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# Virtual Education Series: Yep, It's a Seizure. Now What?

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Here, it's different.™

# DISCLOSURE

No financial relationship with any ineligible companies to report

# OUTLINE

1. The Basics with cases
2. Treatment resistance
3. Specialized scenarios

# INITIAL CONSIDERATIONS:

- Seizure - sudden involuntary time-limited alteration in behavior including change in motor activity or autonomic function, consciousness, or sensation, accompanied by an abnormal electrical discharge in the brain.
- Epilepsy
  - Classic definition - 2 or more *unprovoked* seizures separated by greater than 24 hours
  - New definition (ILAE): an enduring predisposition to generate epileptic seizures and the neurobiologic, cognitive, psychological, and social consequences of this condition.
  - Epilepsy is a *disease* of the brain defined by any of the following conditions:
    - Classic definition
    - One unprovoked seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years. During evaluation, important to determine if other seizure types have previously occurred!
    - Diagnosis of an epilepsy *syndrome*

Fisher RS, et al. A practical clinical definition of epilepsy, *Epilepsia* 2014; 55:475-482.

# INITIAL CONSIDERATIONS:

## Incidence and Epidemiology

- 2.2 million people in the United States (60,000 people in CO)
- 1 out of 150 children is diagnosed with epilepsy during the first 10 years of life, with the highest incidence rate observed during infancy (Norwegian registry study)

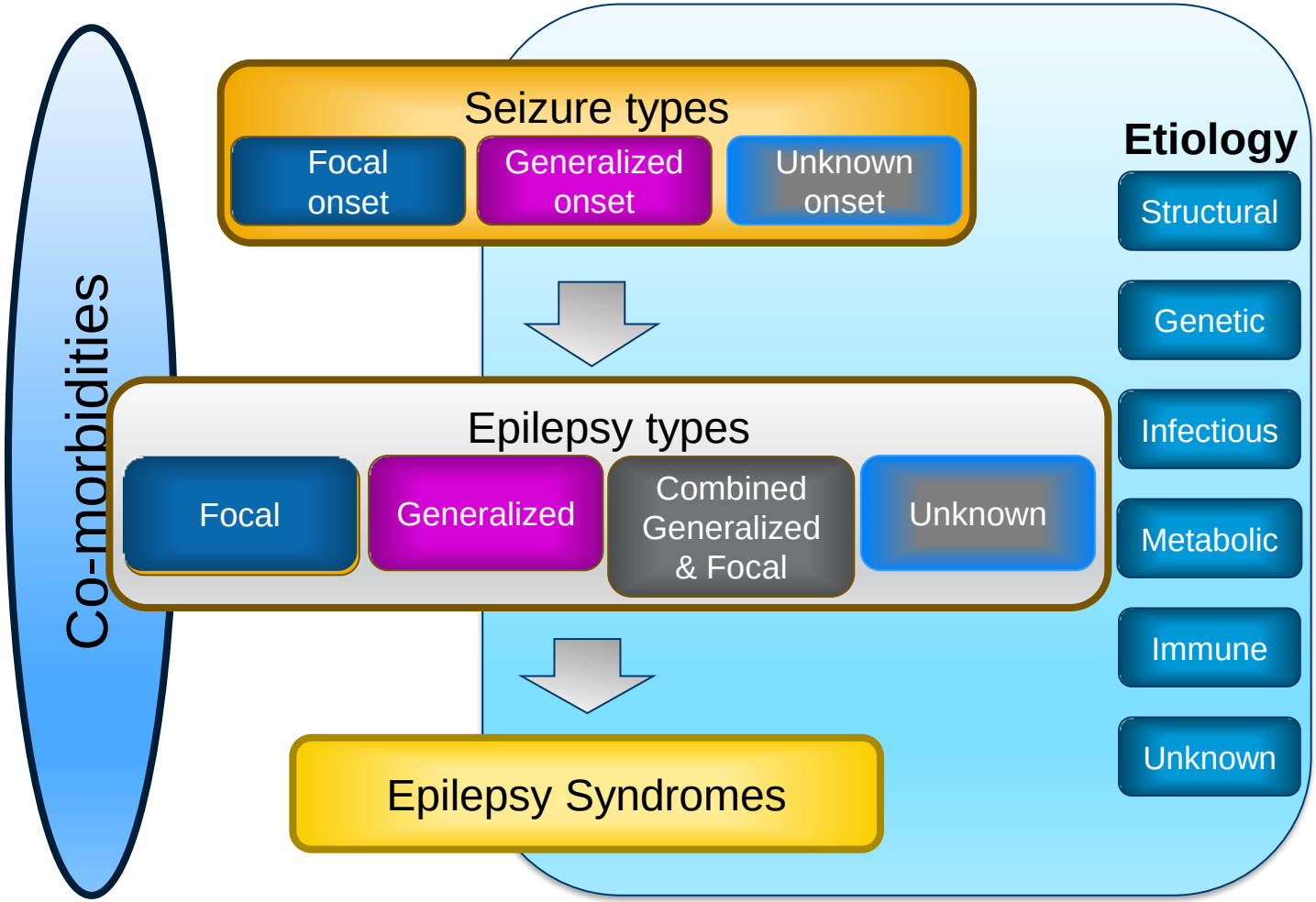
Aaberg KM, et al. Incidence and Prevalence of Childhood Epilepsy: A Nationwide Cohort Study. *Pediatrics* (2017) 139 (5): e20163908.

