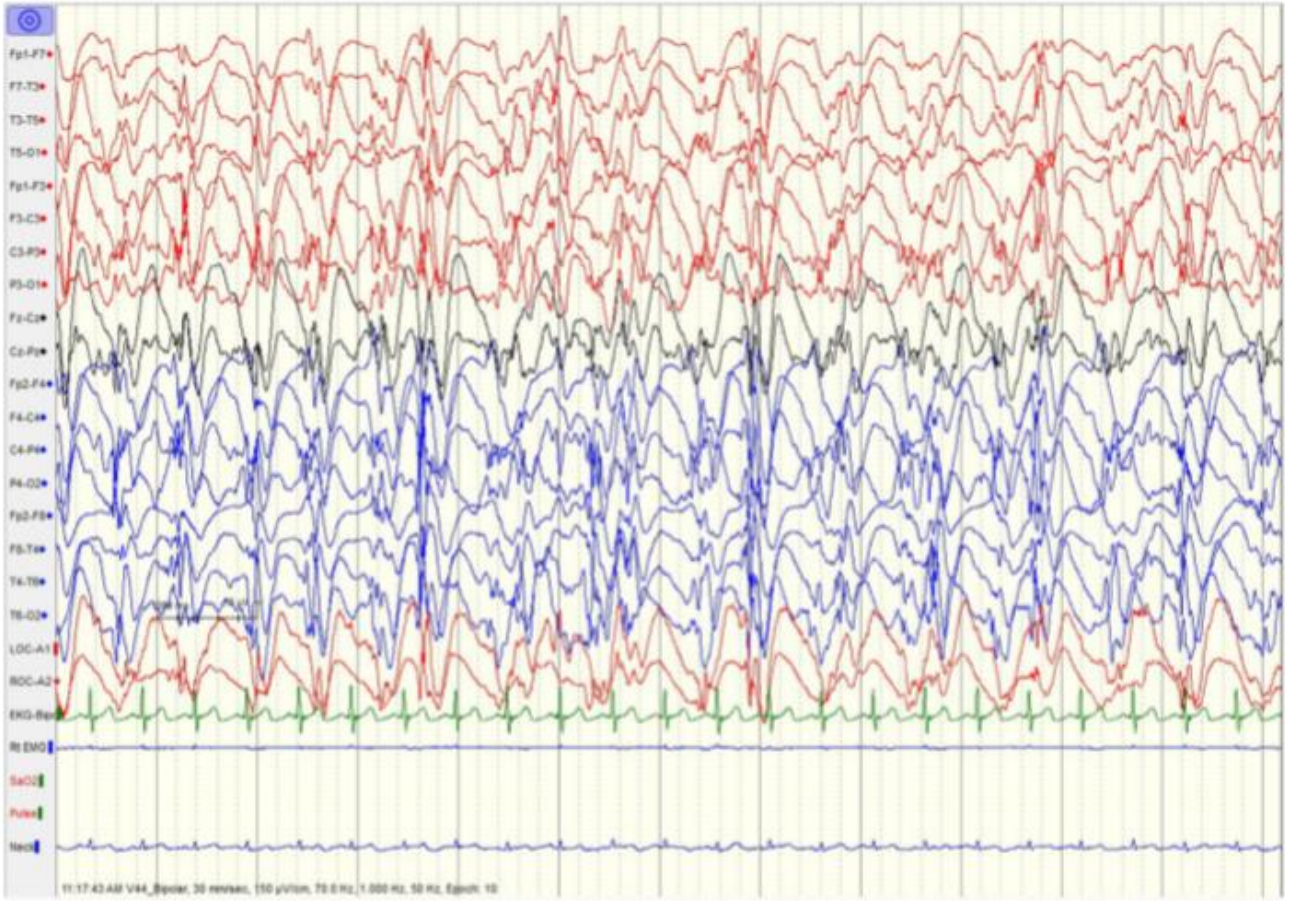
In 20 – 60% of cases, developmental delay precedes onset of epilepsy

By age 5 years, 90% of children will have cognitive impairment after seizure onset

