Non-Medical Therapies: VNS Therapy & The Ketogenic Diet

Vagus Nerve Stimulation
Dr. Jim Wheless

Ketogenic Diet
Dr. Doug Nordli
Patient Profile

Chief Complaint

- Refractory drop attacks (atonic seizures)

History of Present Illness

- 5-year-old male
- Febrile seizure at age 18 months
- Generalized tonic-clonic seizure without fever onset at age 3.5 years
- Staring spells (possible atypical absence seizure) onset at age 4 years
- Drop attacks onset at age 4 years
- Prior AEDs: Valproate, zonisamide, levetiracetam, lamotrigine, rufinamide, ethosuximide
Patient Profile

Past Medical History

Birth: Full-term, no problems
Development: Mild delay noted at age 3 years, plateau last 12 months

Current Medication

Topiramate, 100 mg BID (8 mg/kg/d)
Clobazam, 10 mg BID (0.8 mg/kg/d)

Physical / Exam

25 kg, wearing a helmet
General: Unremarkable
Neurologic: Alert, speech delay, ambulatory, non-focal
Evaluation

MRI (3T, epilepsy protocol): Normal

EEG (interictal): Mild diffuse slowing of background
Generalized 2-2.5 Hz S+SW complexes
Generalized polyspike bursts in sleep

V-EEG (ictal): Multiple, daily drop attacks—generalized onset
Rare atypical absence—generalized onset
Rare GTC seizure—generalized onset

Neuropsychology: Vineland Composite 60
Drop Attack (Atonic Seizure)
Drop Attack (Myoclonic Tonic)
Lennox-Gastaut Syndrome: Treatment Options

- AEDs (controlled studies)
  - Felbamate, topiramate, lamotrigine, rufinamide, clobazam

- AEDs (anecdotal, open-label, retrospective studies)
  - Valproate, clonazepam, vigabatrin, zonisamide, levetiracetam

- Ketogenic diet

- Vagus nerve stimulation

- Complete corpus callosotomy

- Helmet
Patient Profile

The parents’ questions are:

- Will my child’s development improve if the seizures are controlled, or is this from the medicine?
- What treatment options are there for the daily drop attacks?
- Tell us the benefits and risks of the ketogenic diet or VNS Therapy?
- Doctor, what do you suggest we do now?
What do you do when AEDs fail?

1\textsuperscript{st} AED Monotherapy $\rightarrow$ 2\textsuperscript{nd} AED Monotherapy $\rightarrow$ Re-evaluate $\rightarrow$ Consider Other Treatments

- Epilepsy Surgery
- Vagus Nerve Stimulation
- Ketogenic Diet

OR

Polytherapy Trials $\rightarrow$ Medication
Pharmacoresistant Epilepsy

What do you do when AEDs fail?

- 1st AED Monotherapy
- 2nd AED Monotherapy
- OR
- Polytherapy Trials

Re-evaluate

Consider Other Treatments

- Epilepsy Surgery
- Vagus Nerve Stimulation
- Ketogenic Diet
- Felbamate
Pharmacoresistant Epilepsy

What do you do when AEDs fail?

1st AED Monotherapy → 2nd AED Monotherapy OR Polytherapy Trials → Re-evaluate

Re-evaluate → Consider Other Treatments

Consider Other Treatments → Complete Corpus Callosotomy OR Vagus Nerve Stimulation OR Ketogenic Diet → Medication
Lennox-Gastaut Syndrome (LGS): Treatment Selection, Expert Opinion 2005

- Healthy 6-year-old child
- Infrequent generalized tonic-clonic and atypical absence seizures
- Multiple daily astatic seizures
- Rate appropriateness of each treatment (considering the dominant seizure type)

Neurostimulation for Epilepsy: Focus on Vagus Nerve Stimulation

James W Wheless, M.D.
Professor and Chief of Pediatric Neurology
Le Bonheur Chair in Pediatric Neurology
University of Tennessee Health Science Center
Director, Neuroscience Institute &
Le Bonheur Comprehensive Epilepsy Program
Le Bonheur Children’s Hospital
Memphis, TN
VNS Therapy: Use in Pediatrics

