Other treatments: KD& VNS

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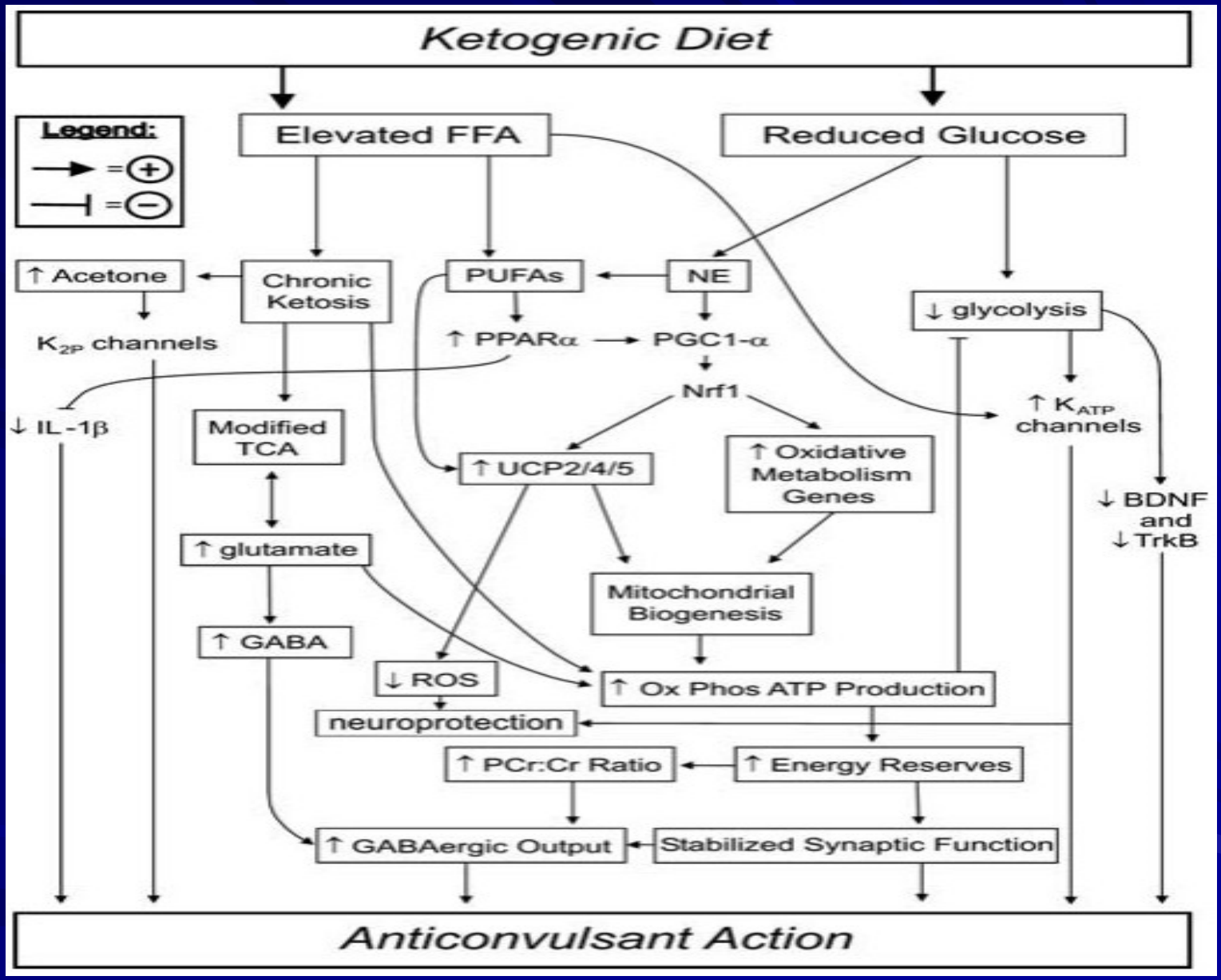
Ketogenic diet (KD)*

- High fat
- Low carbohydrate
- Calorie control
- Adequate protein

- Therapeutic diet for epilepsy
- As effective as an AED or VNS



Bough K., et al., *Anticonvulsant Mechanisms of the Ketogenic Diet.*Epilepsia, Vol. 48, No. 1, 2007

