Other treatments: KD& VNS

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EPILEPSY

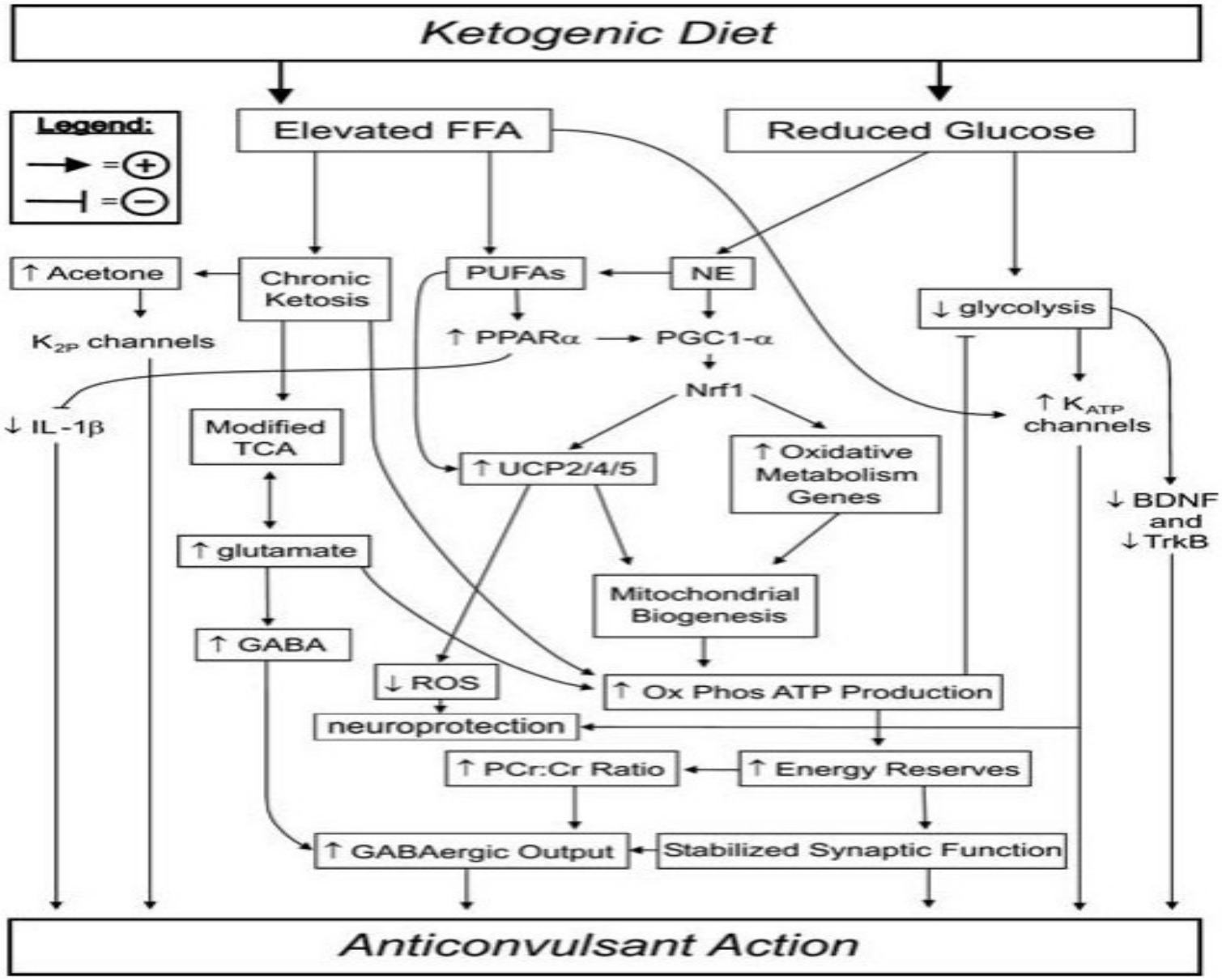
- 1/3 remain resistant.
- Ketogenic diet offer an effective alternation for children and adult with drug resistant epilepsies.

Elia M, Klepper J, Leiendecker B, Hartmann H. Ketogenic diets in the treatment of epilepsy. Curr Pharm Des. 2017 Aug 9

Ketogenic diet (KD)*

- High fat
- Low carbohydrate
- Calorie control
- Adequate protein
- Therapeutic diet for epilepsy
- As effective as an AED or VNS

Elia M, Klepper J, Leiendecker B, Hartmann H. Ketogenic diets in the treatment of epilepsy. Curr Pharm Des. 2017 Aug 9



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

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
- Dravet syndrome
- Infantile spasms
- Lennox Gastaut Syndrome
- Myoclonic-astatic epilepsy
- Rett syndrome
- infants or enterally fed patients

Epilepsia, 52(Suppl. 2):83–89, 2011
doi: 10.1111/j.1528-1167.2011.03010.x

DRAVET SYNDROME

The ketogenic diet for Dravet syndrome and other epileptic encephalopathies: An Italian consensus

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Summary

Ketogenic diet is a nonpharmacologic treatment for childhood epilepsy not amenable to drugs. At the present time, two works based on national research, one in Germany and one in the United States provide international guidelines to ensure a correct management of the ketogenic diet. Our Italian collaborative study group was set up in order to formulate a consensus statement regarding the clinical management of the ketogenic diet, patient selection, pre–ketogenic diet, counseling, setting and enforcement of dietary induction of ketosis, follow-up management, and eventual discontinuation of the diet.