The remainder of children will have learning difficulties

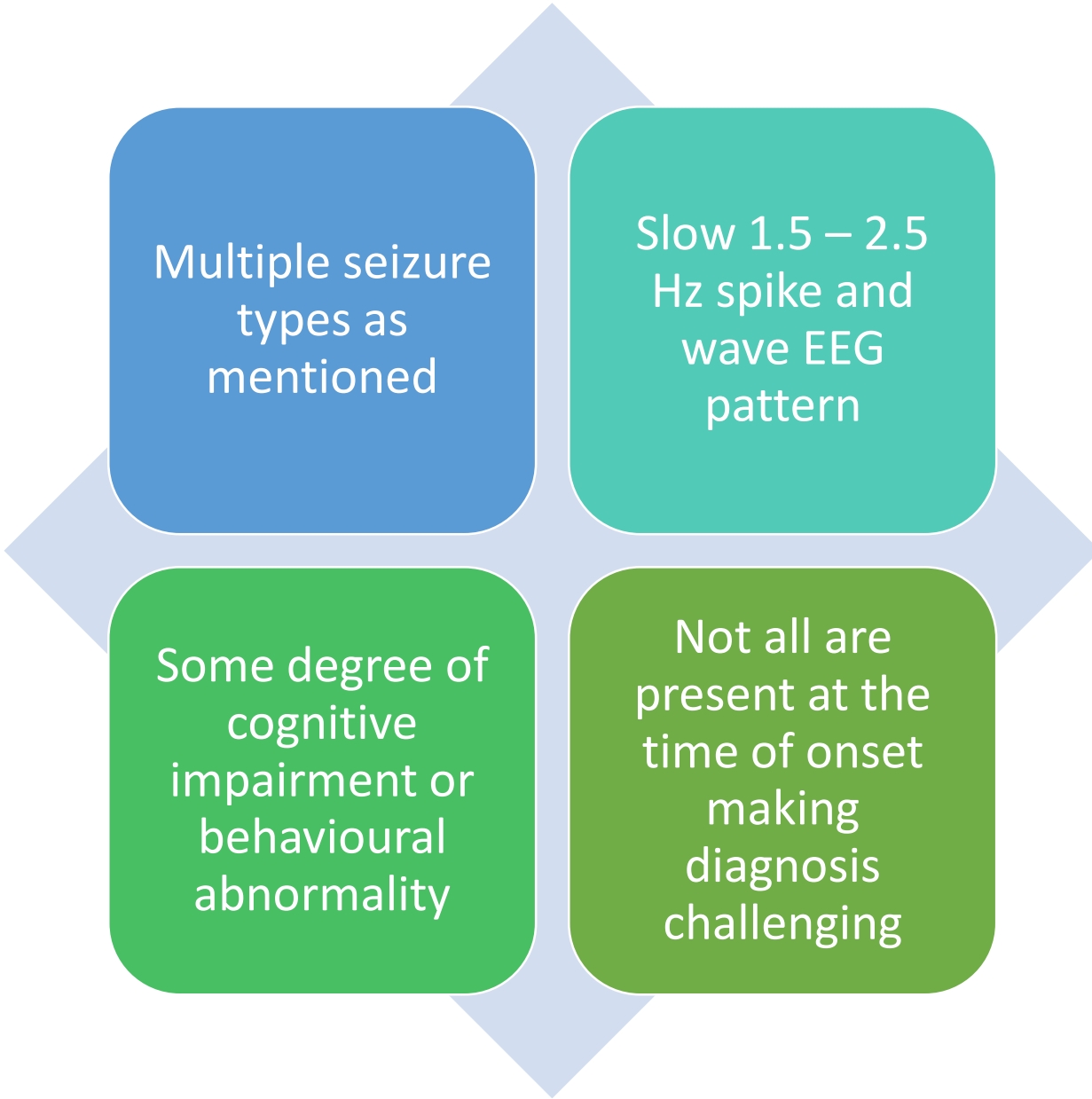
Lancet Neurol 2016; 15: 304 - 16

LGS EEG PATTERN



Semin Pediatr Neurol 23: 134-142, 2016

Diagnostic Triad for Lennox-Gastaut Syndrome



Pellock JM, Nordli DR, Sankar R, Wheless JW (ED's.) Pellock's Pediatric Epilepsy, 4th Edition.Demos Medical. NYC, NY. 2017: 451-466.
https://rarediseases.org/rare-diseases/lennox-gastaut-syndrome/

Common Genes in LGS

- ALG13, CACNA1A, CDKL5, CHD2, DNM, FLNA, CABRB3, SCN2A, SCN8A, STXBP1, SCN1A, GRIN2B, GABRB3, MTOR
- Lancet Neurol 2016; 15: 304-16

