Workshop
Ketogenic diets

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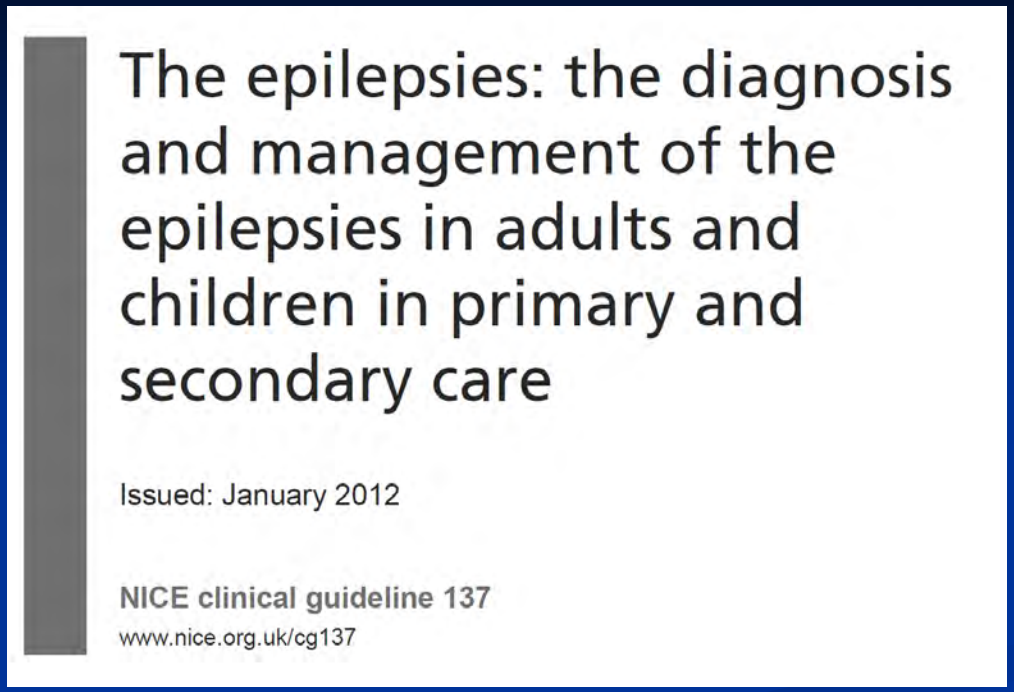


1.12 Ketogenic diet

1.12.1 Refer children and young people with epilepsy whose seizures have not responded to appropriate AEDs to a tertiary paediatric epilepsy specialist for consideration of the use of a ketogenic diet. **[new 2012]**

History

- Fasting suppresses seizure activity:
  - Conklin (*J Am Osteopatic Assoc 1922;26:11-14)*
    Early reports of improving seizure control
    'patient deprived of food……up to 25 days'

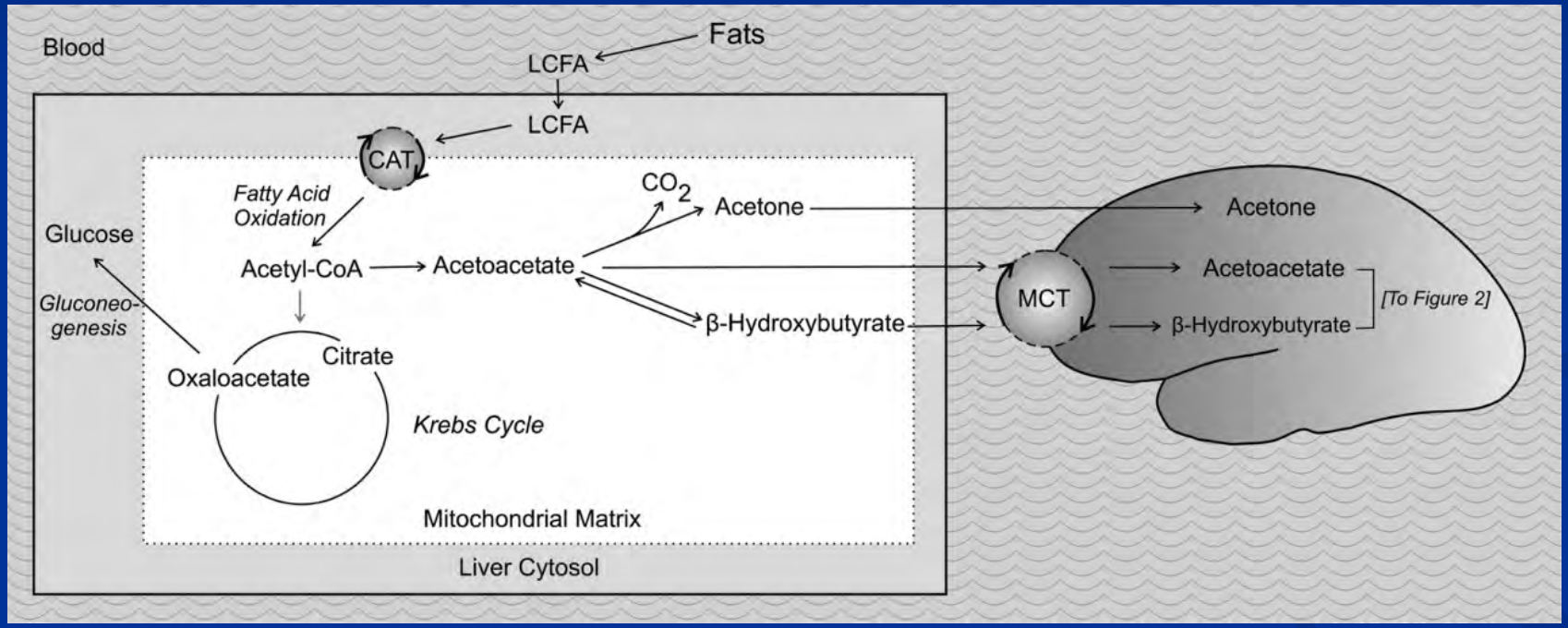
- Discovery of the ketogenic Diet:
  - Wilder (Mayo Clinic Bulletin 1921;2:307)
    '..benefits of fasting could be obtained if **ketonemia was produced by other means** [..] **diets which are rich in fats and low in carbohydrates'**

  - Peterman (Am J Dis Child 1924;28:28-33):
    Calculation and of the proposed ketogenic diet:
    17 patients: 10 seizure free, 4 marked improvement

History

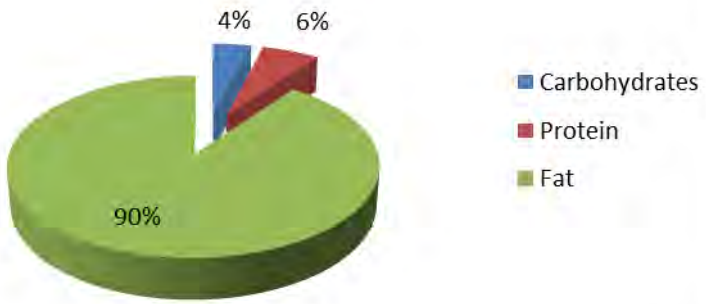
- Medium-chain triglyceride oil (MCT)
  - Huttenlocher *Neurology 1971: 21:1097-1103*
    Classical diet 'unpalatable'
    Medium chain triglyceride oil more ketogenic per calorie, permitted greater allowance of carbohydrates, protein proportion

