Other treatments: KD& VNS

Dr Krisnachai Chomtho MD DCH MRCPCH
Lecturer in pediatric neurology
King Chulalongkorn Memorial Hospital

Pharmocologic Rx

- 1st drug response - 47%
- 2nd & 3rd drug response - 14%
- Polytherapy response - 3%

- Many are intractable
- Uncontrolled by 2 drugs at proper dose

Kwan, P. and M.J. Brodie, *Early identification of refractory epilepsy.* N Engl J Med, 2000. **342**(5): p. 314-9.

Surgical options

- Possible cure

- Not all are surgical candidates
- Surgical risk
- Limited centers
- High cost

Dietary options

- Ketogenic diet (KD)
  - LCT
  - MCT

- Modified Atkins *
- low GI diet *

* satisfactory preliminary result

Neuromodulations

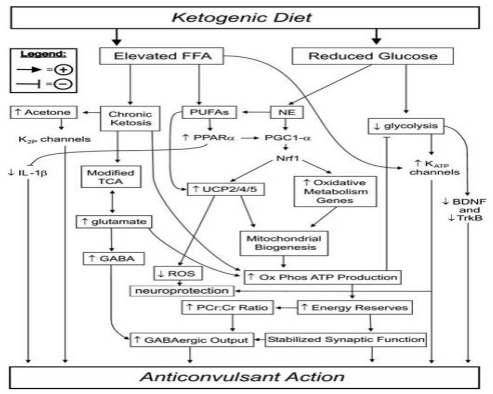
- Vagal nerve stimulation (VNS)

- Deep brain stimulation (DBS) *
- Responsive neuro-stimulation (RNS) *
- External Trigeminal Nerve Stimulation * (eTNS)
- Transcranial magnetic stimulation * (TNS)

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

Diet Rx in adults

- KD & MAD
- Adolescents & adults
- Study type:
  - small prospective, open label (11 adults)
  - retrospective
- 47 - 85 % → > 50% Sz reduction

Kossoff EH et al., A prospective study of the modified Atkins diet for intractable epilepsy in adults. Epilepsia 49:316–319.
Mady et al., The ketogenic diet: adolescents can do it, too. Epilepsia 44:847–851.
Sirven et al., The ketogenic diet for intractable epilepsy in adults: preliminary results. *Epilepsia 40:1721–1726.*

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

*Eric H. Kossoff, †Beth A. Zupec-Kania, ‡Per E. Amark, §Karen R. Ballaban-Gil, ¶A. G. Christina Bergqvist, #Robyn Blackford, **Jeffrey R. Buchhalter, ††Roberto H. Caraballo, ‡‡J. Helen Cross, §§Maria G. Dahlin, §§Elizabeth J. Donner, ¶¶Joerg Klepper, §Rana S. Jehle, ##Heung Dong Kim, §§Y. M. Christiana Liu, ***Judy Nation, #Douglas R. Nordli, Jr., †††Heidi H. Pfeifer, ‡‡‡Jong M. Rho, §§§Carl E. Stafstrom, †††Elizabeth A. Thiele, *Zahava Turner, ¶¶¶Elaine C. Wirrell, ###James W. Wheless, ****Pierangelo Veggiotti, *Eileen P. G. Vining and The Charlie Foundation, and the Practice Committee of the Child Neurology Society

- International Ketogenic Diet Study Group
- 26 ped epileptologists & dietitian (9 countries)
- standardized protocol

Practical approach*

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

Indications

- Intractable epilepsy (any age, Sz type)

Specific for

- Glucose transporter 1 (GLUT1) deficiency
- Pyruvate dehydrogenase deficiency
- Essential energy for brain
- Treat - seizures
  - non-epileptic symptoms

GLUT1 deficiency

- GLUT1 protein
- transfers glucose from blood to CSF

- Low CSF glucose, normal plasma glucose
- No other cause (CNS infection/ SAH)

- Intractable Sz, MR, movement disorder
- Ketone → main energy source

PDHD deficiency

- Mitochondrial dysfunction
- Lactic acidosis
- "Pyruvate-to-Acetyl CoA" defect
- Intractable Sz