Efficacy

- RCT (145 children) published in 2008

- Diet group - 38% = 50% Sz reduction
  - 7 % = 90% Sz reduction
  - 1.5%= Sz-free

Mean Sz frequency dropped by 1/3

No difference between Classical VS MCT

Neal, E.G., et al., *The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial.* Lancet Neurol, 2008. **7**(6): p. 500-6

International guideline

Epilepsia, 50(2):304–317, 2009
doi: 10.1111/j.1528-1167.2008.01765.x

SPECIAL REPORT

Optimal clinical management of children receiving the ketogenic diet: Recommendations of the International Ketogenic Diet Study Group

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- International Ketogenic Diet Study Group
- standardized protocol

Practical approach*

- Case selection
- Pre-KD assessment
- Ketosis induction
- Evaluation
- Maintenance
- KD discontinuation

Primary indications

- Glucose transporter 1 (GLUT1) deficiency
- Pyruvate dehydrogenase deficiency

- Essential energy for brain
- Treat - seizures
  - non-epileptic symptoms

Particular benefit in*

- Tuberous sclerosis complex
- Myoclonic-astatic epilepsy
- Rett syndrome
- Dravet syndrome
- Infantile spasms
- infants or enterally fed patients

Suggestion of benefit in

- Selected mitochondrial disorders (complex I)
- Glycogenosis type V
- Landau-Kleffner syndrome
- Lafora body disease
- SSPE

Absolute Contraindication*

- Carnitine deficiency (primary)
- Carnitine palmitoyltransferase (CPT) I or II deficiency
- Carnitine translocase deficiency
- β-oxidation defects
- MCAD/ LCAD/ SCAD

* lipid metabolism defect

Absolute Contraindication

- Long-chain 3-hydroxyacyl-CoA deficiency
- Medium-chain 3-hydroxyacyl-CoA deficiency.
- Pyruvate carboxylase deficiency
- Porphyria

Pre-KD evaluation*

- Counseling
- Sz assessment
- Nutritional evaluation
- Lab evaluation

Counseling

- Seizure reduction, medication
- Cognitive expectations
- Psychosocial barriers to KD
- Review drugs for CHO content
- Parent-oriented KD information

Nutritional evaluation

- Baseline Wt, Ht, and BMI
- Nutrition intake history
- Establish diet formulation/ route
- Formula selection
  (LCT/ MCT/ mod Atkins/ low GI)
- Calculation of calories, fluid, and KD ratio
- Nutritional supplements
  (Ca, MTV, trace element)

- Ketocalculator/Ketopaq…….+ support to help in menu planning

THE CHARLIE FOUNDATION
TO HELP CURE PEDIATRIC EPILEPSY

MATTHEW'S FRIENDS
Dietary Treatments for Epilepsy
Information – Training – Research – Support



Available formulas

- Classical formula (LCT)
- MCT formula
- Modified Atkins
- Low glycemic index (LGI)

Diet route

- Bottle feed / normal food / tube feed

Classical KD*

- Main fat source = LCT
- 4: 1 ratio of fat: protein - carbohydrate
- Low carb - just to prevent hypoglycemia
- Calorie control = 80 - 100% requirement
- Adequate protein
- Fluid restriction - not necessary

Classical diet

MCT KD*

- Better ketosis from MCT
- 30%-60% fat: total energy
- More carbohydrate allowance
- Less restrictive, bigger meal
- Similar efficay

- MCT can’t be cooked → not palatable

- Sample menu: 1300 kcal, 22 g protein (MCT ~ 48% Carb ~ 10%)

MCT diet


GULFAIR


Care
Cereal Cream
เก็บในตู้เย็น


NATUR

Diet
Coke
SUGAR FREE

Ketosis induction*

- Rapid induction

  - fasting (12 h - whenever ketosis)
  - admission required
  - risk of dehydration, glucose, acidosis

  - diet titrating up to the target ratio

  - caregiver training during admission

Ketosis induction*

- Gradual initiation
  - without fasting
  - admission = optional
  - slower but comparable Sz control at 3 m
  - lower initial side effect