# CASE #1: Caroline

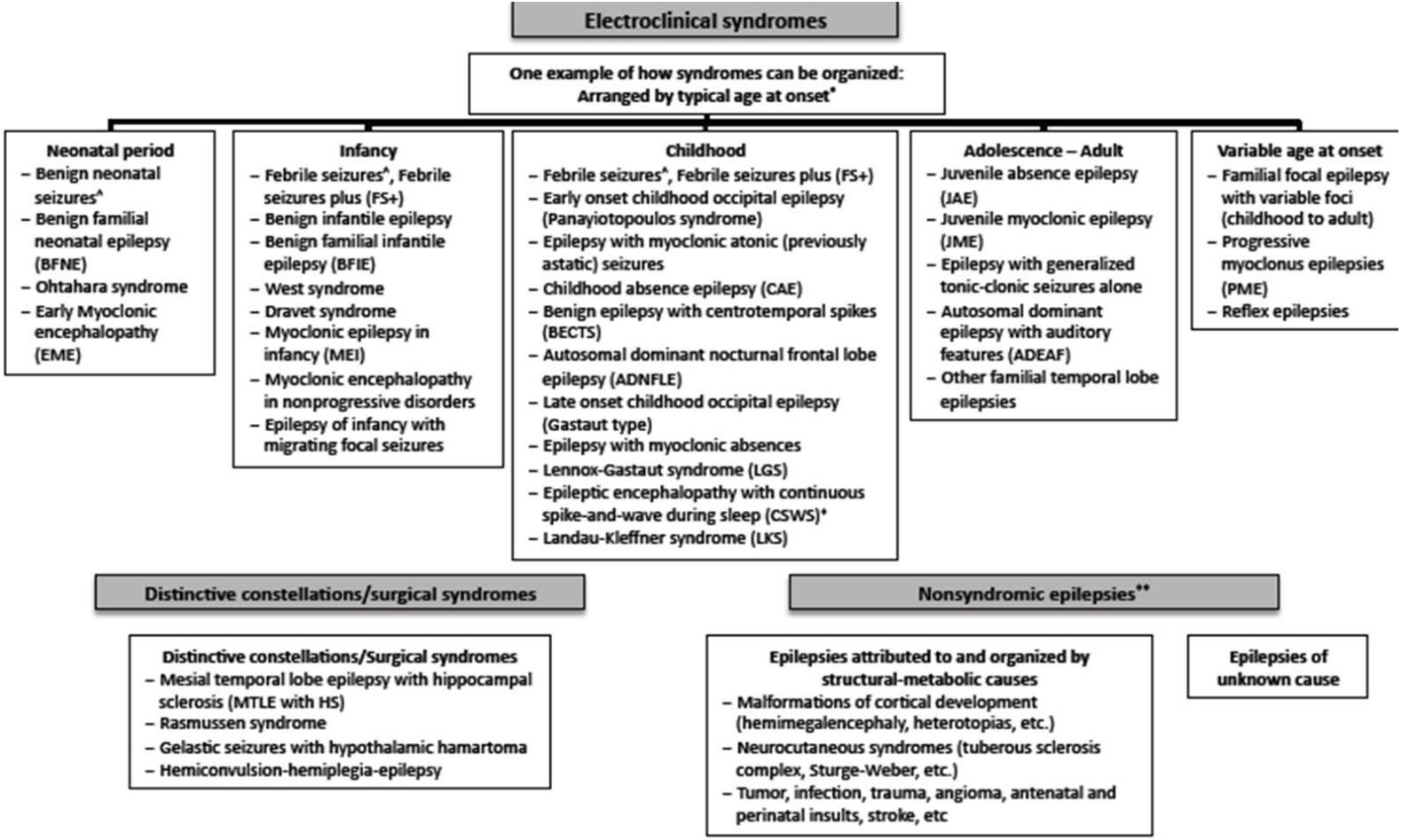
- 7 year-old girl presents to your office after suddenly falling off the monkey bars for no apparent reason and breaking her arm. Parents have been told that she has been staring off at school and have recently noticed her stopping mid-sentence at the dinner table. They wonder if this is what happened at the playground.
- Hyperventilation in the office produces a typical spell
- EEG – 3 Hz spike and wave discharges in runs lasting from 5-10 seconds with an otherwise normal background during wakefulness and sleep