Treatment Strategy for LGS

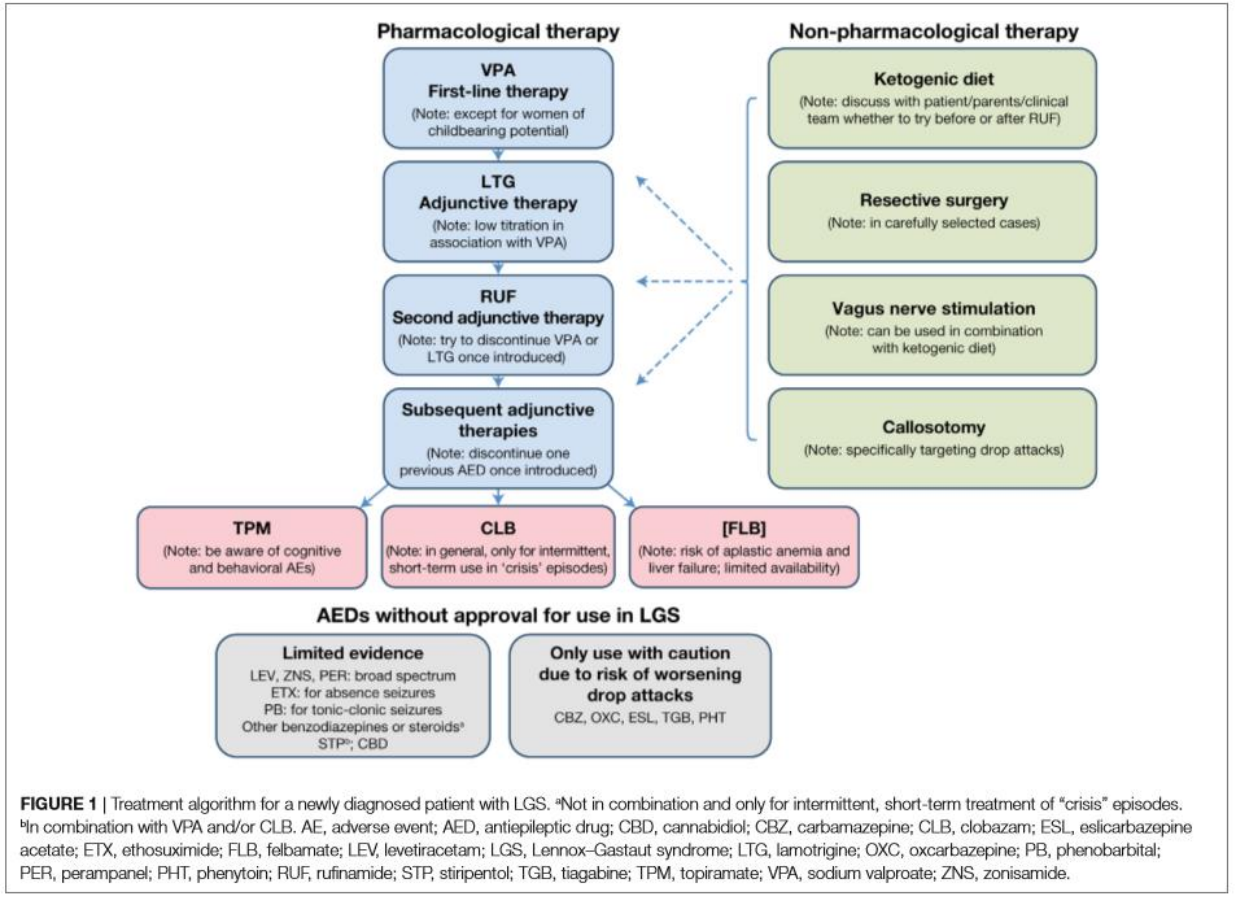


FIGURE 1 | Treatment algorithm for a newly diagnosed patient with LGS. [a]Not in combination and only for intermittent, short-term treatment of "crisis" episodes. [b]In combination with VPA and/or CLB. AE, adverse event; AED, antiepileptic drug; CBD, cannabidiol; CBZ, carbamazepine; CLB, clobazam; ESL, eslicarbazepine acetate; ETX, ethosuximide; FLB, felbamate; LEV, levetiracetam; LGS, Lennox–Gastaut syndrome; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PER, perampanel; PHT, phenytoin; RUF, rufinamide; STP, stiripentol; TGB, tiagabine; TPM, topiramate; VPA, sodium valproate; ZNS, zonisamide.

Front Neurol. 2017; 8: 505.
Published online 2017 Sep 29. doi: 10.3389/fneur.2017.00505

Antiepileptic Drugs (AEDs)/Therapies to Treat LGS

First Line AEDs

- Sodium valproate

Adjunctive AEDs/Treatments

- Lamotrgine
- Clobazam
- Levetiracetam
- Corticosteroids
- Felbamate
- Rufinamide
- Topiramate
- Ketogenic diet
- Vagal nerve stimulation

Semin Pediatr Neurol 23:180-186, 2016

AEDs that May Worsen Epileptic Encephalopathy

Semin Pediatr Neurol 23: 180-186, 2016

- Carbamazepine
- Gabapentin
- Oxcarbazepine
- Pregabalin
- Tigabine
- Vigabatrin

Landau Kleffner Syndrome – Quiz 5

Children with Landau Kleffner Syndrome usually have:

a) Difficulty with vision

b) Auditory verbal agnosia (loss of language comprehension)

c) Aphasia (loss of verbal expression)

d) Both (a) and (b)

Landau Kleffner Syndrome (LKS) - Onset

- Onset between the age of 3 – 7 years
- May occur as early as 18 months of age but rare
- Affected children often appear to have acquired deafness as they fail to respond to verbal language and in some cases to nonverbal sounds
- A significant minority of children with LKS also develops serious behavioral dysfunction - hyperactivity, temper outbursts, or withdrawn behaviors but rarely the severe social impairments seen in autism spectrum disorders
- 70% of affected children have obvious seizures - often focal with or without alteration of awareness and/or atypical absence

Dev Med Child Neurol. 2001;43:243-247.
Nat Genet 2013;45:1061.