- < 12 Yrs Old
- 12 to 20 Yrs Old
- < 20 Yrs Old
- > 21 Yrs Old
Injuries Secondary to Falls (Seizures)
VNS in Pediatric Patients with Refractory Epilepsy

Prior Epilepsy Surgery: Seizure Response
Median Percent Decrease at 3 months

- Prior Lobectomy: 32% (N=15)
- Entire Group: 51.5% (N=95)
- Prior Callosotomy: 79% (N=20)

VNS in Lennox-Gastaut Syndrome

Retrospective, Multi-Center Study

- Number of patients: 50 (32 males)
- Age at implant (yrs): 13 (5-27)
- Age at seizure onset (yrs): 1.4 (0.1-7.5)
- No. previous AEDs: 9 (3-17)
- Prior ketogenic diet: 18 (36%)
- Prior callosotomy: 5 (10%)
- AEDs: VPA (44%), TPM (36%), LTG (30%)

VNS in Lennox-Gastaut Syndrome

Drop Attacks (N=33) Median Seizure Reduction

### VNS Therapy: Lennox-Gastaut Syndrome

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>N</th>
<th>Responder Rate or Median %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hornig G W, 1997</td>
<td>6</td>
<td>83% with &gt; 90% ↓</td>
</tr>
<tr>
<td>Lundgren J, 1998</td>
<td>4</td>
<td>50%</td>
</tr>
<tr>
<td>Parker APJ, 1999</td>
<td>9</td>
<td>34%</td>
</tr>
<tr>
<td>Hosain S, 2000</td>
<td>13</td>
<td>46%</td>
</tr>
<tr>
<td>Majoie HJM, 2001</td>
<td>16</td>
<td>25%</td>
</tr>
<tr>
<td>Frost M, 2001</td>
<td>46</td>
<td>43%</td>
</tr>
<tr>
<td>Benifla M, 2006</td>
<td>10</td>
<td>40%</td>
</tr>
<tr>
<td>Rychlicki F, 2006</td>
<td>8</td>
<td>33%</td>
</tr>
<tr>
<td>Rossignol E, 2009</td>
<td>5</td>
<td>80%</td>
</tr>
<tr>
<td>Shahwan A, 2009</td>
<td>9</td>
<td>78%</td>
</tr>
<tr>
<td>Kostov K, 2009</td>
<td>30</td>
<td>60.6%</td>
</tr>
<tr>
<td>Cersosimo R, 2011</td>
<td>46</td>
<td>65%</td>
</tr>
<tr>
<td>Elliott RE, 2011</td>
<td>24</td>
<td>52.15</td>
</tr>
</tbody>
</table>

Significant activation of brainstem and thalamus (especially centromedian and anterior thalamus) associated with epileptiform discharges in Lennox-Gastaut syndrome.

Symptomatic Generalized Seizures: VNS Therapy or Corpus Callosotomy

<table>
<thead>
<tr>
<th>Center</th>
<th>Seizure Type(s)</th>
<th>Number/Procedure</th>
<th>Responder Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>You SJ, 2008 Seoul, Korea</td>
<td>Drop attacks (LGS) N=24</td>
<td>14 Callosotomy 10 VNS</td>
<td>64.3% 70%</td>
</tr>
<tr>
<td>Retrospective Children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nei M, 2006 Philadelphia, PA</td>
<td>GTC (N=71) Tonic/atonic (N=26)</td>
<td>53 Callosotomy 25 VNS</td>
<td>80% GTC 78% Tonic/atonic 50% GTC 67% Tonic/atonic</td>
</tr>
<tr>
<td>Prospective Adults</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

90% Callosotomy or VNS Therapy in Lennox-Gastaut Syndrome

Methods:
- N= 24, anterior 90% corpus callosotomy (2006-07)
- N= 20, VNS Therapy (2008-09):
  - 30Hz, 500 micros, 30 sec. on/5 min. off; mean 3.0 mA
- MRI normal or non-specific abnormalities, 2 year follow-up.