QUESTIONS:

- Does she have epilepsy?
- Does she have an epilepsy syndrome?
- How should we treat her?



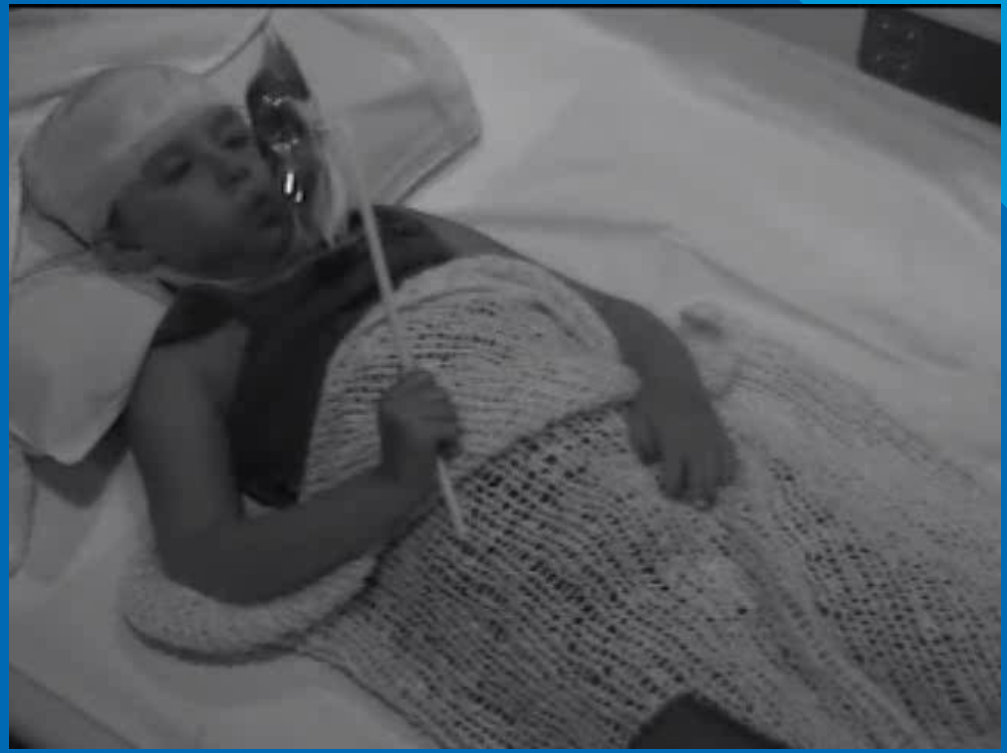

https://www.ilae.org/guidelines




https://www.ilae.org/files/dmfile/ILAE-HandoutV10.pdf

# CHILDHOOD ABSENCE EPILEPSY

- 10-15% of childhood epilepsies
- Females > males (60:40)
- Typically between 5-15 seconds
- May be associated with blinking, lip smacking, or other automatisms
- Occur numerous times per day
- Remission in 80% by adulthood
- Pathophysiology – abnormal oscillatory potentials involving T-type calcium channels in the reticular nucleus of the thalamus



# EVIDENCE-BASED TREATMENT

Glauser TA, et al. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy: initial monotherapy outcomes at 12 months. *Epilepsia*. 2013 Jan;54(1):141-55. PMID: 23167925

- Groundbreaking DB-RCT involving the 3 most prescribed agents in this syndrome
- Assessed both efficacy and neuropsychologic effects providing additional systematic data about outcomes.
- 446 patients, doses adjusted to response (flexible), monitored with EEG
- Key take home points –
  - Efficacy similar between valproic acid (VPA) & ethosuximide (ESX) sustained to 1 year time point (45%)
  - Significantly less response to lamotrigine (LMG) (21%)
  - Highest percentage of subjects discontinuing due to adverse events occurred in the VPA subgroup for weight gain and attentional issues
  - Defined an absence seizure as 3 seconds which is now standard

Caroline's parents call the office because she had a convulsion. Does this change the treatment plan?

# GTC SEIZURES IN CAE

- Occur in 30% of children with onset <8y. Higher incidence in juvenile onset.
- Ethosuximide is not effective in preventing convulsive seizures due to its mechanism of action (T-type $Ca^{++}$ channels)
- Conundrum…..
  - VPA more effective but requires blood monitoring and has a poor side effect profile
  - LMG is much less effective but better tolerated
- Emergency medication
  - Intranasal Midazolam ***
- Does not indicate intractability or affect prognosis