LKS – EEG Findings

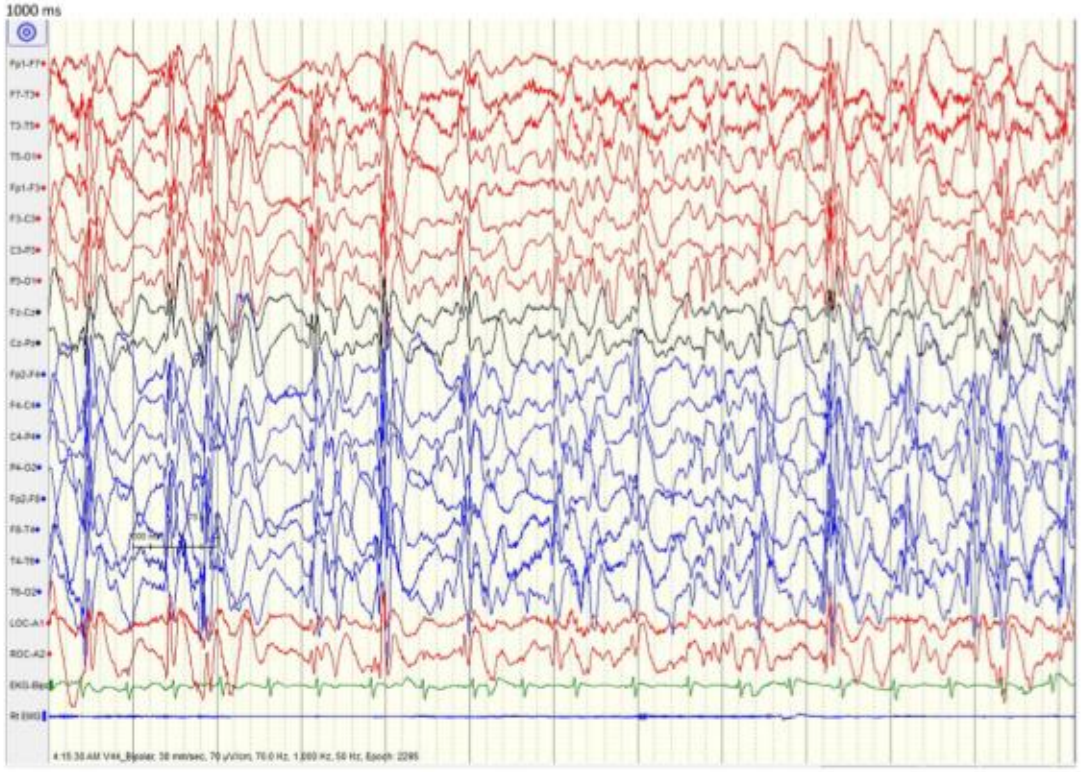
Focal or bilateral centrotemporal spikes with activation

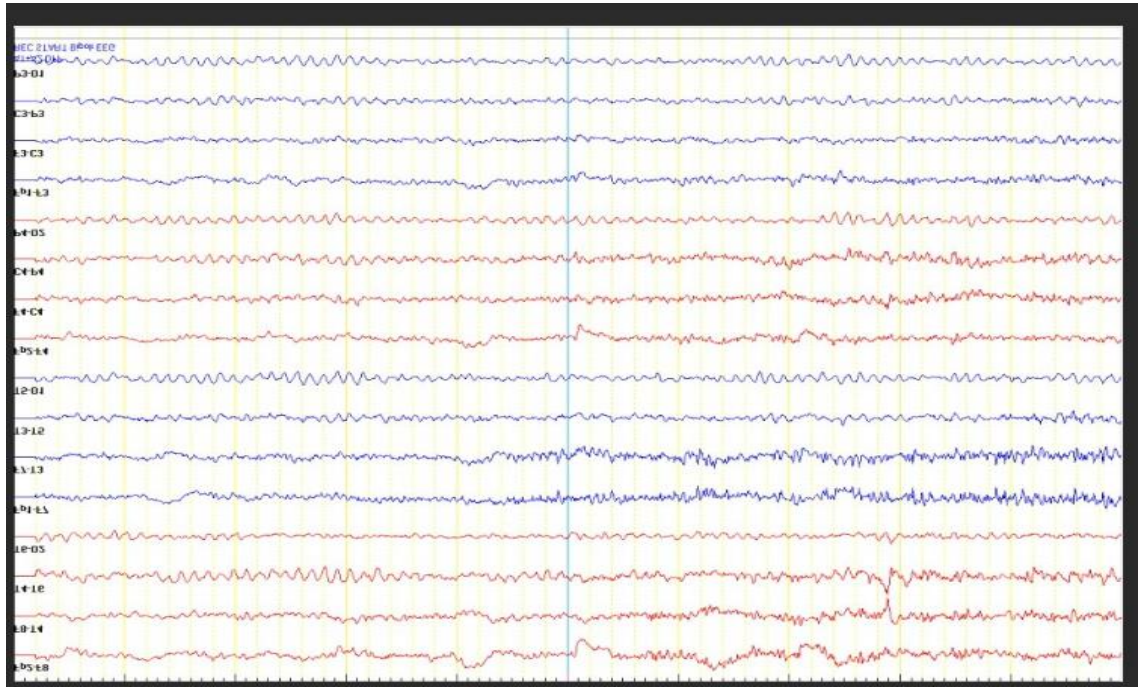
At times during sleep may have electrical status epilepticus of sleep (ESES)