Results:

<table>
<thead>
<tr>
<th></th>
<th>Atypical Absence</th>
<th>Gen T-C</th>
<th>Gen Tonic</th>
<th>Myoclonic</th>
<th>Atonic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Callosotomy</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>VNS</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Factors to Consider in the Decision of VNS Therapy vs. Corpus Callosotomy

<table>
<thead>
<tr>
<th></th>
<th>VNS Therapy</th>
<th>Corpus Callosotomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>High frequency seizure</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Tall, heavy child</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Unable to tolerate complications</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Interictal EEG – bilateral, independent spikes</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

With either procedure, judge outcome by response after 6 months
Combining Palliative Procedures (VNS Therapy, Corpus Callosotomy) in Lennox-Gastaut Syndrome

AAN Guideline Update: VNS Therapy for Epilepsy

1999 AAN Guideline Conclusions:
- VNS indicated > 12 years old, refractory partial-onset seizures, not surgery candidate.
- Patients undergo a thorough evaluation prior to implant.

Update, 1996 – 2012 literature
- Addressed 8 questions.

Endorsed by the American Epilepsy Society.

Morris GL III et al. Neurol, 2013
1. Use of VNS in children with epilepsy?
   - N = 481, responder rate 55%
   - Seizure free rate 7%
   - Recommendation: Use in partial or generalized epilepsy.

2. Use of VNS in patients with Lennox-Gastaut Syndrome?
   - N = 113, responder rate 55%
   - Recommendation: Use in Lennox-Gastaut Syndrome.

3. Does VNS improve mood?
   - Recommendation: In adults, improvement in mood may be an additional benefit.

Morris GL III et al. Neurol, 2013
4. Does VNS improve seizure control over time?
   • Recommendation: VNS may be considered progressively effective.

5. Rapid cycling/stimulation vs. standard stimulation?
   • Recommendation: Optimal VNS settings are unknown.

6. Does use of VNS magnet help (at seizure onset, aura)?
   • Recommendation: Magnet activation may be associated with seizure abortion, and over all response.

Morris GL III et al. Neurol, 2013
7. Any new safety concerns?
   • No new concerns, caution if also having sleep apnea, cardiac rhythm disturbance.

8. Do children have unique/different adverse events?
   • May have a greater risk for wound infections.

Morris GL III et al. Neurol, 2013
VNS Therapy: Effect on Healthcare Utilization

n = 138 denotes all patients in analysis
n = 137 excludes patients with high utilization (outliers)

Bernstein AL et al. Epilepsy Behav 10:134, 2006
VNS Therapy: Pediatric Candidates – Take Home Message

Features Which Help Identify Candidates

Seizure Type
- Drop attacks (astatic events)
- Symptomatic generalized tonic-clonic seizures
- Simple partial $\rightarrow$ complex partial/secondary GTC
- Partial onset seizures (non-lesional)
- Refractory primary generalized epilepsy (JME, absence)

Patient Factors
- Sensitive to antiepileptic drug (AED) side effects
- Co-morbid mood disorder / depression
- Poor adherence with AED regimen
- Frequent ED visits / hospitalizations
- Failed prior epilepsy surgery
? Questions ?
I hope this has stimulated your thinking about the treatment of epilepsy!

Thank you!
Ketogenic Diet: Mechanisms of Action

Douglas R. Nordli, Jr., MD
Director, Pediatric Epilepsy
Children’s Memorial Hospital
Northwestern University
Chicago, IL
A “Miraculous” Treatment

Matthew 17:20
“But this kind does not go out except by prayer and fasting.”