Aaberg KM, et al. Incidence and Prevalence of Childhood Epilepsy: A Nationwide Cohort Study. *Pediatrics* (2017) 139 (5): e20163908.

# CASE #2: Damion

- 11 year-old boy presents to your office after a single convulsion. Astutely, you ask about SSSSS……..Turns out, he has been having staring spells for about a year during which he also hears slightly muffled noises and feels sick to his stomach. These episodes last about 1 minute - he feels tired and has a headache afterwards. They occur about once a week.
- EEG is normal.
- MRI is normal.
- What to do? What to do?
  - Salinsky M. Effectiveness of multiple EEGs in supporting the diagnosis of epilepsy: an operational curve. *Epilepsia* 1987; 28: 331-4.
  - 1,021 studies from 429 adult patients
  - 50% interictal epileptiform activity is present on the 1st study, 84% by the 3rd, and in 92% by the 4$^{th}$
  - Similar statistics for pediatrics patients – 438 consecutive EEGs, 55% of first studies were abnormal, repeat study twice as likely to be abnormal

# CASE #2: Damion

- Videotape events – assess for impairment of consciousness and other subtle movements (lip smacking, fidgeting)
- Too infrequent to admit to the Epilepsy Monitoring Unit
- Empiric therapy based on semiology – temporal lobe
  - Why not absence?
- Treatment recommendations:
  - Limited Class 1 evidence for comparative efficacy
  - Levetiracetam (LVT) – frequent choice in the ED
    - Can be orally or IV loaded
    - Limited interaction with other medications
    - Does not require blood monitoring and typically has mild side effects
    - Can be associated with behavioral issues/irritability
    - Comes in liquid formulation (100 mg/mL)
    - Dose range 20-60 mg/kg/d

# ADDITIONAL CONSIDERATIONS:

Marson A, et al. The SANAD II study of the effectiveness and cost-effectiveness of levetiracetam, zonisamide (ZNS), or lamotrigine for newly diagnosed focal epilepsy: an open-label, non-inferiority, multicentre, phase 4, randomized controlled trial. *The Lancet*, 10-16 April 2021, 397 (10282): 1363-1374.