Severe epileptiform activity on EEG particularly during non-REM sleep

Semin Pediatr Neurol 23:180-186, 2016

EEG - ESES During Sleep vs Normal EEG





LKS – Onset and Development

- Lancet Neurol 2016; 15: 304-16

- Onset between 3-7 years
- Prior to seizure onset development is normal in the majority of children
- Regression seen with seizure onset – language, global, or motor
- Variability in outcome delay ranging from normal to severe delay

LKS - Etiology

J Child Neurol 2014;29:1291-8.

Nat Genet 2013;45:1061.

- Cause of Landau-Kleffner syndrome unknown
- Spectrum of epileptic conditions including LKS has been described in individuals with *GRIN2A* gene mutations and other candidate genes including *RELN, BSN, EPHB2* and *NID2* have been suggested
- Response in some patients to immunosuppression has raised the question as to an autoimmune cause or other inflammatory mechanisms

Approach to Treatment of LKS

- Antiepileptic drugs, in particular “spike-suppressing” medications such as divalproex, ethosuximide, levitiracetam, and benzodiazepines
- Some use a combination o f corticosteroids and pulse benzodiazepines
- Other antiepileptic drugs that may be beneficial - lamotrigine and felbamate
- Supportive team approach to help re-establish some communication skills
- Appropriate speech and language therapy important for affected children
- Augmentative and alternative communication devices, even sign language training may be useful for some affected children with little or no understanding of language
- Special education classes for children with severe speech and language disorders

Mantovani JF. Landau-Kleffner Syndrome. In: The NORD Guide to Rare Disorders, Philadelphia, PA: Lippincott, Williams and Wilkins; 2003:547-8.
Epilepsia 2014;55:858-65.

LKS – Treatment

First Line AEDs

- Corticosteroids
- Clobazam

Adjunctive AEDs/Therapies

- Sodium valproate
- Ethosuxamide
- Sulthiame
- Clobazam
- Multiple subpial transection
- Ketogenic diet

Semin Pediatr Neurol 23:180-186, 2016

AEDs that May Worsen LKS

- Carbamazepine
- Phenobarbital
- Phenytoin

Semin Pediatr Neurol 23:180-186, 2016

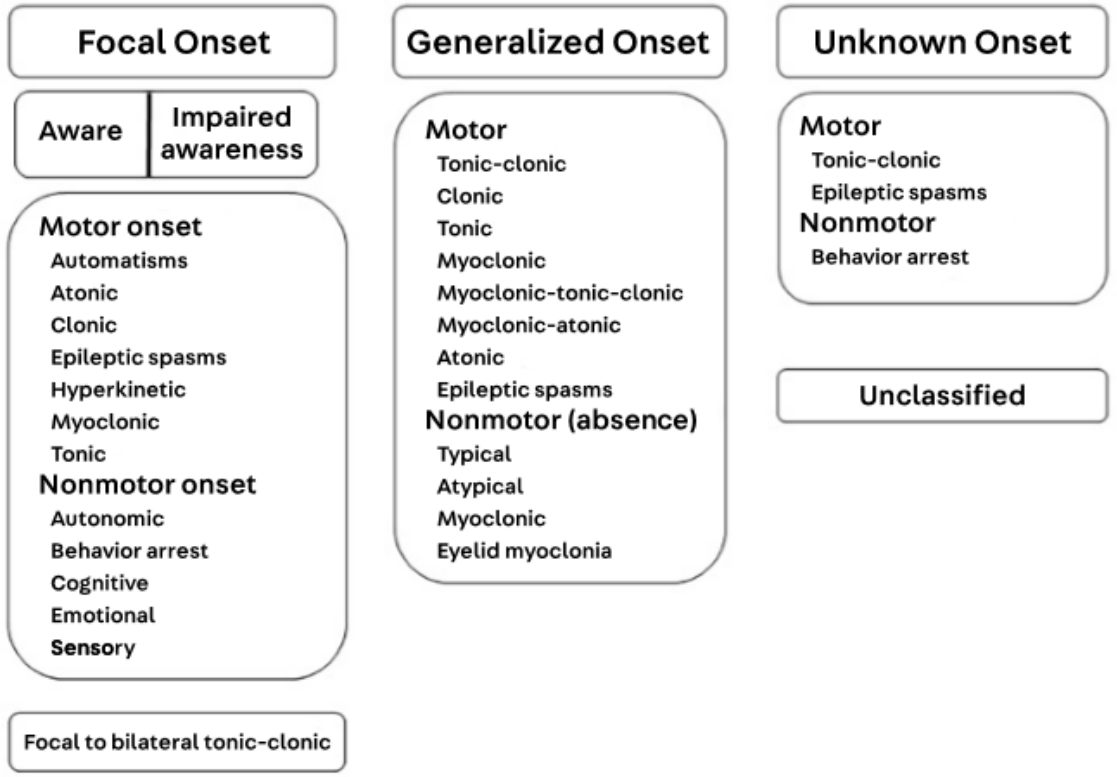


FIGURE 1-2

Expanded version of 2017 International League Against Epilepsy seizure type classification.

