Approaches to Treatment of Epilepsy Syndromes

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Approaches to Treatment of Epilepsy Syndromes

- Overview of pediatric epilepsy syndromes
- Focus on a few syndromes
  - Infantile spasms
  - Lennox-Gastaut syndrome (LGS)
  - Dravet syndrome
- Role of newly-approved CBD
- When medications do not work?
  - Dietary therapy of epilepsy
Epilepsy in Children

*Children Are Different*

- Children have different types of seizure disorders
  - Age-related seizures
  - Benign syndromes
- Differential diagnosis is broader
- Etiologies of seizures are different
- Treatments and drugs are different
  - Several antiepileptic drugs (AEDs) used off-label
  - Different pharmacokinetics
  - Different adverse events
- Children are more likely to “outgrow” epilepsy
Pediatric Epilepsy

Seizures and Syndromes

• Pediatric epilepsy is a spectrum of disorders
  • Many different types of seizures
  • Many etiologies
  • Many syndromes and types of epilepsy

• Seizure classification
  • Tonic, tonic-clonic, atonic, absence, myoclonic, focal, etc.

• Syndrome classification
  • Characterized by seizure types, electroencephalogram (EEG) characteristics, and now genetic etiologies
Pediatric Epilepsy

The Spectrum of Syndromes

Many epilepsy syndromes have multiple seizure types

- Lennox-Gastaut syndrome
- Dravet syndrome
- Myoclonic astatic epilepsy
- Juvenile myoclonic epilepsy
- Childhood absence epilepsy
- Benign occipital epilepsy
- Etc.
Pediatric Epilepsy

The Spectrum of Syndromes

Many syndromes can result from multiple etiologies

• Lennox-Gastaut syndrome—tuberous sclerosis complex (TSC), hypoxic ischemic encephalopathy (HIE), lissencephaly, etc.
• Infantile spasms—TSC, HIE, CDKL5, Aicardi syndrome, etc.
• Juvenile myoclonic epilepsy
• Myoclonic astatic epilepsy
• Etc.
Pediatric Epilepsy

The Spectrum of Syndromes

Many genetic syndromes are characterized by multiple seizure types and epilepsy syndromes

• Tuberous sclerosis complex
  • Seizures—infantile spasms (IS), complex partial seizures (CPS), secondarily generalized seizures generalized tonic-clonic (GTC), tonic, atonic, atypical absence
  • Epilepsy syndromes—IS, LGS

• Aicardi syndrome
  • Seizures—CPS, secondarily generalized GTC
  • Epilepsy syndromes—IS, LGS

• Dravet syndrome

• Angelman syndrome

• Etc.
Many genetic syndromes are characterized by multiple other symptoms—many central nervous system (CNS)—related, especially epileptic encephalopathy!

- Dravet syndrome
- Angelman syndrome
  - CNS—expressive language delay, ataxia, sleep disorder
  - Other—gastrointestinal (GI) issues
Many genetic syndromes are characterized by multiple other symptoms—some CNS related, but some not!

- Tuberous sclerosis complex
  - CNS—subependymal giant cell tumor (SEGA), intellectual disability (ID), autism, anxiety, self-injurious behaviors
  - Other—renal angiomyolipoma (AML) and cysts, cardiac rhabdomyoma, pulmonary lymphangioleiomyomatosis (LAM), retinal hamartoma, facial angiofibroma, etc.
Childhood Epilepsy Syndromes

- **Neonatal seizures**
  - 0-1 mo

- **Simple febrile seizures**
  - 0-6 wk

- **Benign myoclonic epilepsy**
  - 1-2

- **Lennox-Gastaut syndrome**
  - 1-8

- **Juvenile absence**
  - 3-7

- **GTC seizures on awakening**
  - 10-15

- **Rolandic epilepsy**
  - 4-13

- **Childhood absence**
  - 6-22

- **Juvenile myoclonic epilepsy**
  - 13-19

- **Infantile spasms**
  - 6 mo-1

- **EMEE/EIEE**
  - 0-6 wk

**Age (y) at Seizure Onset**
Case Study

Baby J

• 6 months old
• CC—episodes of twitching starting at 5 months
  • Normal perinatal history
  • Normal development, although less interactive recently
  • Jerks forward, increasing in frequency
  • Several per day, usually one after the other
  • Cries after these episodes
Case Study