Ketogenic Diet
High fat , low carbohydrates (Glucose)

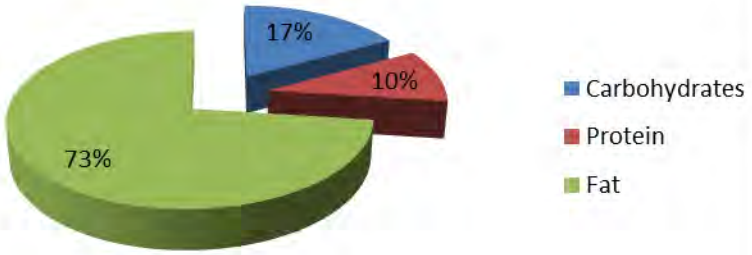


Hartman et al, Ped Neurol, 2007

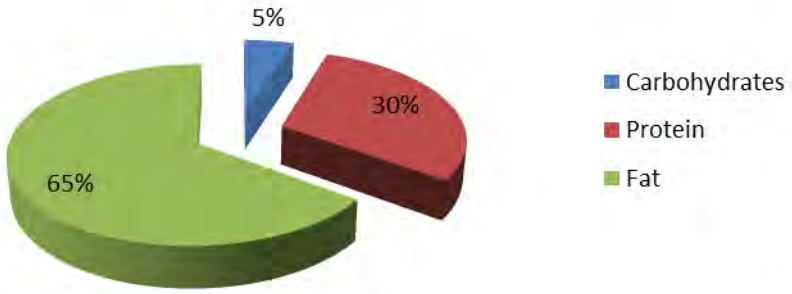
Classical Ketogenic Diet 4:1 ratio (LCT)



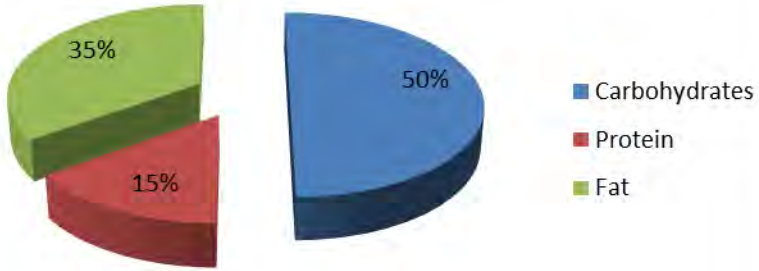
MCT Ketogenic Diet



Modified Atkins Diet (1:1 ratio)



Normal Diet

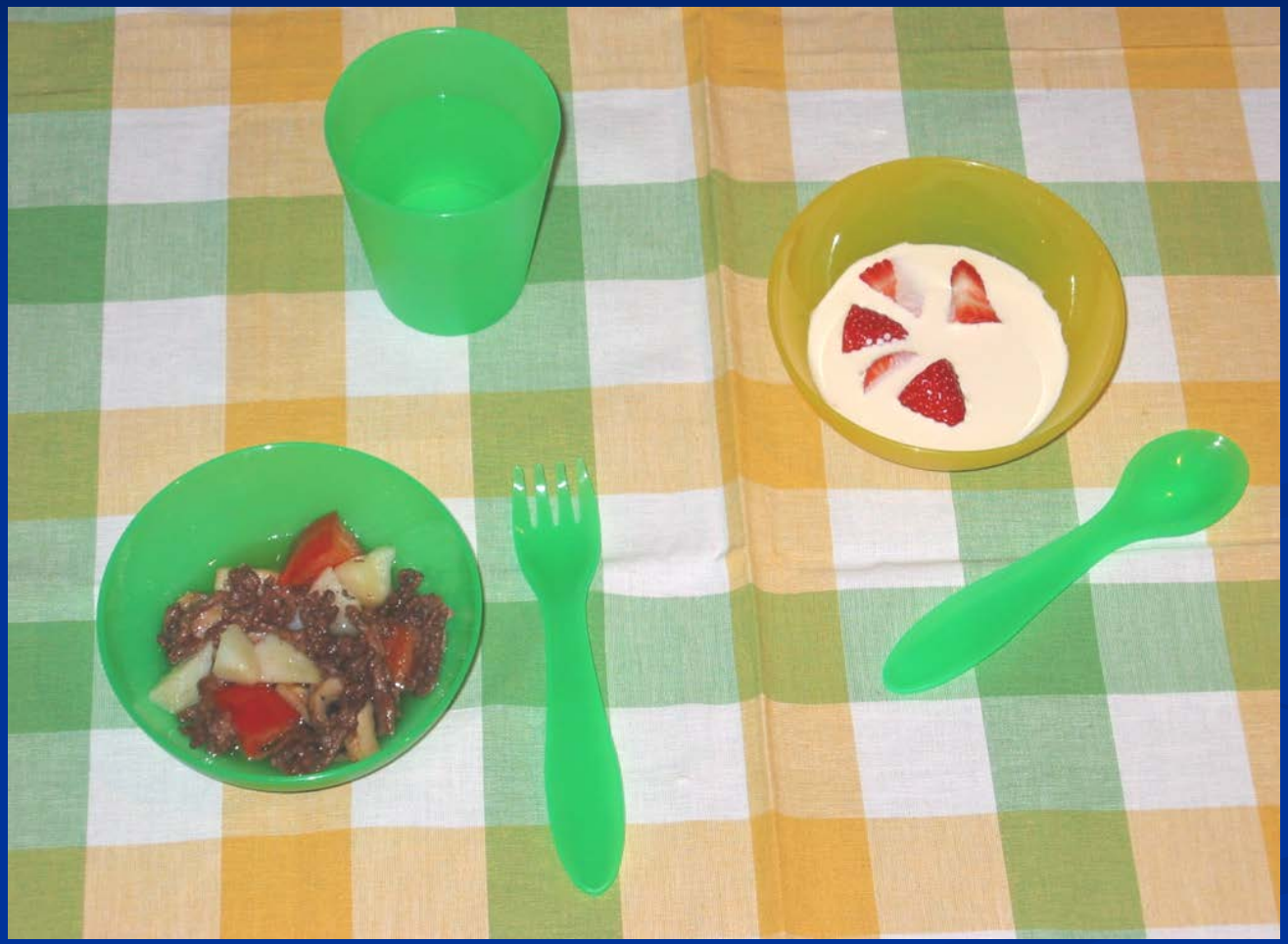


E. Neal, 2012
Dietary Treatment of Epilepsy, Wiley-Blackell

Types of the KD

- Classical Diet:
  - Composition of meals :
    3:1 or 4:1 fat : (carbohydrate + protein ratio)
  - 90% of total calories from fat
  - Strict meal/snack recipes, all in correct ratio
- MCT Diet:
  - 40-60% of daily calorie intake as MCT oil / MCT liquigen (overall 73% fat)
  - Greater choice of foods – less carbohydrate restricted (15-20% of total calories)