KEY WORDS: Ketogenic diet, Clinical management, Drug-resistant epilepsy.

DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY ORIGINAL ARTICLE

Efficacy of the ketogenic diet in Lennox–Gastaut syndrome: a retrospective review of one institution's experience and summary of the literature

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This article is commented on by Cross on pages 394–395 of this issue.

PUBLICATION DATA
Accepted for publication 21st December 2011.
Published online 22nd March 2012.

ABBREVIATION
LGS Lennox–Gastaut syndrome

AIM To determine the efficacy of the ketogenic diet for children with Lennox–Gastaut syndrome (LGS) at our institution and in the literature.
METHOD The records of children with LGS initiated on the ketogenic diet at our institution from 1994 to 2010 were reviewed. Inclusion criteria included the presence of ≤2.5Hz spike-and-wave complexes on electroencephalogram, multiple seizure types including tonic, atonic, or atypical absence, developmental delay, and age under 1 year. We additionally reviewed the literature for cases of LGS treated with the ketogenic diet and their outcomes.
RESULTS Seventy-one children (41 males, 30 females, median age 3y 6mo, range 18mo–18y), with LGS were initiated on the ketogenic diet. Using an intent-to-treat analysis, after 6 months, 36 (51%) achieved more than 50% seizure reduction, 16 (23%) experienced more than 90% seizure reduction, and 1 (1%) achieved seizure freedom. Results were similar after 12 months. Age, sex, side effects, valproate use, and history of infantile spasms were not predictive of more than 90% seizure reduction. In the literature, 88 of 189 (47%) children with LGS had more than 50% seizure reduction after 3 to 36 months of ketogenic diet treatment.
INTERPRETATION The ketogenic diet is efficacious in the treatment of LGS, with approximately one-half of children responding at 12 months.

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
- ß-oxidation defects
- MCAD/ LCAD/ SCAD

lipid metabolism defect

Absolute Contraindication

- Long-chain 3-hydroxy acyl-CoA deficiency
- Medium-chain 3-hydroxy acyl-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)

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 ,3:1 ratio of fat: protein - carbohydrate
- Low carb - just to prevent hypoglycemia
- Calorie control = 80 - 100% requirement
- Adequate protein
- Fluid restriction - not necessary

TABLE 1.

Typical Ketogenic Diet Plan at a 3:1 Ratio[a] for a 5-Year-Old Patient

7:30 am Breakfast

70 g Heavy whipping cream[b]
20 g Strawberries, cantaloupe, or pineapple
40 g Scrambled eggs
4 g American cheese
8 g Butter

10 am Snack

27 g Heavy whipping cream[c]
17 g Strawberries, cantaloupe, or pineapple

12 pm Lunch[d]

70 g Heavy whipping cream[e]
20 g Cooked broccoli, green beans, or carrots
21 g Beef patty
7 g American cheese
7 g Melted butter (pour over vegetables)

3 pm Snack

27 g Heavy whipping cream[c]
90 g Sugar-free gelatin dessert

5:30 pm Dinner[d]

70 g Heavy whipping cream[e]
15 g Cooked broccoli, green beans, or carrots
19 g Grilled or baked chicken breast (no skin)
6 g American cheese
11 g Mayonnaise

[a]Ratio of fat to carbohydrate and/or protein.
[b]Whip the cream then weigh. Melt butter and mix with eggs, then make an omelet with cheese. Serve with water.
[c]Whip then weigh heavy whipping cream. Serve cream in a cup with lid and straw, and water.
[d]Serve with water, salt, and pepper
[e]Measure in milliliters and serve as a beverage.

Luat AF, Coyle L, Kamat D
The Ketogenic Diet: A Practical Guide for Pediatricians. Pediatr Ann. 2016 Dec 1;45(12):e446-e450

MCT KD*

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

- MCT : more palatable

Trauner DA (1985) Medium-chain triglyceride (MCT) diet in intractable seizure disorders. Neurology 35:237–238

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

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)

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

- More suitable for adult

Schoeler NE, Cross H (2016)
Ketogenic dietary therapies in adults with epilepsy: a practical guide.
Pract Neurol 16:208–214

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

VIEWS & REVIEWS

Dietary treatment in adults with refractory epilepsy

A review

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Ivana Tyrlikova, MD
Gregory C. Mathews, MD, PhD

Correspondence to Dr. Klein: kleinp@epilepsydc.com

ABSTRACT

We review adjunctive ketogenic diet (KD) and modified Atkins diet (MAD) treatment of refractory epilepsy in adults. Only a few studies have been published, all open-label. Because of the disparate, uncontrolled nature of the studies, we analyzed all studies individually, without a meta-analysis. Across all studies, 32% of KD-treated and 29% of MAD-treated patients achieved ≥50% seizure reduction, including 9% and 5%, respectively, of patients with >90% seizure frequency reduction. The effect persists long term, but, unlike in children, may not outlast treatment. The 3:1 and 4:1 [fat]:[carbohydrate + protein] ratio KD variants and MAD are similarly effective. The anticonvulsant effect occurs quickly with both diets, within days to weeks. Side effects of both diets are benign and similar. The most serious, hyperlipidemia, reverses with treatment discontinuation. The most common, weight loss, may be advantageous in patients with obesity. Potential barriers to large-scale use of both diets in adults include low rate of diet acceptance and high rates of diet discontinuation. The eligible screened/enrolled subject ratios ranged from 2.9 to 7.2. Fifty-one percent of KD-treated and 42% of MAD-treated patients

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

- 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

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

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

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

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

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

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

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

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

Conclusion

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