Mark 9:14-29
“One who is confronted with the task of controlling seizures in a person with epilepsy grasps at any straw. When some 6 or 8 years ago, an osteopathic practitioner in Michigan stated that fasting would cure epilepsy, this seemed like a very frail straw.”
A. Increased formation of glycogen, less glycolysis

B. Decreased PDH activity

C&D. Maximal TCA function

E. Increased flow through GABA shunt
Mean Voltage to Produce Minimal Convulsion by Time on Diet*

Electroconvulsive shock (volts)

maximal seizures

*Abstracted from original data to reflect general trends

Appleton DB, DeVivo DC. An animal model for the ketogenic diet. Epilepsia 15:211, 1974
<table>
<thead>
<tr>
<th>Determination</th>
<th>Control (N=22)</th>
<th>High-fat diet (N=13)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate/pyruvate</td>
<td>14.8</td>
<td>15.1</td>
<td>NS</td>
</tr>
<tr>
<td>Energy charge</td>
<td>0.872</td>
<td>0.884</td>
<td>P&lt;0.005</td>
</tr>
<tr>
<td>ATP/ADP</td>
<td>3.63</td>
<td>4.08</td>
<td>P&lt;0.005</td>
</tr>
<tr>
<td>Energy reserve</td>
<td>23.6</td>
<td>26.4</td>
<td>P&lt;0.005</td>
</tr>
<tr>
<td>Brain/blood glucose</td>
<td>0.303</td>
<td>0.367</td>
<td>P&lt;0.005</td>
</tr>
</tbody>
</table>

**Brain Lactate Rises During Complex Partial Seizures: Measured by MRS**

- Cendes F, Stanley JA, Dubeau F et al. Ann Neurol 41:74, 1997. Proton magnetic resonance spectroscopic imaging for discrimination of absence and complex partial seizures. Significant increase in lactate to creatine plus phosphocreatine (lactate/creatine) values, reflecting an imbalance in energy supply and demand or an adaptation in response to ictal neuronal discharges, during and soon after complex partial seizures. (Andermann)
Children Are Not Small Adults

Byzantine, 11th C.
Met. Mus. Art

Bartolomeo, c. 1490,
Met. Mus. Art
GABA: $\text{H}_2\text{N} - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{C} - \text{OH}$

Acetoacetate: $\text{CH}_3 - \text{C} - \text{CH}_2 - \text{C} - \text{OH}$

β Hydroxybutyrate: $\text{CH}_3\text{CHOH} - \text{CH}_2 - \text{C} - \text{OH}$

γ Hydroxybutyrate: $\text{HO} - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{C} - \text{OH}$
Acetone: Potent Anticonvulsant

<table>
<thead>
<tr>
<th>Type of test</th>
<th>$ED_{50}$ (mmol/kg, 95% confidence interval)</th>
<th>$TD_{50}$ (mmol/kg, 95% confidence interval)</th>
<th>Therapeutic index</th>
</tr>
</thead>
<tbody>
<tr>
<td>MES</td>
<td>6.6 (4.2–10.2)</td>
<td>28.4 (26.8–30.1)</td>
<td>4.3</td>
</tr>
<tr>
<td>PTZ</td>
<td>9.7 (7.6–12.3)</td>
<td>27.5 (25.6–29.7)</td>
<td>2.8</td>
</tr>
<tr>
<td>Kindled</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalized</td>
<td>13.1 (7.9–21.8)</td>
<td>30.5 (28.6–32.5)</td>
<td>2.3</td>
</tr>
<tr>
<td>Focal</td>
<td>26.5 (21.3–32.8)</td>
<td>24.0 (21.5–26.9)</td>
<td>1.2</td>
</tr>
<tr>
<td>AY-9944</td>
<td>4.0 (3.7–4.4)</td>
<td>24.0 (21.5–26.9)</td>
<td>6.0</td>
</tr>
</tbody>
</table>

Likhodii SS, Burnham WM. Stafstrom and Rho, 2004
Direct Anticonvulsant Effects of Ketones

- Acetoacetate, acetone, and dibenzylamine exhibit direct anticonvulsant actions in vivo
- Frings audiogenic seizure-susceptible mice
Ketogenic D Suppresses Epileptogenesis

- Todorova, Tandon, Madore, Stafstrom, Seyfried
  - The ketogenic diet inhibits epileptogenesis in EL mice: a genetic model for idiopathic epilepsy
  - Epilepsia, 2000