Example of a classical diet



330 calorie meal

23g minced beef
30g mushrooms
20g tomato
17g oil

Dessert

15g strawberries
25g double cream

Example of an MCT diet

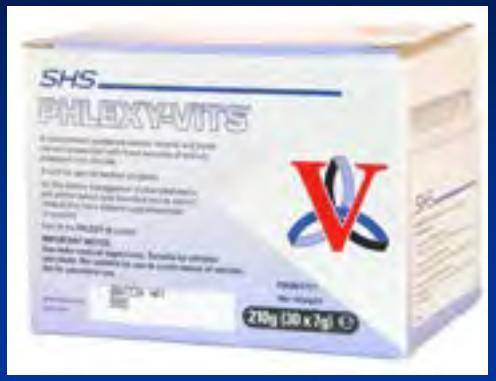
<u>330 calorie meal</u>
32g minced beef
40g potato
15g mushrooms
35g tomato
10g MCT oil
5g olive oil

<u>Dessert</u>
20g strawberries
21g Liquigen
in sugar free jelly

THE CHARLIE FOUNDATION
TO HELP CURE PEDIATRIC EPILEPSY

MATTHEW'S FRIENDS
The Ketogenic Diet
A Brighter Future For Childhood Epilepsy

- Supplements
  - Vitamin, minerals and trace elements



- Feeding by PEG or nasogastric tube
  - Ketocal – complete 4:1 ratio feed

Modified Atkins diet (MAD)

- Carbohydrate restriction (10-20g/day)
- Encourages consumption of high fat food
- No limit on proteins
- (No limit on total calories)
- Fat : (carbohydrate + fat) 1:1 ratio
- 65% fat, 30% protein, 7% carbohydrates

Case

FB age 20 months

- Background:
  - uncomplicated pregnancy
  - Birth: failed instrumental delivery, emergency CS, left parietal bone fracture, subdural + subarachnoid haemorrhage, apnoeic at birth, resuscitated and ventilated, day 1 right motor focal seizures, controlled with PHB
  - Age 4 m: seizure recurrence, asymmetric tonic spasms in clusters (Tx: CBZ, Val)
  - Age 7 m – more symmetrical infantile spasms
    Tx: Prednisolone – remission for 4 months
  - Age 15 m: sz recurrence: tonic sz (rt arm and trunk stiffening), clusters of epileptic spasms daily (tx Val)

FB

- Other information:
  - Global developmental delay – pulling up to kneeling in cot, not walking, pre-verbal language
  - Right spastic hemiplegia, cortical visual impairment
  - Brain MRI: parenchymal injury (contusions left parietal, also right sided hemispheric involvement)
  - EEG: multifocal discharges, tonic sz and epileptic spasms documented
  - Fed orally , general heath good
- Question:
  - Which treatment options would you discuss at this point ?

Parent's question:

- Does the KD work ?
- What are her chances to respond ?

Animal seizure models

Table 1. Anticonvulsant effects of ketogenic diets in mice

Model	Mouse strain	KD composition	Efficacy of the KD	Reference
Maximal electroshock	CD1	2.5:1	y	Uhlemann and Nelms, 1972
	DDY	2.8:1	y	Nakazawa et al., 1983
	C57BL/6	6.3:1 (8.6:1[a])	y	Martillotti et al., 2006
6 Hz model	NIH Swiss	6.3:1 (8.6:1[a])	y	Hartman et al., 2008
	CD1	4:1[b]	y/n	Samala et al., 2008
	CD1	6:1[b]	y	
Fluorothyl	C3H	4:1	y	Rho et al., 1999
	129 x C57BL/6	4:1	y	Szot et al., 2001
	CD1	4:1[b]	n	Samala et al., 2008
	CD1	6:1[b]	y/n	
Kainate	ICR	4:1	y	Noh et al., 2003
	C3H	4:1[b]	n	Samala et al., 2008
Pentylenetetrazole	CD1	4:1[b,c], 6:1[b,c]	n	Samala et al., 2008
Spontaneous seizures	EL mice	4.75:1	y	Todorova et al., 2000
	EL mice	5.3:1[c,d]	y	Mantis et al., 2004

Efficacy (y, yes; n, no) of the KD in different mouse seizure models. Experimental details, such as the mouse strains and the KD composition (parts of fat relative to parts of protein + carbohydrate on a weight basis) are indicated.

[a]F3666 diet (8.6:1 according to its datasheet), [b]balanced control and ketogenic diets, [c]calorically restricted diet, [d]note that calorie restriction by itself protected against seizures. y/n denotes seizure protection in some experiments, but not all.

Borges K, Epilepsia 2008; 49suppl8:64-66

Efficacy in childhood epilepsy

D Keene Ped Neurol 2006;35:1-5
A systematic review

- 26 studies;14 met criteria for inclusion
- Outcome measures degree of seizure control, duration patient remained on diet, occurrence of adverse events
- Total collective population N=972
- At 6m
  - 15.6% (CI 10.4-20.8) seizure free
  - 33.0% (CI 24-41.8) >50% reduction

Efficacy in childhood epilepsy

Table 1. Efficacy of ketogenic diet 6 months after initiation

Author	Diet Fast	Design	Total Sample	% Sample at 6 Months	% Seizure -Free*	% Greater Than 50% Reduction*
DiMario [2]	y	R	48	50	8	35
Coppola [3]	y	R	56	38	7	20
Maydell [4]	y	R	146	66	16	12
Hassan [5]	y	R	53	39	11	26
Kankirawatana [6]	y	R	35	57	17	40
Kang [7]	y	R	199	61	33	58
Nordli [8]	y	R	32	66	19	22
Vining [9]	y	P	51	69	12	53
Freeman [10]	y	P	150	77	3	51
Kossoff [11]	y	R	23	78	17	55
Kinsman [12]	y	R	58	?	29	38
Ruthenstein [13]	y	R	13	77	6	15
Lion François [14]	y	R	29	?	10	35
Wirrell [15]	n	R	14	86	14	14
Vaisleib [16]	n	R	65	100	32	22

Response rates – percentages based on initial sample size

Keene D, Pediatr Neurology, 2006; 35, 1-5

Table 2. Time patient remains on ketogenic diet

Author	Total Sample	% Sample at 3 Months	% Sample at 6 Months	% Sample at 12 Months
DiMario [2]	48	?	50	37
Coppola [3]	56	75	38	7
Maydell [4]	147	80	66	48
Hassan [5]	52	68	39	13
Kankirawatana [6]	35	62	57	12
Kang [7]	199	88	61	27
Vining [9]	51	88	69	47
Freeman [10]	150	83	71	55
Ruthenstein [13]	13	85	77	50
Kossoff [11]	23	91	78	56

Keene D, Pediatr Neurology, 2006; 35, 1-5

Efficacy - longterm

Freeman et al 1998, Hemingway et al 2001

TABLE 1. Long-Term Outcomes of the Original 150 Patients After Initiating the Ketogenic Diet

Time on the Diet	Number on Diet 150 (100%)	Discontinued	Current Seizure Status (Patients Initially Averaged 410 Seizures/Month)			
			Seizure-Free	90%–99%	50%–90%	<50%
<3 mo	125 (83%)	25 (17%)*†	—	—	—	—
3–6 mo	106 (71%)	19 (11%)*†	5	43	29	29
At 12 mo	83 (55%)	67 (45%)*	11/150 (7%)	30/150 (20%)	33/150 (22%)	9/150 (6%)
12–24 mo	58 (39%)	25 (17%)†				
24–36 mo	30 (20%)	28 (19%)				
36–48 mo	19 (13%)	11 (7%)				
>48 mo	15 (10%)	4 (3%)	20/150 (13%) 1 on diet	21/150 (14%) 8 on diet	24/150 (16%) 4 on diet	18/150 (12%) 2 on diet

* Time on the diet of a patient who subsequently died; no one died while on the diet.
† Time of last contact before child moved out of the country or was lost to follow-up.