- Ketone → bypass to TCA cycle

Particular benefit in*

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

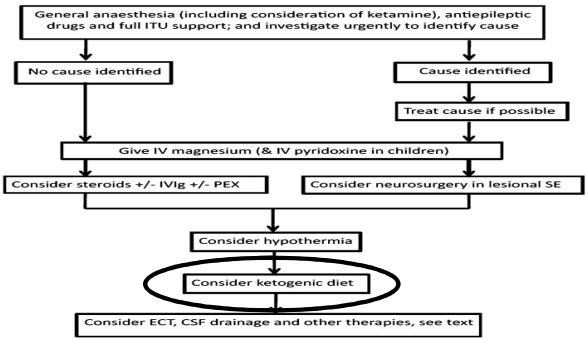
Recent indication

- Super refractory status epilepticus
  - status epilepticus
  - continues or recurs
  - despite general anesthesia Rx for 24 h

- 20 cases report (no RCT yet)

S. Shorvon and M. Ferlisi, The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. Brain 2011: p1-17

Super refractory SE



S. Shorvon and M. Ferlisi, The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. Brain 2011: p1-17

Absolute Contraindication

- PrimaryC arnitine def
- Carnitine palmitoyl transferase (CPT) def
- Carnitine translocase def
- β-oxidation defects
- MCAD/ LCAD/ SCAD
- Long-chain 3-hydroxyacyl-CoA def
- Medium-chain 3-hydroxyacyl-CoA def
- Pyruvate carboxylase def
- Porphyria

Fatty acid transport & oxidation defect

Pre-KD evaluation*

- Counseling
- Sz assessment
- Nutritional evaluation
- Lab evaluation

Available formulas*

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

Diet route

- Bottle feed / normal food / tube feed

Classical KD

- Widely used
- 4: 1 ratio of fat: protein - carbohydrate
- Main fat source = LCT

- Adequate protein > 1 g/kg
- Low carb - just to prevent hypoglycemia

- Calorie control = 75 - 100% requirement
- Fluid restriction - not necessary

Classical diet

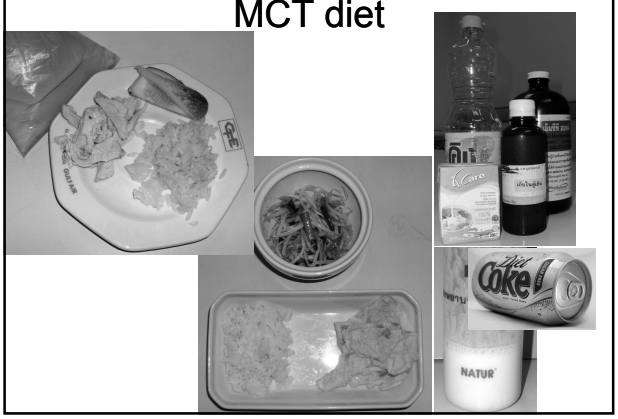
MCT KD

- Increasingly used→ better ketosis
- 30%-60% fat: total energy

- More carbohydrate allowance
- Less restrictive, bigger meal
- Similar efficacy to LCT

- MCT can't be cooked → not palatable

MCT diet



Examples LCT

- 6-year old girl, BW 20 kg
  - 1400 kcal/day, 24 gm protein (1.2 g/kg/day)
  - Classic 3:1 = 135 gm fat: 46 gm prot+carb

→ 22 gm carb /day !!

Examples MCT

- 6-year old girl, BW 20 kg
  - 1400 kcal/day, 24 gm protein (1.2 g/kg/day)
  - MCT 50% total calories = 84 g/day
  - Protein ~ 7% Carb ~ 15% = 53 g/day
  - LCT ~ 28% = 44 g/day
  - K:AK 1.66:1

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

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

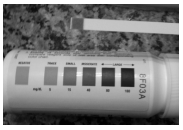
Ketosis induction

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

Bergqvist, A.G., et al., *Fasting versus gradual initiation of the ketogenic diet: a prospective, randomized clinical trial of efficacy.* Epilepsia, 2005. **46**(11): p. 1810-9.