Reprinted with permission from Fisher RS, et al, Epilepsia.[1] © 2017 John Wiley and Sons.

General Approach to Diagnosis and Treatment

- CONTINUUM (MINNEAP MINN) 2019;25(2, EPILEPSY):306–321.

General Approach to Diagnosis and Treatment

- CONTINUUM (MINNEAP MINN) 2019;25(2, EPILEPSY):322–342.

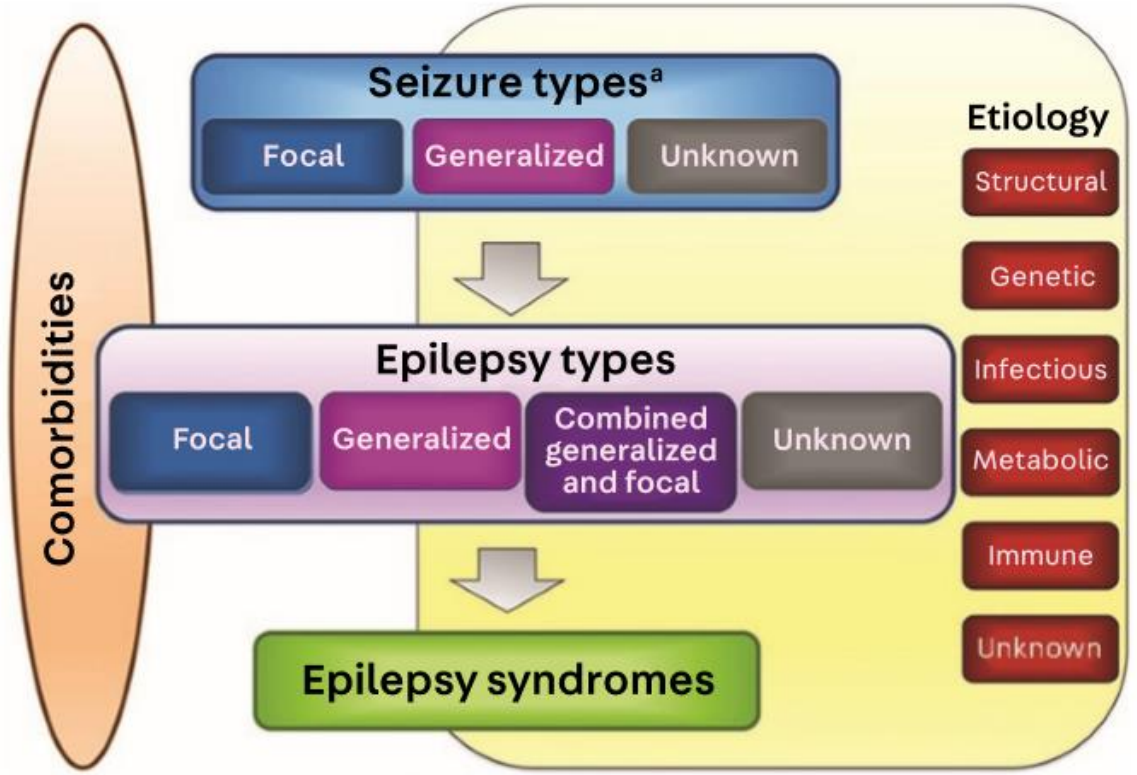


FIGURE 2-1
Classifications of the epilepsies.
[a] Denotes onset of seizure.
Reprinted with permission from Scheffer IE, et al. Epilepsia 2017.[1] © 2017 John Wiley and Sons.

Electroclinical Seizures – Age of Onset

- CONTINUUM (MINNEAP MINN) 2019;25(2, EPILEPSY):322–342.

Neonatal Period

- Benign familial neonatal epilepsy
- Early myoclonic encephalopathy
- Ohtahara syndrome

Infancy

- Epilepsy of infancy with migrating focal seizures
- West syndrome
- Myoclonic epilepsy in infancy
- Benign infantile epilepsy
- Benign familial infantile epilepsy
- Dravet syndrome
- Myoclonic encephalopathy in nonprogressive disorders

Childhood

- Febrile seizures plus (can start in infancy)
- Panayiotopoulos syndrome
- Epilepsy with myoclonic atonic (previously "astatic") seizures
- Self-limiting epilepsy with centrotemporal spikes
- Autosomal dominant nocturnal frontal lobe epilepsy
- Late-onset childhood occipital epilepsy (Gastaut type)
- Epilepsy with myoclonic absences
- Lennox-Gastaut syndrome
- Epileptic encephalopathy with continuous spike-and-wave during sleep
- Landau-Kleffner syndrome
- Childhood absence epilepsy

Metabolic Etiology Work Up

- CONTINUUM (MINNEAP MINN) 2019;25(2, EPILEPSY):322–342.