Baby J

• Family history unremarkable
• Exam
  • Normal general exam
  • Neuro exam normal except for poor visual fixation, uninterested baby and slightly low truncal tone
Differential Diagnosis

1. Infantile spasms
2. Reflux
3. Benign myoclonus of infancy
Epilepsy Syndromes

*Infantile Spasms and West Syndrome*

- Onset is usually at 3–7 months
- Seizure type—Flexor or extensor spasm, “salaam”
- Etiologies include
  - **Prenatal**—cerebral malformations, TSC, infection, intrauterine hypoxic-ischemic insults (HIE), metabolic, genetic
  - **Perinatal**—HIE, hemorrhage, trauma, infection, metabolic disorders
  - **Postnatal**—HIE, hemorrhage, trauma, metabolic disorders, infection, neoplasm
Infantile Spasms

*With Electrodecremental Event (EDE)*

Hypsarrhythmia

- High voltage
- Disorganized background
- Multifocal spikes
- **Awake** interictal EEG pattern

Electrodecremental

- **Event**—sudden EEG “flattening” represents the ictal portion of the EEG

Infantile Spasms and West Syndrome

Treatment and Prognosis

• Treatment
  • Adrenocorticotropic hormone (ACTH) or oral steroids
  • Vigabatrin
  • Ketogenic diet
  • Other (valproate, topiramate, benzodiazepines, zonisamide)
  • Surgery (focal dysgenesis, tumor, cyst)
  • Learning disabilities affect 90% of cases and are often severe
  • Many evolve into Lennox-Gastaut syndrome

Baby J

- Treated with vigabatrin for 2 years, seizure free
- Vigabatrin tapered off
- 8 months later—head drops and absence seizures
Epilepsy Syndromes

**Lennox-Gastaut Syndrome**

- Intractable seizures of mixed types
- Atypical absence
- Myoclonic
- Tonic
- Mean age of onset 3 years, range 1–8 years
- EEG—bilateral slow spike-and-wave complexes
- 60% with preexisting encephalopathy, 20%–30% with prior infantile spasms
- Learning difficulties in 80%–90% of cases
Lennox-Gastaut Syndrome

Etiologies

- 2/3 to 3/4 with abnormal brain on imaging
- Cortical dysgenesis most common
  - Bilateral perisylvian and central dysplasia
  - Subcortical laminar heterotopias
  - Focal cortical dysplasia
  - Other—hypothalamic hamartoma, Sturge-Weber syndrome, tumors
Lennox-Gastaut Syndrome

EEG Features

- Slow spike-wave activity
- 1–2 Hz bilateral synchronous discharges
- Often associated with ictal episodes, also occurs interictally
  - Can be difficult to differentiate ictal from interictal behaviors
- Not activated by photic stimulation, unlike myoclonic epilepsies

Lennox-Gastaut Syndrome

**Predictors of Poor Prognosis**

- Symptomatic etiology
- Early age of onset
- Prior infantile spasms
- High frequency of tonic seizures
- Frequent episodes of nonconvulsive status epilepticus (NCSE)
- Slow EEG background
Lennox-Gastaut Syndrome
Why Can Diagnosis Be Missed or Delayed?

- Types of seizures not pathognomonic for LGS, and not necessarily present at onset!
  - Tonic seizures may not be present at onset, also may be very subtle
- EEG pattern of slow spike-wave not pathognomonic, and not necessarily present at onset!
- Multiple different causes—no biologic marker for LGS
- Tonic seizures and patterns of fast rhythms may be best indicators—sleep EEG may be necessary!
Lennox-Gastaut Syndrome
A Syndrome with Transition

- Early on, characteristic seizures and EEG patterns may not be present!
- Later on, characteristic seizures may not be present!
  - Seizures during awake state improve
  - Tonic seizures continue during sleep, but may be subtle
  - Increase in focal, tonic-clonic seizures
- EEG patterns may change!
  - Waking background EEG may improve
  - Interictal slow spike-wave may be absent
Lennox-Gastaut Syndrome