- 990 patients 5 and older in the UK, unblinded with dosing guidelines
- 12 month remission superior with LMG compared to LVT and ZNS.
  - LMG found to be non-inferior to oxcarbazepine (OXC) in SANAD I trial but better tolerated
- LVT did not meet the criteria for non-inferiority in the intention to treat analysis.
  - Initial licensing studies only assessed outcome at 6 months which may have been insufficient
- Higher incidence of side effects in the other agents (33% vs 44% and 45% respectively)
- Lamotrigine –
  - Comes in chewable tablets but not liquid
  - Risk for Stevens-Johnson syndrome
  - Requires a prolonged titration schedule (8-12 weeks) so may not be appropriate for frequent seizures
  - Does not require blood monitoring

# TREATMENT OUTCOMES

- In population-based cohorts, approximately 60% of childhood epilepsy is focal onset.
- Approximately 70% of patients will achieve seizure freedom with medical management
- 60-75% of children who are seizure-free for 2-4 years can maintain this after discontinuation of medication.
- Favorable prognostic factors:
  - Etiology and epilepsy syndrome
  - Childhood onset (<10 years)
  - Early response to treatment
  - Low seizure burden/frequency
- Data suggests there may be negative long-term consequences for education, marital status, employment, and fertility

Shinnar and Pellock. Update on the Epidemiology and Prognosis of Pediatric Epilepsy. *Journal of Child Neurology*. 2002 Jan; 17(S1): 4-17

# Damion….CONTINUED

- Started on LVT and titrated to a goal dose of 50 mg/kg/d with persistent seizures and emerging behavioral side effects.
- Cross-titrated onto OXC but had an allergic reaction.
  - Serial monotherapy prior to polytherapy
  - Different mechanisms of action
- Started on LMG and having now daily small seizures at 5 mg/kg/d
- TREATMENT RESISTANCE: refractory, intractable, pharmacoresistant
  - Continued disabling seizures despite appropriate trials of two antiseizure drugs, either alone or in combination.
  - Appropriate = correctly chosen, therapeutic doses, compliant/adherent, acceptable duration to assess efficacy
  - After the failure of an appropriate drug, only 11% of patients will become seizure free. That number drops to 3% after failure of the second medication.
- Mental checklist for the intractable patient
  - Right diagnosis? In adult series, up to 25% of patients are misdiagnosed.
  - Right dose and frequency? Consider drug levels to assess metabolism.
  - Alternative options available?

# WHEN MEDICATION FAILS THE PATIENT

## ADJUNCTIVE THERAPY

- Ketogenic and related diets

## SURGERY

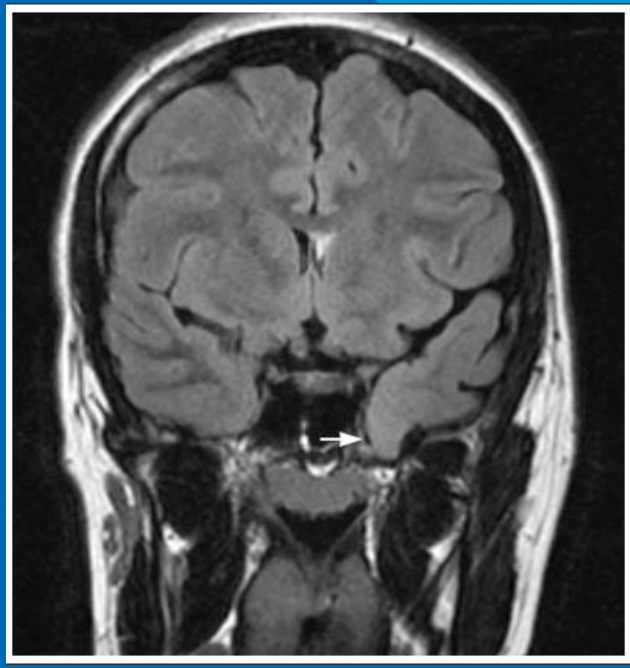
- Discussed for focal onset seizures from a structural cause (resective/curative)
- Corpus callosotomy (palliative)