Maintenance phase

- Efficacy evaluation after 3 month
- seizure control
- GI & nutritional assessment
- urinary ketone
- Blood tests

Maintenance

- MTV, mineral supplements recommended
- Citrate - prevents kidney stones
- 3 monthly Visits with ready access
- Rare serious effects, mostly no need to discontinued KD

side effects

Early

- Dehydration
- N/V, diarrhea
- Hyperlipidaemia
- Hyperuricaemia
- HypoCa, HypoMg
- Metabolic acidosis

Late

- Osteopenia
- Renal stones
- Low carnitine
- Fe def anemia
- Cardiomyopathy(rare)

*** GI & metabolic effect**

***Mostly transient**

Discontinuation

- Diet maintenance - 2 years if effective
- longer as necessary for GLUT-1, PDHD

- Sudden glucose intake / diet cessation → Sz
- Slow weaning over 2-3 months

- overall recurrence risk - 20%
- Higher in TSC, abnormal EEG, MRI

Martinez, C.C., P.L. Pyzik, and E.H. Kossoff, *Discontinuing the ketogenic diet in seizure-free children: recurrence and risk factors.* Epilepsia, 2007. **48**(1): p. 187-90.

Compliance of KD

Family

- Food measuring & weighing
- Difficult recipe

Patient

- Limited Cal, but high fat = small meal
- Little carb = little staple = small meal

Modified Atkins*

- Similar composition to classical KD
- 1: 1 ketogenic ratio
- Restrict carbohydrate
- No limit on protein, fluids, and calories
- Easier meal planning