Management

• Epilepsy referral at onset for diagnosis and management
  • Important due to variable features at presentation, variable etiologies
• EEG recording including sleep; if normal, should be repeated as indicated
• Broad-range anticonvulsant medications should be used early
• If seizures are refractory, nonpharmacologic therapies should be considered, including dietary therapy, vagus nerve stimulation (VNS), surgery
• Recognize and address comorbidities
### Lennox-Gastaut Syndrome

**Treatment**

<table>
<thead>
<tr>
<th>FDA Approved</th>
<th>Some Evidence</th>
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<tr>
<td>Lamotrigine</td>
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<td>Topiramate</td>
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<td>Felbamate</td>
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<td>Clobazam</td>
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<td>Cannabidiol</td>
<td>Vagal nerve stimulation</td>
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<td></td>
<td>Corpus callosotomy</td>
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</table>

FDA Prescribing Information; VanStraten AF, Ng YT. *Pediatr Neurol*. 2012.
Significant Needs Exist Despite Currently Available AEDs

Lennox-Gastaut Syndrome

- Treatment of multiple seizure types requires broad spectrum AEDs and/or polypharmacy
- AEDs effective for one seizure type may worsen another seizure type or provoke status epilepticus (SE)
- Treatment response is poor; 94%–96% of patients develop intractable epilepsy

**Diagnosis**

First-line therapy: sodium valproate

If treatment aims not achieved

Second-line therapy, one or two of:
- Clobazam
- Lamotrigine
- Levetiracetam
- Rufinamide
- Topiramate
- Zonisamide

If treatment aims not achieved

Nonpharmacologic Intervention, one of:
- Ketogenic diet
- Vagus nerve stimulation

If treatment aims not achieved

Alternative second-line agent(s) and/or alternative nonpharmacologic intervention

If treatment aims not achieved

Third-line therapy:
- Acetazolamide
- Bromides
- Carbamazepine
- Ethosuximide
- Felbamate
- Phenobarbital
- Phenytoin
- Vigabatrin

*All drugs except bromides and felbamate are licensed for the treatment of LGS and/or partial and/or generalized seizure types. Zonisamide is not recommended for use in patients under 18 years of age.
* Benzodiazepines can be considered as second-line agents for Lennox-Gastaut Syndrome (although not specifically indicated as such), but it may be better to use them in short courses to treat convulsive and nonconvulsive status epilepticus and to break cycles of very poor seizure control.

Epilepsy Syndromes

Dravet Syndrome

- Genetic epilepsy—due to mutation in SCN1a gene in 70%–90%
- Clinical features
  - First seizure at 6 months of age in setting of febrile illness
  - Development normal prior to seizure onset
  - Initial EEG usually with nonspecific features
  - Onset of highly refractory epilepsy second year of life
    - Tonic-clonic, atypical absence, and myoclonic
    - Seizures frequently triggered by heat, fever
  - Usually associated with developmental plateau or regression

Optimizing the Diagnosis and Management of Dravet Syndrome: Recommendations From a North American Consensus Panel

Elaine C. Wirrell MD, Linda Laux MD, Elizabeth Donner MD, Nathalie Jette MD, Kelly Knupp MD, Mary Anne Meskis, Ian Miller MD, Joseph Sullivan MD, Michelle Welborn Pharm D, Anne T. Berg PhD
Until Recently, No FDA-approved Medications for Dravet Syndrome

SCN1A = sodium voltage-gated channel alpha-1; subunit; sz = seizure. Treatment algorithm for Dravet syndrome. *Ketogenic diet is not suitable for all patients; its use is not required before moving to third-line therapies. \(^{a}\)Agreed upon by moderate consensus. \(^{b}\)Agreed upon by strong consensus. \(^{c}\)Stiripentol not approved for use in all jurisdictions.