## NEUROSTIMULATION

- VNS – vagal nerve stimulation
- RNS – responsive neuro-stimulation
- DBS – deep brain stimulation

# Damion….CONTINUED

- Was that MRI really normal?
  - Technique – thin coronal cuts through temporal lobe
  - Interpretation – Neuroradiologist
  - Sequences – FLAIR, MPR
- Structurally mediated focal onset epilepsy
  - More likely to be treatment resistant
  - Surgically amenable with >50% chance of seizure freedom
- Difficult discussions – “You want to remove part of my child’s brain?”
  - Additional testing – Neuropsychology, advanced imaging, seizure localization on EEG
  - Consequences – quadrantanopsia, memory?
  - Earlier intervention = better outcomes (plasticity, kindling)
- Not every case is as straight forward!

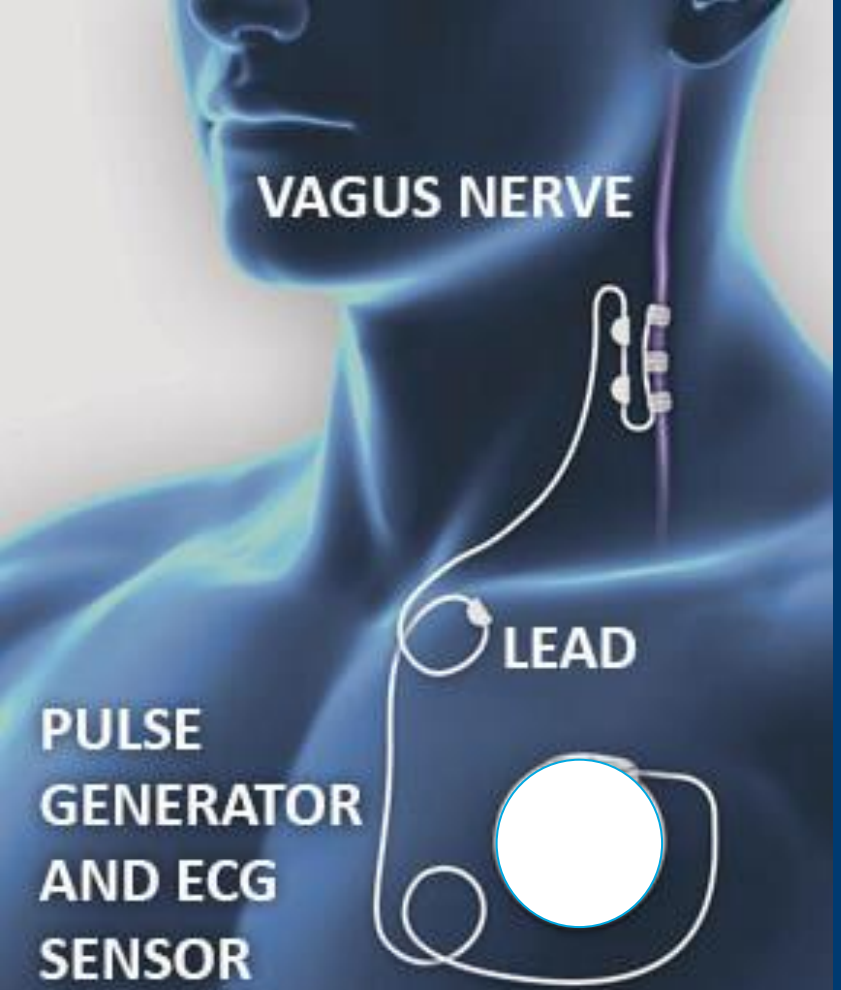


https://www.pedneur.com/article/S0887-8994(17)30591-X/fulltext

# DIETARY THERAPY:


- Mimics starvation within the body by restricting carbohydrates and forcing the use of fat for energy resulting in the production of ketone bodies.
- Sufficient protein for growth is allotted.
- Side effects (just like medication) –
  - Decreased bone mineral density
  - Renal calculi
  - Constipation, reflux
  - Hyperlipidemia
- Can be nutritionally insufficient and produce dangerous nutrient deficiencies so should be monitored by a dietician
- Typically used in children with frequent seizures due to compliance but adult/adolescent data is emerging.
- Efficacy –
  - Meta-analysis 2006 looking at 11 studies comprising ~600 patients
  - Seizure freedom rates varied between 0 (n=5)-36% and greater than 90% reduction in 30-67%

Henderson, CB, et al. Efficacy of the Ketogenic Diet as a Treatment Option for Epilepsy: Meta-analysis. *J Child Neurol* 2006; 21: 193-198




Epilepsy Society (2019).https://epilepsysociety.org.uk/about-epilepsy/treatment/vagus-nerve-stimulation

# NEUROSTIMULATION: VNS

- Animal data (1993) showed desynchronization of the EEG and decreased spikes with intermittent stimulation (cats) and ability to abort systemically induced seizures (dogs/primates)
- Approved by the FDA in 1997 for adjunctive treatment of refractory partial epilepsy in adults and children >12 years
- Expanded use to younger children, generalized epilepsy, and catastrophic syndromes (LGS)
- Tonic and on-demand stimulation pre-programmed, HR detection in newer device
- Side effects –
  - Hoarseness/cough with stimulation
  - Vomiting