Seizure improvement continued after coming of the diet

? KD disease modifying effect or

? Natural progress of epilepsy (relapsing and remitting)

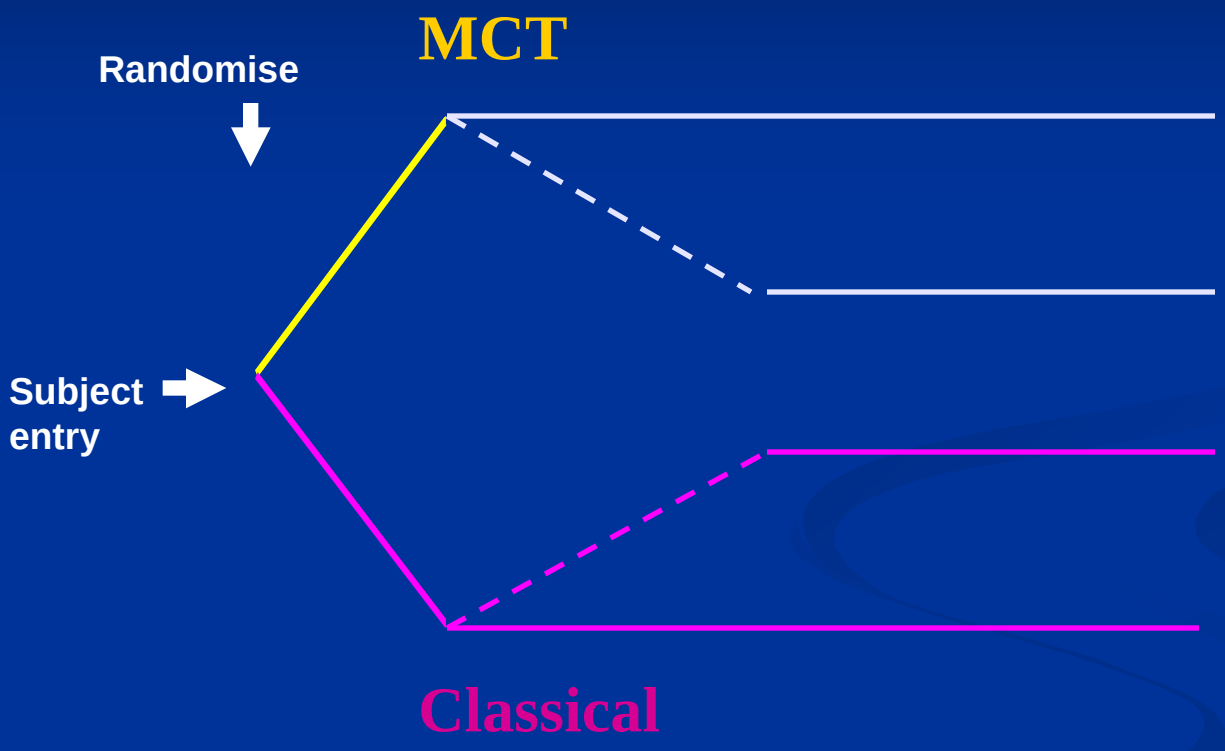
The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial

Elizabeth G Neal, Hannah Chaffe, Ruby H Schwartz, Margaret S Lawson, Nicole Edwards, Geogianna Fitzsimmons, Andrea Whitney, J Helen Cross

Lancet Neurology, 2008;7(6): pp 500-506

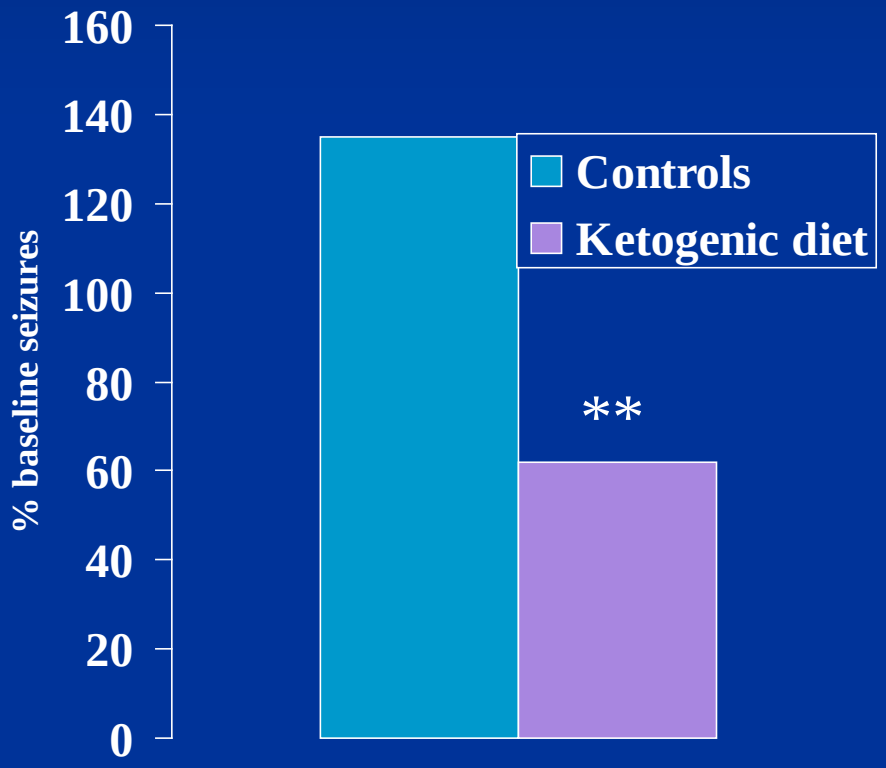
- Comparing
  - seizure control in children (2-16 years) on the KD against control group (not on diet)
  - the classical type and MCT type

Randomised controlled trial



Neal et al 2007

After 3 months



**Diet vs control p<0.001

50% reduction in seizures

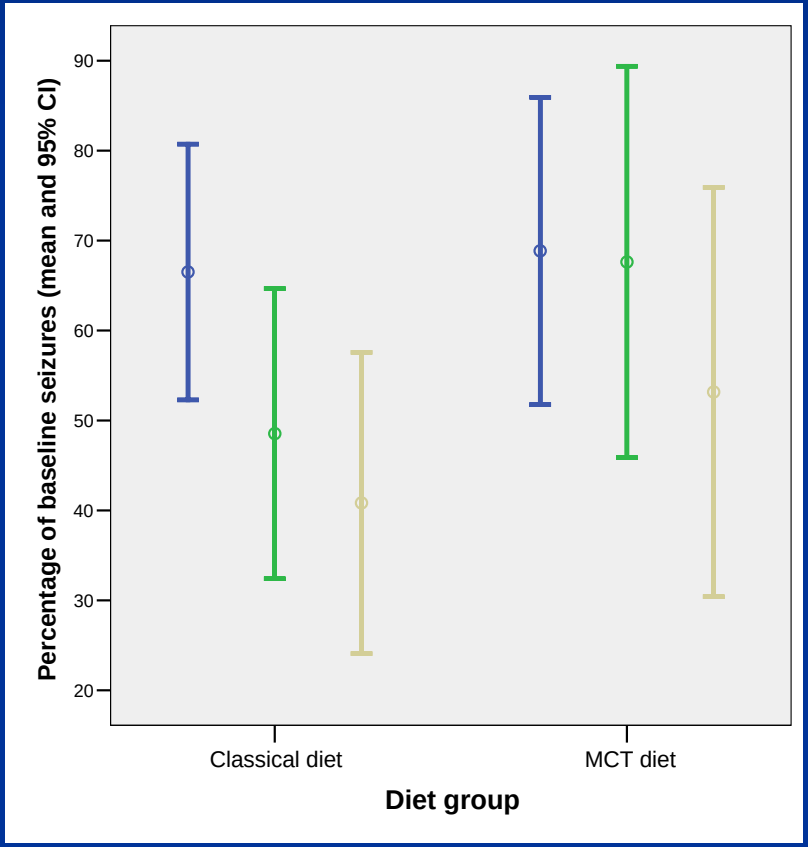
- 28/73 (38%) diet vs 4/72 (6%) controls (p<0.001)