Making a Case for Cannabidiol

Use of Cannabis in Treating Epilepsy

• 1911—Massachusetts was first state to outlaw cannabis (in setting of prohibition of alcohol)
  • Other states quickly followed with marijuana prohibition laws
• 1970—U.S. Controlled Substances Act passed, classifying marijuana as a drug with “no accepted medical use”
Making a Case for Cannabidiol

Use of Cannabis in Treating Epilepsy

• 1996—California becomes first state to legalize medical marijuana
• 2015—Medical marijuana legalized in 23 states
  • Regulated at state level
  • Cannabidiol (CBD) specifically made legal in an additional 16 states
• Increasing anecdotal reports about efficacy of medical marijuana, especially CBD–enriched formulations in the treatment of refractory pediatric epilepsy
• 2018 – FDA approves cannabidiol oil
  • For treatment of Lennox-Gastaut and Dravet syndromes
CBD Oral Solution

• Expanded access program
  • 5 initial sites, several added
  • MGH enrolled 57, initial 25 started April 2014
  • Currently >1000 patients in EAP, including state programs

• Dravet syndrome
  • 2 randomized controlled trials (RCT)—results published from first trial

• Lennox-Gastaut syndrome
  • 2 RCTs—results from both trials released

• Tuberous sclerosis complex
  • RCT, recently completed enrollment

June 25, 2018
“The U.S. Food and Drug Administration today approved cannabidiol (CBD) oral solution for the treatment of seizures associated with two rare forms of epilepsy, Lennox-Gastaut syndrome and Dravet syndrome, in patients two years of age and older.”

FDA News Release. Available at: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm611046.htm
Audience Question

Cannabidiol oral solution was recently approved by the FDA for the treatment of Lennox-Gastaut and Dravet syndromes in patients two years of age and older. How would you describe your openness to using cannabidiol in your practice?

A. Very hesitant; I don’t plan to use it
B. Somewhat hesitant; I would consider it for select patients only
C. Somewhat open; I believe it has a viable place in my practice
D. Very open; I plan to use it
Audience Question

What do you perceive as the most significant barrier to integrating cannabidiol into current clinical practice?

A. Drug availability
B. Excessive cost and lack of insurance coverage
C. Social stigma
D. The status of cannabidiol as a Schedule 1 substance
Audience Question

Given the FDA approval, how many patients do you see each month who have Lennox-Gastaut syndrome or Dravet syndrome that are now indicated for cannabidiol therapy?

A. None
B. 1–10
C. 11–19
D. 20 or more
Audience Question

Once the FDA-approved formulation of cannabidiol oil becomes available, how would you distinguish its clinical utility from other available forms of cannabidiol?

A. I see no substantial difference
B. There is a difference, but it will have a limited impact on my practice
C. I will preferentially use the FDA-approved formulation, but am also open to other non-approved formulations
D. I will exclusively use the FDA-approved formulation
E. I don’t plan to use any form of cannabidiol in my practice
Ketogenic Diet (KGD)
Ketogenic Diet vs American Diet

**Ketogenic Diet**
- Fat: 90%
- Protein: 6%
- Carbohydrates: 4%

**American Diet**
- Fat: 35%
- Protein: 15%
- Carbohydrates: 55%
Ketogenic Diet

Formulation

- Calories—based on age, ideal body weight, and current intake
- Protein—RDA or above
- Vitamins and minerals—RDI

Ketogenic ratio:

\[
\text{Ratio (by grams)} = \text{Fat} : (\text{Protein} + \text{Carbohydrate})
\]

-ie, 4:1 ratio implies 4 grams of fat to 1 gram combined of protein and carbohydrate

- Ratio is limited by protein requirement

Ketogenic Diet

Food Groups

- Cream
- Fat
- Fruit or vegetable
- Protein

No bread, pasta or grains
No sugar
No starchy fruit or vegetable

Vigilant exclusion/monitoring of extra carbohydrates
(eg, in medications, non-nutritive sweetener formulations, toothpastes)

## Ketogenic Diet Efficacy in Children with Intractable Epilepsy

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<th>Author</th>
<th>Year</th>
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<td><em>et al.</em> –MCT</td>
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<td><strong>overall</strong></td>
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<td><strong>762</strong></td>
<td><strong>37%</strong></td>
<td><strong>30%</strong></td>
<td><strong>33%</strong></td>
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The Ketogenic Diet

Side Effects

• Elevated lipids
• Constipation
• Kidney stones
• Growth retardation
• Vitamin deficiencies

Thiele EA. *Epilepsia.* 2003.
Consensus Recommendations

• Should be offered after two AEDs have been used unsuccessfully (unless patient is a potential surgical candidate)
• First line for glucose transporter defect and pyruvate dehydrogenase deficiency
• Probably very beneficial in Doose syndrome, Dravet syndrome, infantile spasms, Rett syndrome, and tuberous sclerosis

