DIETARY TREATMENTS IN GLUT1DS

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Deficiency of glucose transporter protein
Low CSF glucose (with normal blood glucose), ratio <0.45
Classical phenotype: 90%
- early epileptic encephalopathy,
- acquired microcephaly
Epilepsy syndromes: CAE, MAE, other IGE
Atypical/non-classical: paroxysmal movement disorder, ataxia, choreoathetosis, headaches.
Approx 300 patients diagnosed so far.
Mechanisms of GLUT1DS symptoms:

Brain energy failure!

Glu: needed for neurotransmitter synthesis:
Balance of excitation and inhibition: epilepsy

GLUT1: less excitation but even lower inhibition

But, it remains incompletely understood disorder!
Complex and rare condition-heterogenous

More than one type of glucose transporters in the brain.

? Interaction with other genes-modifying symptoms
(20-30% have no mutation in SLC2A1 gene)

Glucose transporters in other tissues: heart, retina etc
In the **fed** state, nutrients are stored; In the **fasting** state, they are oxidized for energy production.

### Carbohydrates
- **Glucose** (sugar)
  - Metabolic pathway of **Glycolysis**
    - Stored as glycogen or fat
    - Oxidized for energy
  - Fatty Acids used to create ketone bodies for body fuel
  - Glycerol used to create glucose for brain/blood cells

### Fats
- **Fatty Acids and Glycerol**
  - Metabolic pathway of **Beta-Oxidation**
    - Stored as triglycerides in fat cells
    - Oxidized for energy
  - Metabolic pathway of **Transamination**
    - Stored as glycogen or fat
    - Made into new protein compounds

### Proteins
- **Amino Acids**
  - Metabolic pathway of **Transamination**
    - Stored as new protein compounds
    - Oxidized for energy

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**Starvation State**

**Kreb’s Cycle (Mitochondria)**
- ATP created to fuel body
- Carbon dioxide and water are exhaled
Treatments in GLUT1DS:
Strategy to bypass the block in glucose supply to brain: ketogenic diet- ketones enter brain via monocarboxylase transporters (MCT)

GLUT1DS mice: ketotic by themselves on normal diet (double the ketones)
Humans: cannot establish ketosis on normal diet.
**KD is the only recommended and established treatment at present:**

KD: since 1921-mimics biochemical effects of starvation
Figure 1  Ketosis and brain energy metabolism. Glucose enters the brain via the facilitated glucose transporter GLUT1 (■); ketones penetrate the blood—brain barrier (BBB) via the MCT1-transporter (●). Both substrates enter the citric acid cycle as acetyl-CoA for energy production. ① GLUT1 DS is caused by a defect in GLUT1-mediated glucose transport into brain. ② Pyruvate dehydrogenase deficiency impairs acetyl-CoA production. In both conditions, ketones bypass the transport/enzyme defect as acetoacetyl-CoA and provide acetyl-CoA.
High fat, carbohydrate restricted, adequate protein diet

- Classical: suits infants and young children
- MCT: children and adolescents
  - over 400 children reported
- As effective as classical/MCT in epilepsy.
- Low GI: not suitable for GLUT1
MCT DIET

- MCT (Medium Chain Triglyceride) - manufactured from Coconut Oil.
- Metabolised a lot faster than LCT fat.
- Highly ketotic.
- Diet worked out on Percentages NOT ratio.

For Example:
2000 Calories required per day:
40-50% given as MCT energy
10 - 12% Protein
15-19% CHO
Remaining as LCT Fat
BASICS OF MAD/MKD

- No Calorie Restriction.
- Carbohydrates limited to 10g per day raising to 20g per day after the first couple of months (UK start higher)
- Unlimited protein.
- Promotion of fatty foods – need about 65% fat per day in diet.
- Blood tests required
- Supplementation Required.
NORMAL UK DIET, CLASSICAL KD AND MCT KD

Normal UK
- Fat: 35%
- Protein: 15%
- Carbohydrate: 50%

Classical
- Fat: 90%
- Protein: 6%
- Carbohydrate: 4%

MCT
- Fat: 73% (30-60% MCT)
- Protein: 10%
- Carbohydrate: 17%

Copyright: Matthew's Friends 2011
Ketogenic diet (Ratio 2.5 : 1)