Maintenance phase

- Efficacy evaluation after 3 month
- Neuro
  - seizure control
  - cognitive improvement
- urine ketone - compliance
- serum ketone - Sz control



Maintenance*

- GI & nutritional assessment
- Blood tests
- Supplements
- Oral citrate
- Adverse effects
- Sick rules

Sick rules

ข้อแนะนำเมื่อมีอาการป่วย

1. แจ้งแพทย์ และแสดงบันทึกนี้ทุกครั้ง
2. งดการให้ยาน้ำเชื่อมทุกชนิด
3. หลีกเลี่ยงยาเม็ดและยาฉีดที่มีส่วนผสมของน้ำตาล แอลกอฮอล์ และ แป้ง ในจำนวนสูง
4. หลีกเลี่ยงการให้น้ำเกลือ ถ้าจำเป็นต้องให้ห้ามให้น้ำเกลือชนิดที่มีน้ำตาลผสมอยู่
5. จำกัดปริมาณน้ำตามที่กำหนดไว้ในแต่ละวัน
6. ถ้ามีการเสียน้ำ เช่น อาเจียน ท้องเสีย เพิ่มปริมาณน้ำได้ชั่วคราวตามเหมาะสม
7. ถ้าป่วยหนัก จำเป็นต้องนอนโรงพยาบาล ควรตรวจน้ำตาลในเลือดตามเหมาะสม

* ถ้ามีข้อสงสัย ติดต่อ pediatric neurology fellow รพ. จุฬาลงกรณ์ 022564996 ต่อ 130

บันทึกการชัก

ผู้ป่วย ketogenic diet

ภาควิชากุมาร รพ. จุฬาลงกรณ์

ชื่อ .....

HN .....

สูตรอาหาร .....

วันที่เริ่ม .....

Diagnosis .....

.....

.....

.....

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.

Draw back*

- Family - Difficult recipe
- Patient - Limited meal

Options
- MAD
- LGIT

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

Modified Atkins

- Similar composition to classical KD
- 1: 1 ketogenic ratio
- Restrict carbohydrate (10-20 g/d)
- No limit on protein, fluids, and calories
- Easier meal planning

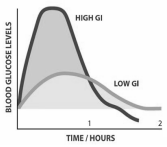
- Preliminary effective

Kossoff et al. Epilepsy Behav 2007:432–436.

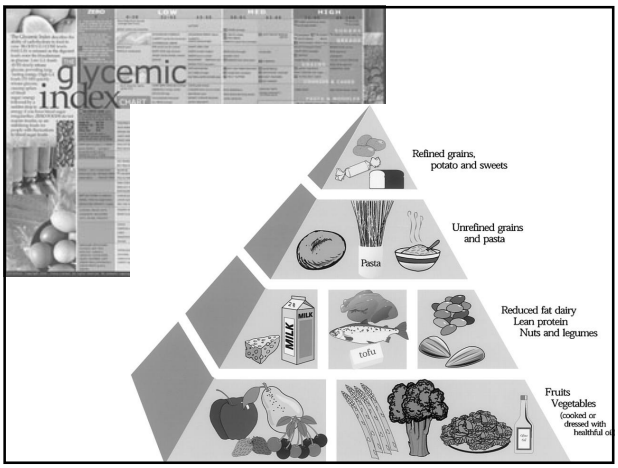
Low GI

- Less fat than KD
- More carbohydrate 40–60 g/day
- CHO type → low glycemic index <50
- e.g.lentils, grapefruit, whole grain bread

- Less ketone level than KD
- Still preliminary effective



Pfeifer and Thiele. Neurology 2005:65:1810–1812.