  - Infection of surgical site
- Efficacy –
  - 50% responders, few patients seizure-free
  - Typically anti-seizure medications are continued
  - Can reduce incidence of status epilepticus

# SPECIALIZED SCENARIOS

# WHEN THINGS DON'T SEEM RIGHT

- 5 year-old normally developing kid, negative birth history, with new onset epilepsy
- EEG suggests CECTS, MRI normal
- Family history of epilepsy in sister and mother
- 3 years later – still having frequent convulsions, worsening on LMG, has tried 4 meds for a typically benign syndrome
- Genetic testing 5y later shows an SCN1A mutation that segregates within the family
- Typically associated with Dravet syndrome
- Opens up new medication options – seizure free on VPA and EPD

# EPILEPSY IN NEURODEVELOPMENTAL DISORDERS

- 30% of individuals with ASD have epilepsy
  - Incidence of abnormal EEG is 15-40% of patients with ASD without seizures
- Epilepsy is associated with a higher incidence of ID and other neurologic disorders (ADHD, cerebral palsy, brain malformations, etc)
- Shared biology with overlapping causes and phenotypes
- Precise diagnosis can be important for treatment - in some studies up to 40% of patients with a genetic diagnosis had a change in management
- Frequently refractory to medical management and less likely to resolve over time
- Treatment can be complicated by other comorbidities – sleep problems, behavioral issues, medical diagnoses

Engel J. Approaches to refractory epilepsy. *Ann Indian Acad Neurol*. 2014 Mar; 17(S1): S12–S17. PMID: 24791078

# EPILEPTIC ENCEPHALOPATHIES:

- Overall rare – incidence 0.5-1/40,000 live births, male:female:2:1
  - 3-5% of epilepsies that develop in the first year of life
- Defined by age and characteristic features:
  - Otahara syndrome
  - Infantile spasms
  - Doose syndrome
  - Lennox-Gastaut syndrome
- Typically treatment resistant with poor prognosis
- Multiple seizure types and characteristic EEG patterns
- Many different etiologies – structural, acquired, genetic/metabolic
- Treatment strategy –
  - Use EEG monitoring to ensure that all events being treated are seizures
  - Balance side effects with QOL if seizure freedom is not a reasonable goal
  - Rare medications may be indicated – Felbamate, Fenfluramine, Acetazolamide
  - If an incompletely effective agent is to be continued as part of polytherapy, decrease the dose from maximum tolerated to the range with the maximum efficacy and least SE