>90% reduction in seizures

- 5/72 (7%) diet vs no controls (p<0.03)

Neal et al 2008

Classical vs MCT diet



Responder rates	MCT	Classical
3m	*N=72*	*N=73*
>50% reduction	21 (29.2%)	18 (24.7%)
>90% reduction	2(2.7%)	5(6.8%)
6m		
>50% reduction	14 (19.4%)	18(23.7%)
>90% reduction	4(5.6%)	6(8.2%)
12m		
>50% reduction	16(22.2%)	13(17.8%)
>90% reduction	7(9.7%)	7(9.6%)

P>0.1

Neal et al 2008

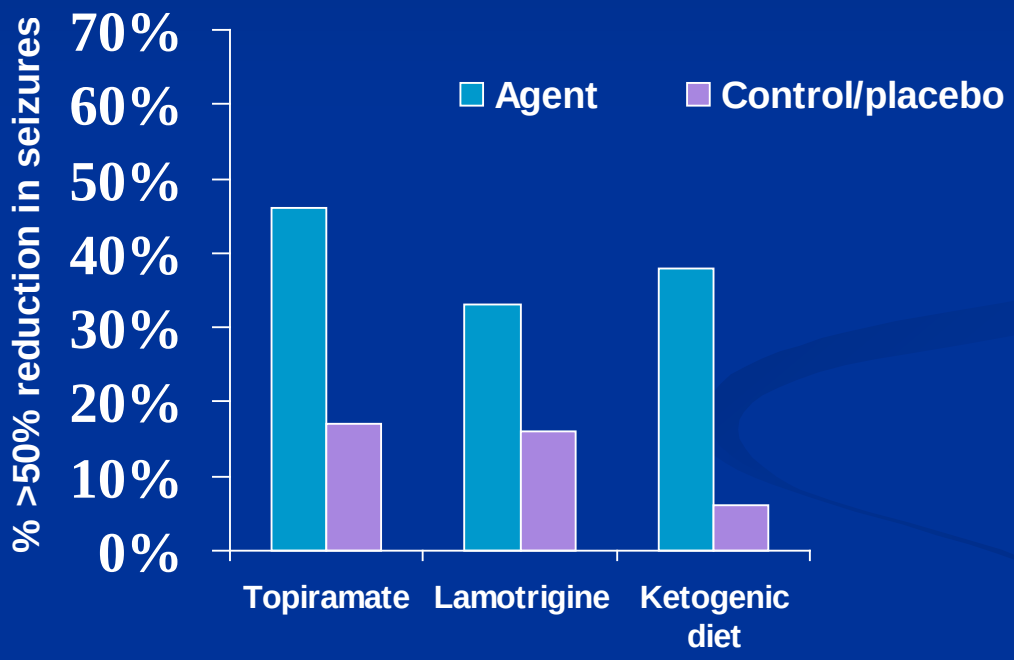
Table 2. Percentage of baseline seizure numbers at 3, 6, and 12 months in classical and MCT diet groups

	Percentage of baseline seizures (%)			
Time	Mean	Standard deviation	Range	Median
3 months				
Classical diet (n = 45)	66.50	47.34	0–200.00	58.14
MCT diet (n = 49)	68.85	59.47	0–385.71	58.12
6 months				
Classical diet (n = 30)	48.53	43.21	0–160.53	37.51
MCT diet (n = 34)	67.62	62.36	0–300.00	62.05
12 months				
Classical diet (n = 22)	40.83	37.77	0–123.72	36.55
MCT diet (n = 25)	53.16	55.10	0–196.52	31.29

n, number providing seizure data at that time point.

Neal et al , Epilepsia 50(5):1109-1117, 2009

Comparative randomised controlled trials with newer AEDs in refractory epilepsy



Biton et al 1999, Motte et al 1997, Neal et al 2008

Efficacy MAD

- Chen, Kossoff; J Child Neurol 2012, 27(6):754-758
  - follow up data on 56/87 patients
    54 on MAD > 6 months (mean age 8.1 y, SD 4.2)
    34/87 (39%) on MAD at 12 months
  - At 6 months (n=54)
    - 36 (64%) > 50% sz reduction, incl 24 (43%) > 90 reduction
  - 12 months (n=35)
    - 28 (50%) > 50% sz reduction, incl 22 (44%) > 90 sz reduction

Efficacy MAD

- Miranda et al, Seizure 20:151-155, 2011
  - Prospective, n=33, 1.1 -15.6 y (mean 8 y)

Table 3
Seizure reduction in children actively receiving the MAD at each time point.

Time MAD	3 months ($n=33$)	6 months ($n=33$)	12 months ($n=17$)
>50% seizure reduction*	**17 (52%)**	**13 (39%)**	**9 (27%)**
50–90% seizure reduction	3 (9%)	7 (21%)	5 (15%)
>90% seizure reduction	9 (27%)	6 (18%)	4 (12%)
Seizure-free	5 (15%)	0	0

All percentages are calculated from the total of patients ($n=33$).
* Total figures in bold.

Low GI diet

- 'Glycaemic Index'
  - Fewer fluctuations in glucose lead to effective sz control
  - Carbohydrate restriction – 40-60 gm/day

Low GI Diet

- Muzykewicz et al 2009; Epilepsia
  Boston, Massachusetts
  - Retrospective
  - N=76 (89% had tried >=3 AEDs)
  - > 50% sz reduction
    - 54% after 6 month
    - 66% after 12 months

Table 1. Comparison of the four major ketogenic diets

	Classic ketogenic (4 : 1)	MCT	Modified Atkins	LGIT
Fat [g (% calories)]	100 (90%)	78 (70%)	70 (70%)	60 (45%)
Protein [g (%)]	17 (7%)	25 (10%)	60 (25%)	40 (28%)
Carbohydrates (%)	8 (3%)	50 (20%)	10 (5%)	40 (27%)

MCT, medium chain triglyceride; LGIT, low glycemic index treatment.