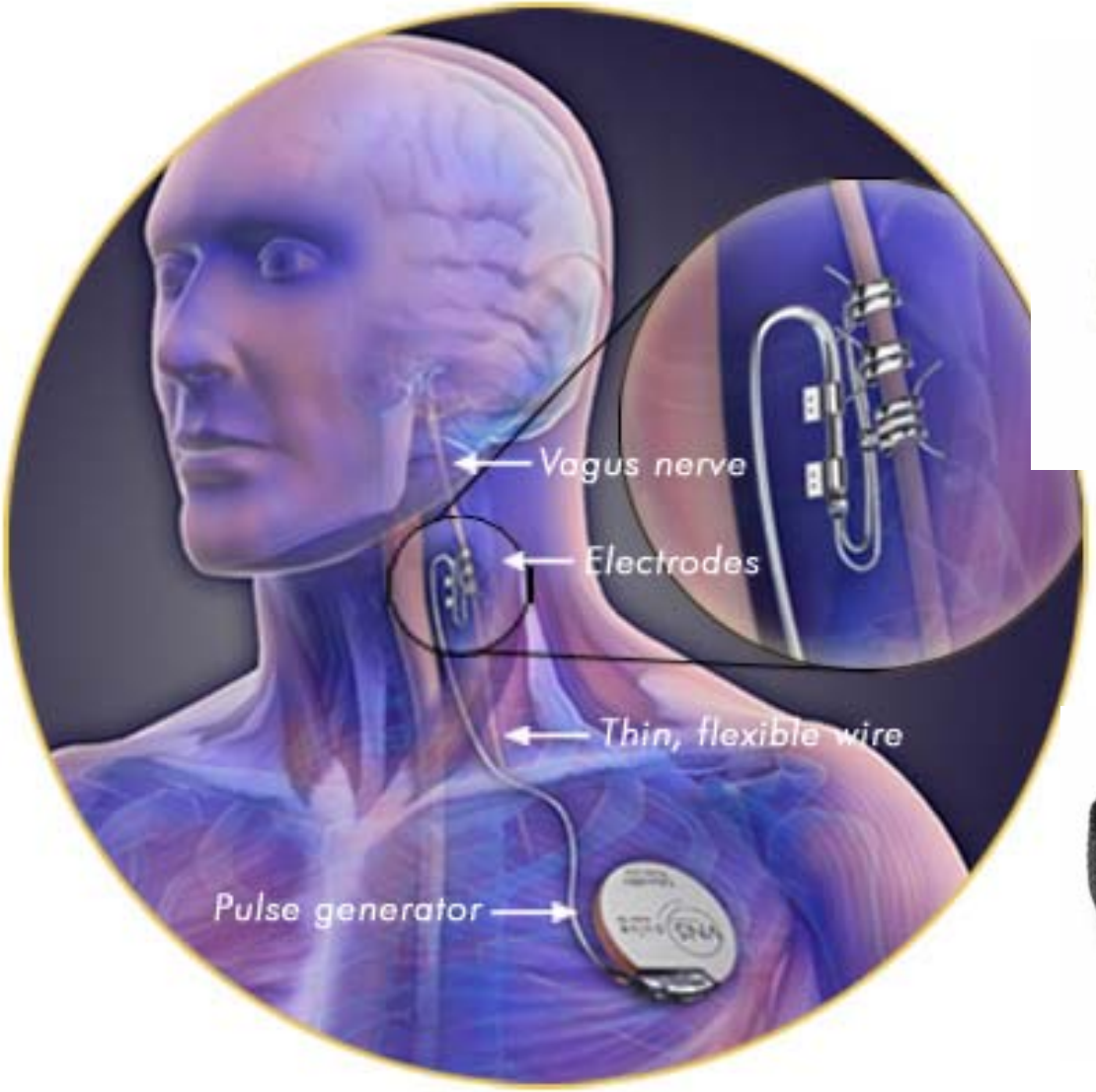
- Preliminary effective

Neurophysiologic Stimulation

Vagal nerve stimulation

- A repetitive stimulation via left vagal nerve
- beneficial effects on Sz
  - acute abortive effect
  - acute prophylaxis
  - long-term progressive prophylaxis
- proven in focal& generalized & in pediatrics

VNS device


Vagus nerve
Electrodes
Thin, flexible wire
Pulse generator

VNS device

- A device similar to a cardiac pacemaker
- Electrodes wrapped around left Vagal nerve
- A pulse generator implanted in chest wall
- Stimulation parameters are programmed
- A magnet controlled by the patient can initiate stimulation or turn off the device

Stimulation parameters

- Pulse width
- Pulse frequency
- Current intensity
- On/off cycles

<u>A typical regimen</u>

- intermittent stimulation for 30 seconds every 5 to 10 minutes

Stimulation Parameter Setting

		MEDIAN SETTINGS PED	
PARAMETER	**TYPICAL RANGE**	**3 M**	**12 M**
Output current	0.25–3.5 mA	1.25 mA	1.75 mA
Signal frequency	20–30 Hz	30 Hz	30 Hz
Pulse width	250–500 µs	500	500
Signal on time	7–270 s	30 s	30 s
Signal off time	12 s–180 min	5 min	3 min

Efficacy

- High was better than low stimulation
- Well tolerated in both high and low setting
- 50% Sz reduction = 30 - 50%
- Median Sz frequency reduced by 23 - 58% at 3 m, and 31 - 58% at 6 m
- Magnet activation reduced 40 -60% in duration and intensity of Sz

- Steven C. Schachter, Dieter Schmidt. Vagus Nerve Stimulation, 2nd Ed.
- Morris G, et al. Evidence-based guideline update: Vagus nerve stimulation for the treatment of epilepsy. Neurology 2013;81:1453–1459