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

- similar to a cardiac pacemaker
- Electrodes around left Vagal nerve
- A pulse generator in chest wall

- Stimulation parameters are programmed

- A magnet controlled by the patient
  → initiate stimulation

VNS device

http://us.cyberonics.com/en/vns-therapy-for-epilepsy/healthcare-professionals/vns-therapy/about-products/

Stimulation parameters

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

A typical regimen

- intermittent stimulation for 30 seconds every 5 to 10 minutes

http://us.cyberonics.com/en/vns-therapy-for-epilepsy/healthcare-professionals/vns-therapy/about-products/

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

Adverse effects

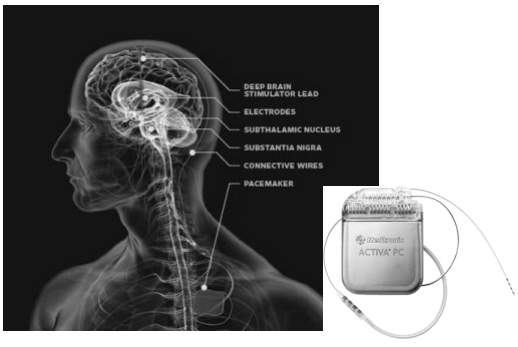
Associated with implantation

- hoarseness
- cough
- pain
- paresthesia.

Associated with stimulation

- hoarseness
- dyspnea

Deep brain stimulation



Deep brain stimulation

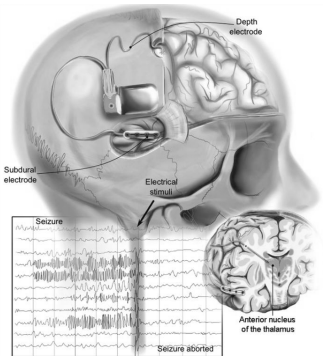
- Disrupts regulatory feedback loops
- Closed-loop, continuous stimulation

- VNS disrupts the loops indirectly
- DBS disrupts the loops directly.

Deep brain stimulation

- Different stimulation targets being studied
- Several small studies - good efficacy
- A Large RCT in 2010 (SANTE)
  - 110 pt
  - Anterior Nucleus of the Thalamus
  - 40- 60% decrease in median Sz frequency in 1 & 2 y

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)

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%

eTNS

eTNS

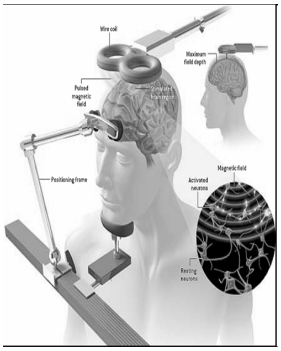
- Non-invasive
- 12 h during sleep
- An RCT in 2013
  - 50 pt →18 wk
  - 50% Sz reduction in 40% (p=0.78)

Phase III- ongoing

Table. Trigeminal Nerve Stimulation: Major Results

Endpoint	Treatment	Control	Significance
Median change in number of seizures per month	-1.4	-0.5	*P* within group, .10; between groups, .51
50% responder rate at 18 weeks (%)	40.5	15.6	*P* within group, .0136; between groups, .078
50% responder rate, entire treatment period (%)	30.2	21.1	*P* between groups, .31; odds ratio, 1.73
Time to fourth seizure at baseline (d)	12.5	23	
Time to fourth seizure with treatment (d)	15.0	18	
Seizure frequency, response ratio	-13.9	-9.0	*P* within group, .04; between groups, .06
Change in Beck Depression Inventory score	-8.13	-3.95	*P* within and between groups, 0.02; odds ratio for remission, 5.5 (*P* = .002)

Transcranial megnetic stimulation



rTMS

- brief, high-current magnetic pulse
- Low frequency decrease cortical excitability
- rapid-rate can induce a seizure

rTMS

- small non-RCT
- Only 1 small RCT
- decrease Sz frequency & interictal discharges
- Some showed controversial results
- More large, well designed studies required

Conclusion

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

<u>Investigational Rx</u> (need further evidence)

- Mod Atkins - easy, palatable, (effective)
- RNS - (effective)
- DBS - (effective) but inconsistent implant site
- TMS, eTNS - inconsistent efficacy so far