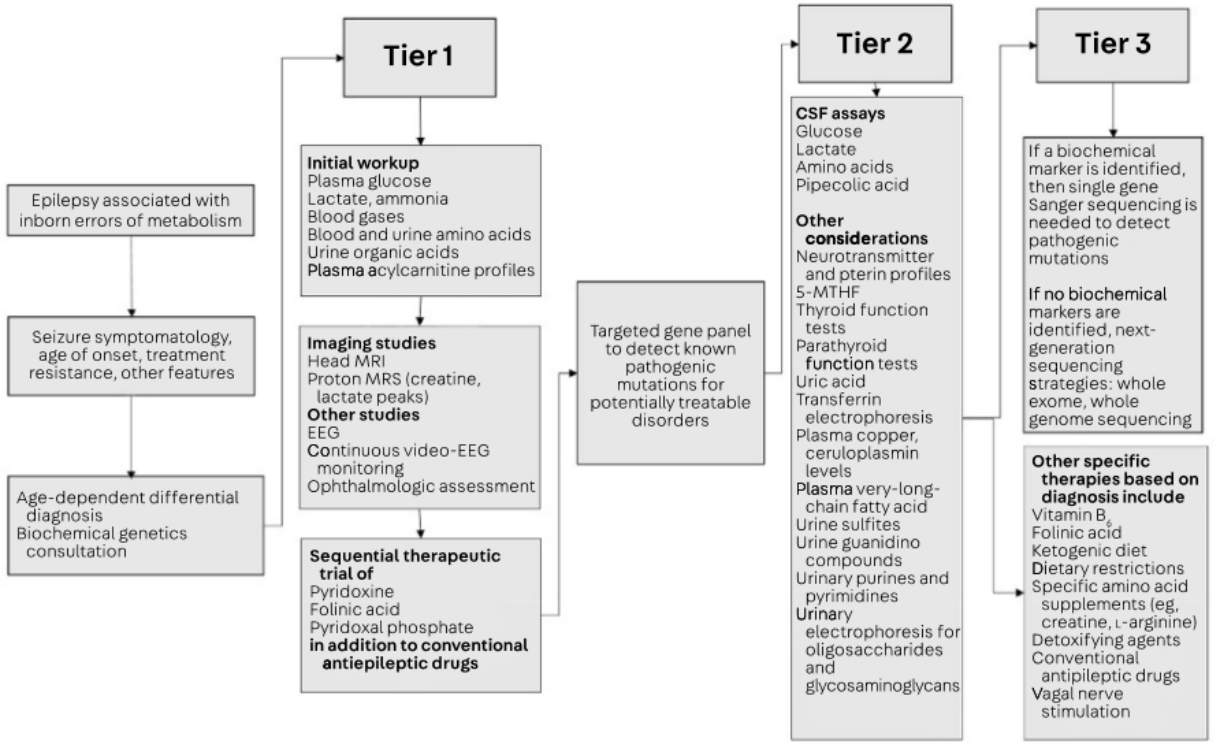


FIGURE 2-7

Epilepsy associated with inborn errors of metabolism.

EEG = electroencephalogram; MRI = magnetic resonance imaging; MRS = magnetic resonance spectroscopy; 5-MTHF = L-methyltetrahydrofolate.

Reprinted with permission from Sharma S, Prasad AN, Int J Mol Sci.[18] © 2017 MDPI AG, Basel, Switzerland.