Engel J. Approaches to refractory epilepsy. *Ann Indian Acad Neurol*. 2014 Mar; 17(S1): S12-S17. PMID: 24791078

# ¿QUESTIONS?

# REFERENCES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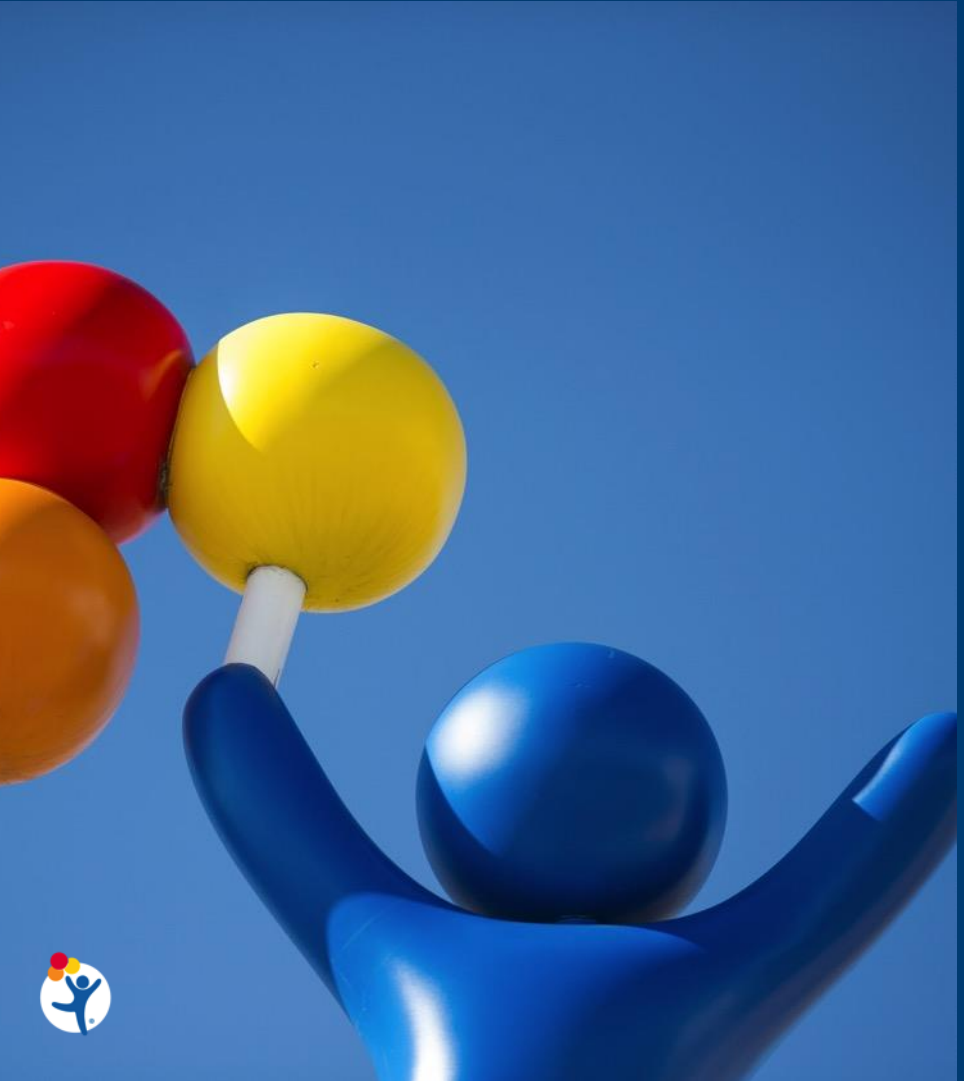

# THANK YOU

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