Kossoff, Hartman 2012

Mechanisms – hypotheses

Bough &Rho Epilepsia 48 (1):43-58, 2007
Rho & Stafstrom Epilepsy Research 2011

- Anti-epileptic effect not only mediated by ketone bodies – but by adaptive metabolic processes induced by ketosis
- Effects mediated by polyunsaturated fatty acids
- Ketosis induces shifts in brain amino acid handling favouring GABA production
- Suppression of seizures mediated by adenosine acting on adenosine A1 receptors

Neuroprotective effects of KD

Maalouf et al 2009 , Brain Research Reviews

Modulation of oxidative stress and mitochondrial function by the ketogenic diet

Julie Milder, Manisha Patel*

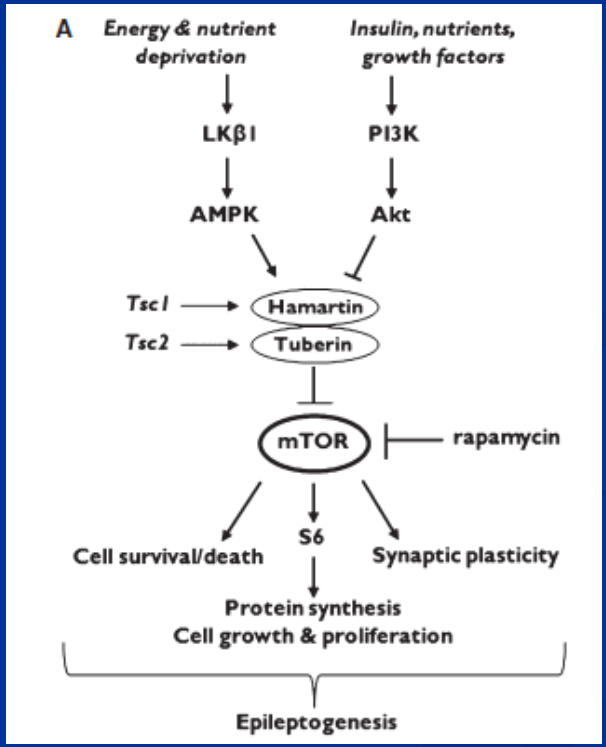
Potential role of KD following brain trauma and in neurodegenerative conditions

- Improvement of mitochondrial function
- Decrease of reactive oxygen species – reduction of oxidative stress
- Increased ATP production
- Inhibition of apoptosis
- Anti-inflammatory effects

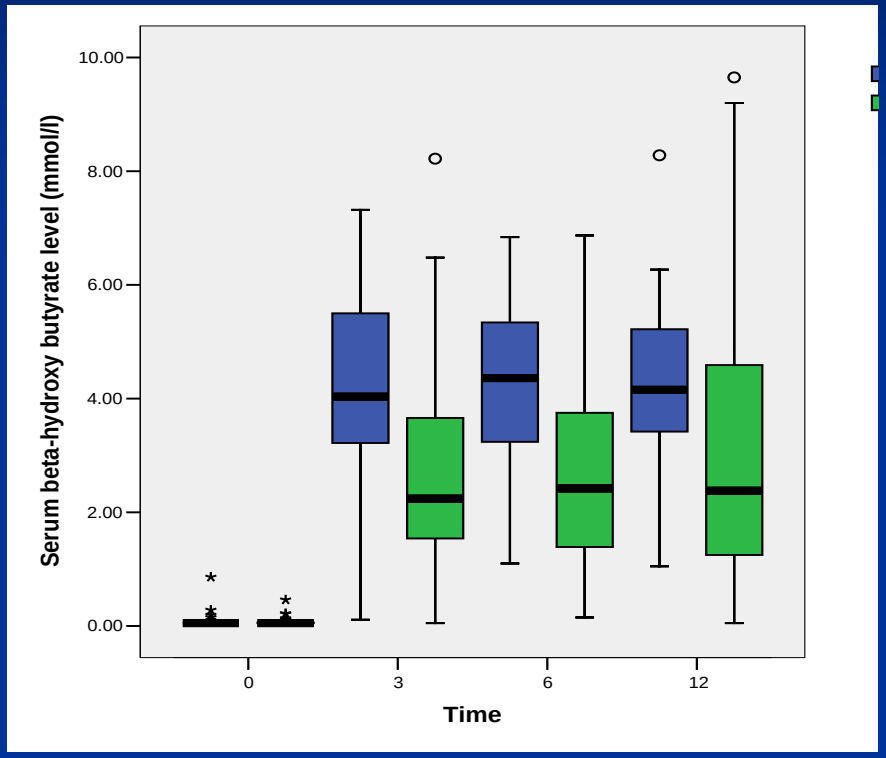
The ketogenic diet inhibits the mammalian target of rapamycin (mTOR) pathway

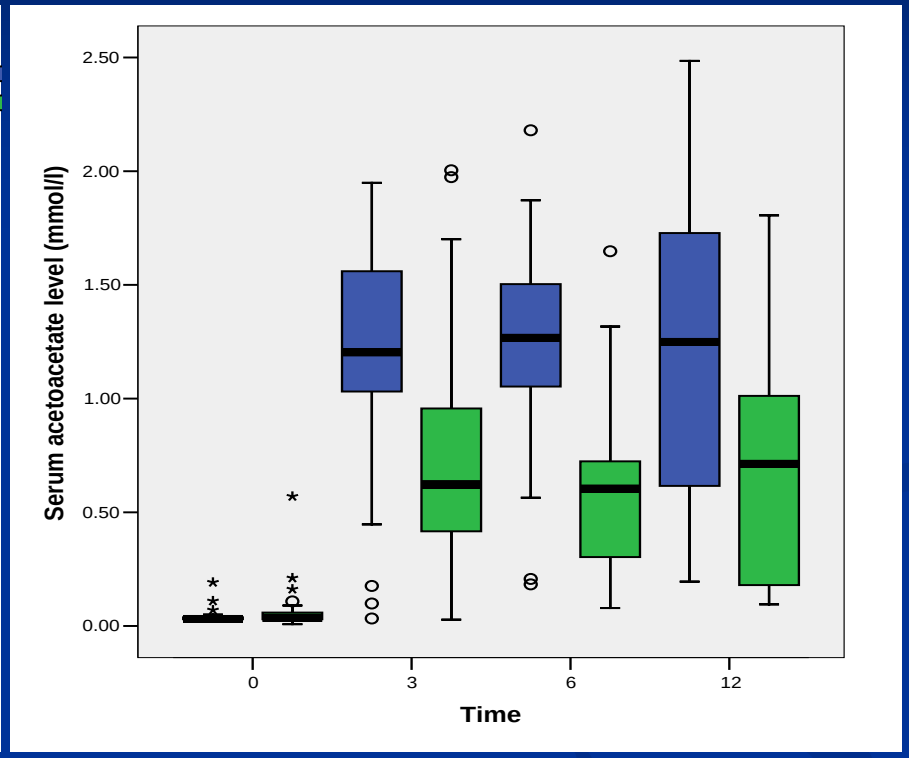
Sharon S. McDaniel, Nicholas R. Rensing, Liu Lin Thio, Kelvin A. Yamada, and Michael Wong

Department of Neurology and the Hope Center for Neurological Disorders, Washington University School of Medicine, St. Louis, Missouri, U.S.A.



Ketones and seizure control





Significant relationship seizure control to ketosis at 3m, but not 6 or 12m

Is the diet safe ?

- Restrictive diet
- Risk of vitamin and mineral deficiencies
- Requires regular monitoring
  - Weight, growth
  - Blood, urine tests
- Side effects

Adverse effects?