Ketogenic Diet 2018

• Fasting probably not required
  • Advantages to initiating without fast
    • Shorter hospitalization
    • Better tolerated with less acidosis, hypoglycemia
    • Less stressful for child and parents

• Inpatient vs outpatient initiation
  • Inpatient recommended

• Ketogenic diet team is crucial!
  • Knowledgeable dietician
  • Pediatric neurologist
  • Epilepsy nurse specialist
Atkins for Seizures

• Case series of 6 patients (4 over age 18 years)
• Prospective open label study of 20 patients 16/20 completed 6 month study
  • Mean age—6.5 years
  • Mean seizure per week—163
  • Mean ACD trials—6.5

Atkins for Seizures

Johns Hopkins Medical Institutions (JHMI)—Modified Atkins Protocol

- Outpatient initiation
- No initial fast
- No caloric, fluid restriction
- No weighing of foods; no specific meal plans
- Carbohydrates (CHO) limited to 10 gm/day for first month; increase to 20 gm after 1–3 months (any CHO)
- Multivitamin, calcium supplementation
- Weekly weights
- Labs (CBC, electrolytes, lipid profile) every 3 months
- Urinary ketones measured semiweekly

Traditional Ketogenic Diet
4:1 Ratio

- Fat: 70%
- Protein: 10%
- Carbohydrates: 3%

Modified Atkins Diet
1:1 Ratio

- Fat: 65%
- Protein: 25%
- Carbohydrates: 10%

Standard Diet
0.3:1 Ratio

- Fat: 49%
- Protein: 16%
- Carbohydrates: 35%

Low-Glycemic Index Treatment (LGIT)

Background

- Anecdotes—sugary treats and seizures
- Remarkable glucose stability on KGD—may have something to do with antiepileptic benefit
- Children on ketogenic diet can be very sensitive to extra carbohydrates, with adverse effects on seizure control
  - Inadvertent D5 infusion
  - M&Ms, candy
  - Change in vanilla extract lot
  - Varieties of grapes
Efficacy, safety, and tolerability of the low glycemic index treatment in pediatric epilepsy

David A. Muzykewicz, David A. Lyczkowski, Naureen Memon, Kerry D. Conant, Heidi H. Pfeifer, and Elizabeth A. Thiele

Department of Neurology, Massachusetts General Hospital, Boston, Massachusetts, U.S.A.
MGH
LGIT Protocol

• Calorie goals are based on current intake according to three-day food records and food frequency questionnaires (to maintain adequate growth and development)

• Individualized goals for grams of protein, fat, and carbohydrates are provided based on calorie needs.

• Carbohydrates are limited to 40–60 grams per day from low-glycemic index sources (GI<50)

• Food is not weighed, but based on portion sizes

• Fluid is not restricted, rather encouraged

• Vitamins and minerals are supplemented to meet individualized needs

• Initiation as outpatient with follow up 1 month post-diet initiation and then every 3 months for duration of treatment
Low-Glycemic Index Treatment

• Effective for partial onset and generalized seizures
• No dramatic change in $\beta$-hydroxybutyrate levels
• Better tolerated than KGD
  • Less restrictive for child
  • Easier to administer for family and clinic
  • Initiation does not require hospitalization
Dietary Therapy in Epilepsy

Where Do We Go from Here?

• Classic KGD
  • Most effective treatment available for intractable epilepsy
  • However, implementation and restrictions difficult for child and family
  • Would initiation without fast and liberalization of fluids make more “doable”?

• Current alternatives—modified Atkins and LGIT
  • Both now widely used, with efficacy thought to be similar to classic ketogenic diet

• Why do these diets work?
Dietary Therapy of Epilepsy

Who, What, When, Where, and Why?

• Proven efficacy in all seizure types
  • Evolving and important role in treatment of infantile spasms
• Proven efficacy with many etiologies
  • Genetic etiologies
    • Myoclonic astatic epilepsy
    • Dravet syndrome
  • Structural/metabolic etiologies
    • Glucose transporter deficiency (GLUT1)
    • Tuberous sclerosis complex
    • Angelman syndrome
• Proven efficacy in children—what about adults?