Genetic Testing

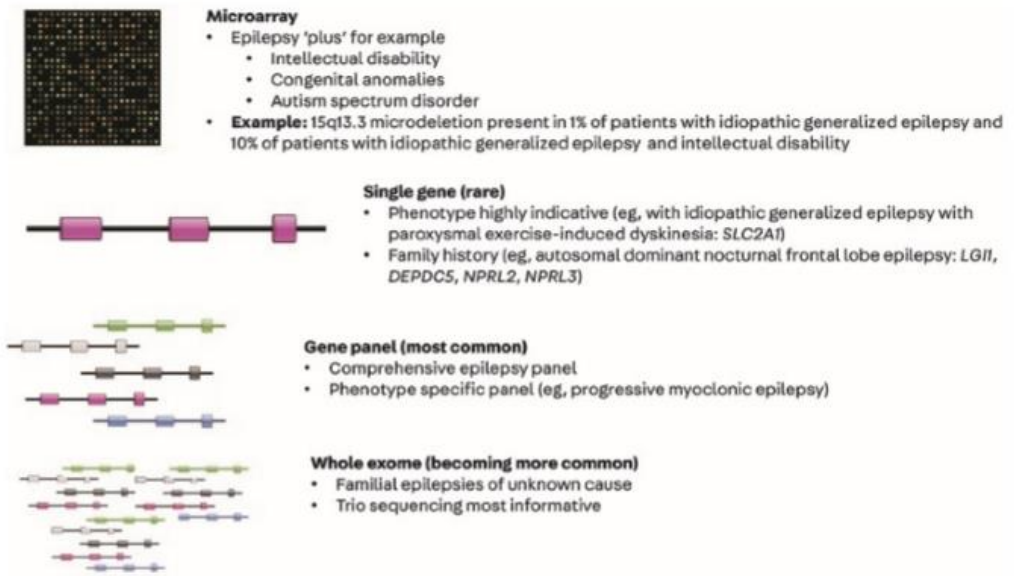


FIGURE 2-8

Genetic testing. Comparative genomic hybridization microarray is typically the first test for patients presenting with epilepsy and developmental delay. Single-gene testing has been largely replaced by gene panels and whole exome sequencing. Gene panels are either targeted for a specific phenotype, eg, a progressive myoclonic epilepsy, or offered as a comprehensive epilepsy gene panel. Whole exome sequencing and whole genome sequencing are usually performed within the setting of a genetic clinic.

Courtesy Gemma Carvill, PhD, Northwestern University.

CONTINUUM (MINNEAP MINN) 2019;25(2, EPILEPSY):322–342.

Genetic Causes of Epilespy Syndromes

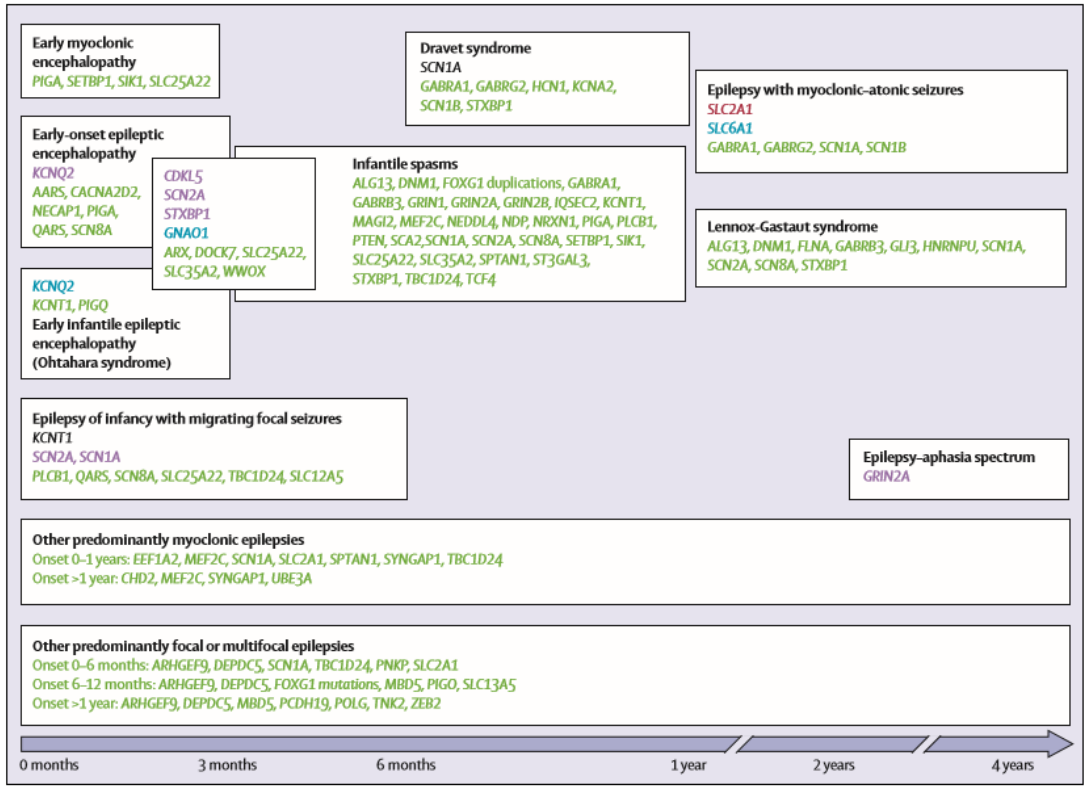


Figure 1: **Genetic causes of epilepsy syndromes**
Genetic causes, and proportion of cases caused by each gene, including only non-chromosomal, non-malformative, and non-metabolic disorders. Only genes with more than one case reported are included. Black font denotes genes that account for at least 50% of cases, purple font 10–50% of cases, and red font 5–10% of cases. Blue font denotes genes that account for less than 5% of cases, and green font denotes genes that account for an unknown percentage of cases.

Lancet Neurol 2016; 15: 304-16