Table 3. Adverse events reported while on ketogenic diet

Side Effect	Number of Cases (n = 1066)	% of Total Sample
Vomiting	59	5.53
Increase serum lipid levels	28	2.63
Acidosis	20	1.88
Increased serum uric acid	19	1.78
Gastric (diarrhea/constipation)	20	1.88
Renal stones	12	1.33
Hypoglycemia	9	0.84
Increased rate of infections	8	0.75
Gallstone formation	4	0.38
Dehydration	3	0.28
Significant elevation of liver enzymes	2	0.19
Protein loss enteropathy	2	0.19
Pancreatitis	1	0.09
Deaths	16	1.50

Keene D, Pediatr Neurology, 2006; 35, 1-5

Tolerability

	Reported at 3m (N=55)	Withdrawals (N=10)
Vomiting	13(23.6%)	1
Diarrhoea	7 (12.7%)	1
Abdominal pain	5 (9.1%)	
Constipation *Medication*	18 (32.7%) *13 (23.6%)*	1
Lack of energy	13 (23.6%)	
Hunger	12 (21.8%)	
Increased seizures		1
Parental unhappiness		3
Behavioural food refusal		2
Extreme drowsiness		1

Neal et al 2008

Tolerability *at 3 months*

	Classical N=47	MCT N=42	p
Vomiting	28%	26%	>0.05
Diarrhoea	15%	14%	>0.05
Abdominal pain	11%	19%	>0.05
Constipation *Treatment*	45% *31%*	33% *26%*	>0.05 *>0.05*
Hunger	26%	33%	>0.05
Taste problems	21%	17%	>0.05
Lack of energy	17/47 (36%)	6/42 (14%)	<0.05

Neal et al 2009

Other Side Effects

- Hypoglycamia (initiation phase)
- Excess ketosis – acidosis (initiation phase)
- Pancreatitis
- **Renal stones (3-6%)**
  - Risk factors: young age, hypercalciuria, (tx with carbonic anhydrase inhibitors: Topiramate, Zonisamide)
  - Prevention – potassium citrate (alkalinisation of urine) reduction from 6.7 to 0.9 % (McNally et al, Pediatrics, 2009)
- Bruising easily
- **Hyperlipidaemia**
- **Weight loss, Inadequate growth**
- Decreased bone density – fractures (Long-term treatment)
- Cardiomyopathy, cardiac arrhythmias

Bleeding disorders

Berry-Kravis et al *Ann Neurol 2000*

- **Increased bruising** **16/51**

  15/41 active followup

  1/10 retrospective review

  Younger age 4.9yrs vs 8.5 yrs

  p=0.016

- **6 studied in detail**

  5 prolonged bleeding times

  6 abnormalities in platelet aggregation

  1 mild Von Willebrand Disease

When would be the KD be contraindicated ?

- Metabolic conditions
  - Beta-Fatty oxidation defects
  - Familial hyperlipidaemia
  - Organic acidurias
  - Pyruvate carboxylase deficiency (lactic acidosis)
- Relative contraindications
  - Feeding difficulties (food refusal)
  - Dysphagia (alternative feeding route: NG tube or PEG)
  - Severe gastro-oesophageal reflux (frequent vomiting)

Evaluation prior to starting diet

- Confirm diagnosis of epilepsy
  - consider video EEG, sleep EEG
- Document if possible aetiology, epilepsy type
- Exclude metabolic contraindications
  - (FBC, U&E, LFTs, Cholesterol, trigycerides, acylcarnitine profile, urine OA, 25 hydroxy Vitamin D, Selenium, Zinc)
- Consider renal U/S (exclude renal stones when risk factors present or in infants)
- Address feeding problems, dysphagia and gastro-oesophageal reflux

Aims

- Discuss parental expectations from dietary intervention
- Document goals for example:
  - reduction of specific distressing seizure types
  - reduction of AEDs
  - Better seizure control in order to be able to do certain activities

Initiation

- Fast prior to initiation, comparative trials
  - No significant difference:
    Kim et al 2004 N=124 (83 fasting),
    Bergqvist et al 2005 N=48 (24 fasting)
- Outpatient vs inpatient setting
  - Vaisleb et al 2004 N=54 (37 outpatients) No difference
- Our practice:
  - Initiation in outpatient setting if age > 1 year and well
  - Infants (< 1 year) – inpatient stay (5 days)

Monitoring the KD

- Minimise side effects (ie GOR)
- Achieve nutritional adequacy
  - vitamin & mineral supplementation required (Phlexy Vits)
  - at least 6 monthly:
    - FBC, U&E, bone health: calcium, phosphate & vitamin D, Urate, Zinc, selenium, Urine calcium/creatinine and Urine urate /creatinine ratio (risk factors for renal stones), blood ketones, (additional consider annual bone dexa scan)
- Maintain growth
  - Regular weight checks - every 2 weeks at home & at 6 monthly clinic visits
  - Height measurements - at 6 monthly clinic visits

- Dietetic telephone calls to families
- MDT outpatient clinics
  - Pre diet assessment
  - 3 & 6 month review after diet initiation & then 6 monthly

Time points

- 3.5 months to assess efficacy
  - Consensus statement Kossoff et al Epilepsia, 50(2):304–317, 2009
  - First effects after 2 weeks
- **Duration of treatment**
  - Initially 2 years (than taper diet)
  - in sz free patients sz control often maintained
    20% relapsed after discontinuation (Martinez et al 2007, Epilepsia)

FB

- Started classical KD now 4:1 ratio
  attends for 3 months review:
  - Wt 15.3 kg (75th centile), Length: 97.7 cm (<91rst centile)
  - Continues to have sz (brief epileptic spasms – now single events, tonic sz 1-2/day , ~ 50% reduction (moderate to good ketosis)
  - But – does no longer enjoy food and eating, parents need long time to feed her required amounts of Ketocal milk
  - Parents feel life quality significantly reduced – would like her to come off the diet
- **What would you advice at this point ?**

FB

- Decided to stay on classical KD
  - Feeding advice (limit feeds to 30 min, - offer greater range of choices)
- 11 months review – age 3.5 y:
  - No clinically apparent seizures for last 6 months
  - Was able to reduce Val dose by half
  - Developmental progress : now standing with support + takes some steps, language –pre-verbal

ZF, age 5 y

- Pregnancy:
  - Oligohydramnios, poor fetal growth
- Birth:
  - emergency CS poor foetal movements @ 36/40, good condition, BW 2.2kg
- Early development:
  - normal milestones but always poor coordination + intermittent toe walking
- Age 11 m: single episode of eyelid flickering
- Age 3-4 y: 5 paroxysmal episodes – unable to sit or walk – whilst completely aware and responsive, 15 min – 2 hours
- Age 4y: episodes of head drops , eyelid flickering + bilateral rhythmic upper limb jerking
- EEG: seizures – starring + rhythmic myoclonic movements bilateral predominantly frontal s/w discharges
- MRI: normal
- Started sodium valproate but continued to have seizures

How would you manage her at this point ?