- Stafstrom, Wang, Jensen
  - Electrophysiological observations in hippocampal slices from rats treated with the ketogenic diet
  - Dev Neurosc, 1999
Optimal clinical management of children receiving the ketogenic diet: Recommendations of the International Ketogenic Diet Study Group

**Table 1. Epilepsy syndromes and conditions in which the KD has been reported as particularly beneficial**

<table>
<thead>
<tr>
<th>Probable benefit (at least two publications)</th>
<th>Severe myoclonic epilepsy of infancy (Dravet syndrome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose transporter protein 1 (GLUT-1) deficiency</td>
<td>Infantile spasms</td>
</tr>
<tr>
<td>Pyruvate dehydrogenase deficiency (PDHD)</td>
<td>Children receiving only formula (infants or enterally fed patients)</td>
</tr>
<tr>
<td>Myoclonic-astatic epilepsy (Doose syndrome)</td>
<td></td>
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<tr>
<td>Tuberous sclerosis complex</td>
<td></td>
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<tr>
<td>Rett syndrome</td>
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</table>

<table>
<thead>
<tr>
<th>Suggestion of benefit (one case report or series)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Selected mitochondrial disorders</td>
<td>Glycogenosis type V</td>
</tr>
<tr>
<td>Landau-Kleffner syndrome</td>
<td>Lafora body disease</td>
</tr>
<tr>
<td>Lafora body disease</td>
<td>Subacute sclerosing panencephalitis (SSPE)</td>
</tr>
<tr>
<td>Table 2. Contraindications to the use of the KD</td>
<td></td>
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<tr>
<td>-----------------------------------------------</td>
<td></td>
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<tr>
<td>Absolute</td>
<td></td>
</tr>
<tr>
<td>Carnitine deficiency (primary)</td>
<td></td>
</tr>
<tr>
<td>Carnitine palmitoyltransferase (CPT) I or II deficiency</td>
<td></td>
</tr>
<tr>
<td>Carnitine translocase deficiency</td>
<td></td>
</tr>
<tr>
<td>β-oxidation defects</td>
<td></td>
</tr>
<tr>
<td>Medium-chain acyl dehydrogenase deficiency (MCAD)</td>
<td></td>
</tr>
<tr>
<td>Long-chain acyl dehydrogenase deficiency (LCAD)</td>
<td></td>
</tr>
<tr>
<td>Short-chain acyl dehydrogenase deficiency (SCAD)</td>
<td></td>
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<tr>
<td>Long-chain 3-hydroxyacyl-CoA deficiency</td>
<td></td>
</tr>
<tr>
<td>Medium-chain 3-hydroxyacyl-CoA deficiency</td>
<td></td>
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<tr>
<td>Pyruvate carboxylase deficiency</td>
<td></td>
</tr>
<tr>
<td>Porphyria</td>
<td></td>
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<tr>
<td>Relative</td>
<td></td>
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<tr>
<td>Inability to maintain adequate nutrition</td>
<td></td>
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<tr>
<td>Surgical focus identified by neuroimaging and video EEG monitoring</td>
<td></td>
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<tr>
<td>Parent or caregiver noncompliance</td>
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</tbody>
</table>
Committee conclusions

The KD should be strongly considered in a child who has failed two to three anticonvulsant therapies, regardless of age or gender, and particularly in those with symptomatic generalized epilepsies. It can be considered the treatment of choice for two distinct disorders of brain metabolism, GLUT-1 deficiency syndrome and PDHD. In the particular epilepsy syndromes of Dravet syndrome, infantile spasms, myoclonic-astatic epilepsy, tuberous sclerosis complex, the KD could be offered earlier.
Side-Effects of Ketogenic Diet

- Death: especially in patients with underlying metabolic defects, PC
- Coma or obtundation
- Kidney stones
- Lipemia
- Bone demineralization
- Pancreatitis
- Change in bowel habits
- Acute-dehydration and hypoglycemia