Adverse effects

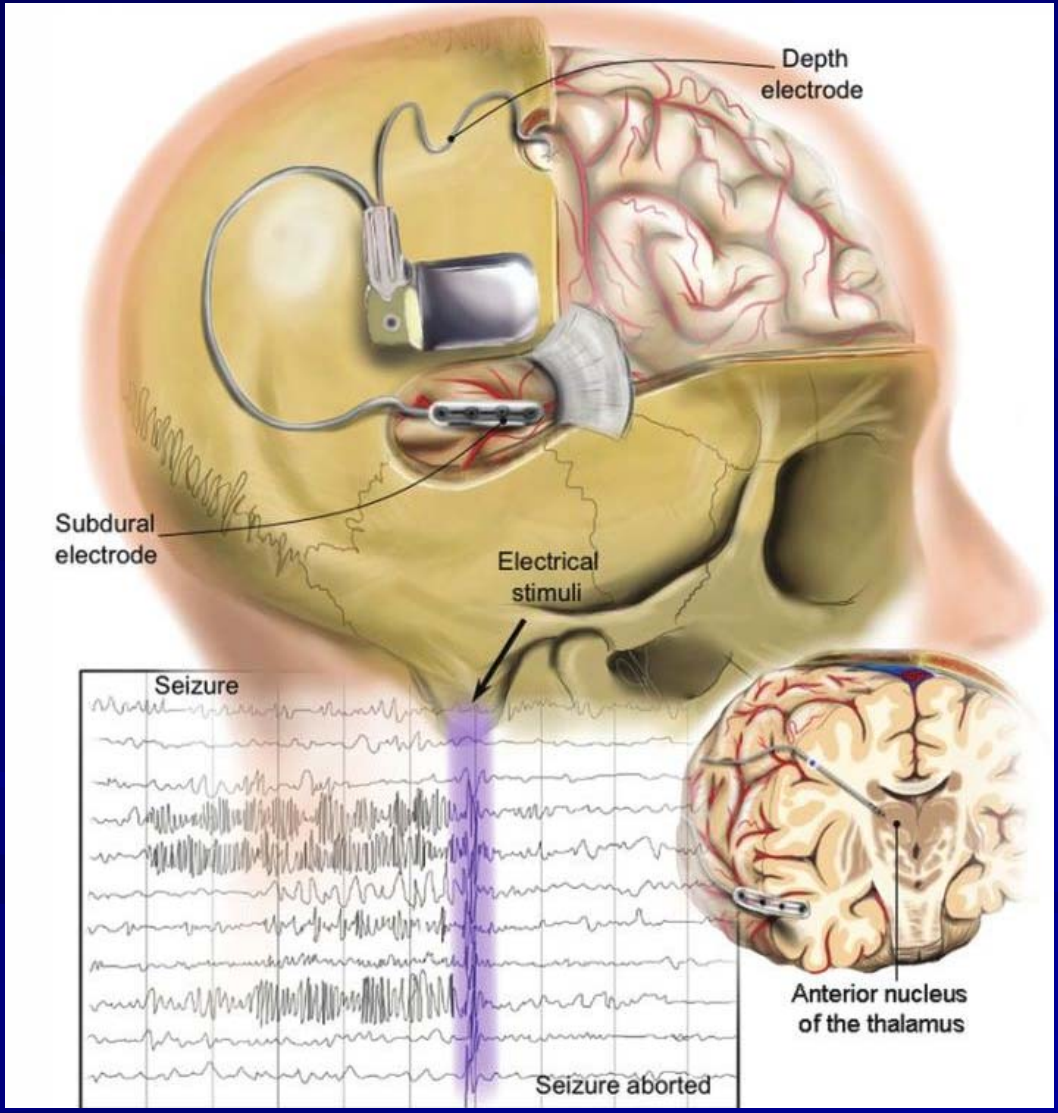
Associated with implantation

- hoarseness
- cough
- pain
- paresthesia.

Associated with stimulation

- hoarseness
- dyspnea

Responsive neuro-stimulation



- Detect & stimulate
- Subdural or depth electrode

RNS

- A Large RCT in 2014
  - 191 pt
  - active VS sham stimulation
  - followed by open-label period

→ 37.9 % VS 17.3% Sz reduction (p=0.012)

→ Sz reduction to 53% at 2 y

→ Responder rate 38% (6m), 53% (2 y)

Heck CN, King-Stephens D, Massey AD, et al. Two year seizure reduction in adults with medically intractable partial onset epilepsy treated with responsive neurostimulation: final results of the RNS® System Pivotal trial. Epilepsia 2014;55(3):432-41

Table 1. Large randomized controlled trials of brain stimulation

Authors & Year	No. of Patients	Target	Seizure Frequency Reduction Group	
			Treatment	Sham
Ben-Menachem et al., 1994	114	VNS	25%	6%
Handforth et al., 1998	196	VNS	28%	15%
Fisher et al., 2010	110	ANT	40.4%	14.5% (median)
Morrell et al., 2011	191	direct-seizure foci	37.9%	17.3%

Conclusion

- KD - proven option, good efficacy
  - need good compliance
- VNS - abortive + acute prophylatic effect
  - High cost