Investigations

- CSF:
  - Glucose 0.8 mmol/l
  - Protein – Normal
  - Lactate - Normal
  - Amine metabolites, folate, pryridoxal phosphate - Normal
  - Amino Acids – N
- Plasma Glucose 4 mmol/l, Glucose CSF / Plasma ratio = 0.2
- DNA: heterozygous mutation SLC2A1 gene

ZF

Diagnosis: Glut 1 transporter deficiency Syndrome

- Commenced on classical KD 4:1 ratio
- Good response – seizure free @ 3 months review, good ketosis
- @ 6 months review – finds it difficult to comply with diet
  - Ratio lowered 3:1 – improved compliance
- Started slowly weaning from Valproate (12 m on diet)
- Making good progress at school, hand writing improved

Glucose transporter 1 deficiency syndrome

- AD, defect in SLC2A1 encoding for GLUT 1
  - Low CSF glucose, low glucose CSF/plasma ratio
- Variable phenotypes:
  - **Classical early onset** < 2y, refractory epilepsy, moderate – severe LD, ~ 70% movement disorder
  - **Classical late onset** , epilepsy, 90% movement disorder, mild – moderate LD
  - **Atypical** – movement disorder, ataxia, paroxysmal movement disorders (exercise induced) + headaches

Glucose transporter 1 deficiency syndrome

- **Reponses to KD** (Leen et al, Brain 2010)
  - KD in 37/46 with classical phenotype
    - 24 **(62%) seizure free**, seizure reduction in 9 (24%)
    - Improvement of movement disorder in 12/29 (41%)
  - KD in atypical phenotype (7/8)
    - Improvement disorder improved in 5 (71%)
- Expanding phenotype
  - SLC2A1 mutation found in 5 % of children with myoclonic astatic epilepsy (Mullen et al 2011)

Is the diet effective in specific epilepsy syndromes ?

- Dravet syndrome
  - Caraballo et al 2005; N=20
    - 12m 13/20 (65%) remained on KD, 2 SF, 8>75% reduction in seizures
  - Nabout et al 2011, Epilepsia 2011
    - N=15, on stiripentol, Val, CLB
    - At 6 m: 8 (53%) >= 75%sz reduction,
      12 m: 6 (40%) >= 75% sz reduction
- Myoclonic astatic epilepsy
  - Oguni et al 2002; N=81 15/26 (58%) 'excellent' response to MCT ketogenic diet
  - Caraballo et al 2006; (N=30, 6/11 continued on diet, 2SF, 2 >75% reduction, 2>50% reduction

Response to diet in infants with epilepsy

Nordli et al 2001 *Pediatrics 108 129-133*

- 32 infants < 2y (19 boys) retrospective series
  - 6 (19.4%) seizure free
  - 11 (35.5%) >50% improvement
  - 14 (45.2%) no worthwhile improvement
- Of 17 with infantile spasms 6 (35.3%) seizure free and 6 (35.3%) worthwhile improvement
- 5 developed complications; *severe vomiting, renal stones, GI bleed, hyperlipidaemia, ulcerative colitis*

Infantile spasms

- Hong et al, Epilepsia 2010
  - Retrospective, n=104, 71% symptomatic aetiology, 71% previously treated with VBT or steroids, mean age 1.2 years, duration of diet mean 1.3 y

Table 2. Spasm reduction outcomes for all 104 infants started on the KD at each follow-up time period

	3 months	6 months	9 months	12 months	24 months
Spasm reduction					
Spasm-free[a]	19 (18%)	29 (28%)	33 (32%)	31 (30%)	34 (33%)
>90%[a]	14 (13%)	12 (11%)	15 (14%)	14 (13%)	12 (11%)
50–90%[a]	33 (32%)	26 (25%)	28 (27%)	35 (34%)	34 (33%)
<50%[a]	38 (37%)	37 (36%)	28 (27%)	24 (23%)	24 (23%)
Number actively receiving the KD	86 (83%)	76 (73%)	53 (51%)	47 (45%)	28 (27%)
>90% spasm reduction[b]	33 (38%)	33 (43%)	27 (51%)	24 (51%)	17 (61%)

[a]Intent-to-treat analysis.
[b]Of those receiving the KD at each time point.

Lennox Gastaut Syndrome

- Lemmon M et al 2012, n=71, mean age 3.6 y

Table II: Outcome data for children treated with the ketogenic diet at The Johns Hopkins Hospital using an intent-to-treat analysis (*n*=71)

Time point	<50% seizure reduction	50–89% seizure reduction	90–99% seizure reduction	Seizure free
3mo	18 (25%)	33 (46%)	17 (24%)	3 (4%)
6mo	35 (49%)	20 (28%)	15 (21%)	1 (1%)
12mo	40 (56%)	17 (24%)	13 (18%)	1 (1%)

KD in refractory status epilepticus (SE)

- Hyun et al, Epilepsia 2011
  - 4 children and 1 adult with refractory SE presumed cause viral encephalitis (no organisms found), response: median 8 days (1-19 days), at 1 months, 2 patients sz free, 1 > 90 sz reduction, 3 > 75% sz reduction
- Nabout et al, Epilepsia 2011:
  - Fever induced refractory epileptic encephalopathy (FIRES)
  - N=9 (mean age 6y)
  - Response in 7/9 within 2-4 days of ketonuria, 4-6 days after starting diet

Consider KD

- Drug resistant epilepsy
- Early in the course of:
  - LGS, MAS, Dravet syndrome
  - ?early onset epileptic encephalopathies (incl infantile spasms)
- ? Poor tolerance to AEDs
- (Rare) metabolic disorders affecting
  - Glut 1 transporter deficiency syndrome
  - Pyruvate dehydrogenase deficiency

Future research

- Focus on efficacy in specific syndromes especially with onset in infancy and early childhood
  Should the diet be considered second rather than third line ?

- In medication resistant epilepsy is there a point when the dietary treatment is more effective than a further trial of an AED?

- Further comparative trials between the newer versions of the diet (MAD, low glycaemic index diet)

Future research

- Efficacy of KD in adolescents and adults
- Course of epilepsy once KD is discontinued (?disease modifying effect of KD)
- Outcome data should also include development/cognition and behaviour

Conclusions

- The ketogenic diet is an effective and safe treatment
- Consider and discuss dietary treatment options early in the course of medication resistant epilepsy

Recommended reading (1)

- Hartman AL, Gasior M, Vining EP, Rogawski MA. The neuropharmacology of the ketogenic diet. Pediatr Neurol 2007; 36: 281-292.
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- Kossoff EH, Zupec-Kania BA, Amark PE *et al*. Optimal clinical management of children receiving the ketogenic diet: recommendations of the International Ketogenic Diet Study Group. Epilepsia 2009a; 50: 304-317.
- Kossoff EH, Zupec-Kania BA, Rho JM. Ketogenic diets: an update for child neurologists. J Child Neurol 2009b; 24: 979-988
- Leen WG, Klepper J, Verbeek MM *et al*. Glucose transporter-1 deficiency syndrome: the expanding clinical and genetic spectrum of a treatable disorder. Brain 2010; 133: 655-670.

Recommended reading (2)

- Pong AW, Geary BR, Engelstad KM, Natarajan A, Yang H, De Vivo DC. Glucose transporter type I deficiency syndrome: epilepsy phenotypes and outcomes. Epilepsia 2012; 53: 1503-1510.
- Neal E (editor): Dietary Treatment of Epilepsy, Practical Implementation of Ketogenic Therapy, Wiley-Backwell, 2012, **ISBN-13:** 978-0470670415
- Eric H. Kossoff EH, Hartman A L , Ketogenic diets: new advances for metabolism based therapies
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