Normal diet

- Fat: 34%
- CHO: 53%
- Protein: 13%

Ketogenic diet

- Fat: 85%
- CHO: 2%
- Protein: 13%

Susan Wood RD February 2012
KETOCGENIC DIET: MECHANISMS

Different mechanisms, different diseases

Direct
Alternative fuel provision

Indirect
Mitochondrial biogenesis
Neurotransmitter metabolism
Antioxidant status

Complicated stuff!
Changes expression of genes-hippocampi

Increased mitochondria in neuronal tissue

Increase production of enzymes involved in energy metabolism

Overall brain tissue is more resistant to metabolic stress – reduces initiation & propagation of seizure activity

Indirect Mechanisms & KD

- Energy Metabolism
- Antioxidant - reduce oxidative stress
- altered neurotransmission: increased GABA synthesis.
- Neuroprotection: membrane stabilization
- Carbohydrate restriction
- ?anti-inflammatory effect
Energy Metabolism

- Diet may take several days before becoming maximally effective
- Alterations in gene expression involved
- Co-ordinated up-regulation of energy metabolism enzymes - hippocampus
- Mitochondrial biogenesis- increased no of mitochondria, increased energy efficiency

Energy Metabolism

Bough et al., Ann Neurol (2006), 60:223-235
Neuroprotection

- KD Protective in model systems
- Increase in calbindin
  - Buffering of calcium
  - Inhibition of caspase
  - Inhibition of cytochrome c release

Carbohydrate Restriction

- Calorie restriction & hypoglycaemia → seizures
- Inhibition of glycolysis → seizures
- Increase stress proteins
  - Suppress ROS production
  - Stabilise intracellular calcium
  - Preserve mitochondrial function

Gasior et al., Behav. Pharmacol (2006), 17, 431-439
Prominent shifts in metabolism seem to underlie the effects of the KD.

Quite likely that different mechanisms at different times of the EEG pattern

Where a drug may work on just one mechanism, the KD may have multiple effects.
Classical: infants: 3:1 or 4:1, may not provide enough protein, good ketosis

MKD: if hypercholesterolemia, compliance issues, growth issues or transitioning from classical KD - 7 patients reported so far
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<thead>
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<th>Diet Type</th>
<th>Ketosis</th>
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<th>School-Age</th>
<th>Adolescents</th>
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<td>Regular diet</td>
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</table>

*Klepper & Leiendecker, J of Child Neurology 2013, 28(8):1045-48*
MKD for GLUT1: Ito et al: DMCN 2011:

6 children with GLUT1DS: all with early onset epilepsy (8.5-19.3 Y age),

1/6: no mutation

Age of onset of symptoms: 2mo-1 year

Age at diagnosis: 6.9-14.7 years

MKD started 7-16 years age, 2/6 switched from MCT to MKD

Duration 1/6: 1mo, 5/6-6-42 months

Consistent ketosis (urinary)
MKD: results: 6 children

All had significant improvement in seizure control

90% reduction in 5/6

also in movement disorder.

Improved EEG features

No change in IQ.

** high ketogenic ratio: 2:1
Managing ketosis:

High levels essential?:

Possibly early: better ability to generate ketones early age, higher energy requirement

Possibly not: no relationship between ketones and seizure control

No definite evidence of efficacy of classical vs MCT
Acetazolamide as treatment for GLUT1 deficiency syndrome: Kinder et al, Neuropediatrics 2012

Case report: improved ataxia and cognition in GLUT1
?
An option for non-tolerance to KD/insufficient response

GLUT1 inhibitors
Ethanol, gree tea, tyrosine kinase inhibitors, dioxine, trycyclic antidepressants, GA, diazepam, Chloral hydrate
Barbiturates, caffeine, methylxanthines:
SVA: inhibits glucose transport
Wong et al, Cellular Biology 2005
In vitro testing glucose transport reduced by 20-40% in normal and GLUT1 deficient RBCs and fibroblasts

Recommended: not to be on SVA
Practical experience differs.

Acetazolamide: for movement disorders

Variable experience of efficacy.
Role of other agents:

Alfa-lipoic acid / Thiocytic acid: GLUT1 activator
Natural organic acid-antioxidant
Co-enzyme in energy metabolism:
Animal studies: may improve (insulin dependent) glucose transport (GLUT4 transporter) in muscle cells.
600-1800 mg/day: experimental treatment
**Triheptanoin:**
C7 oil: castor bean oil- used in foods and cosmetics
- artificial ketone- converts to energy in brain Beta oxidation providing substrate for TCA cycle
Anticonvulsant properties in mouse model. Affordable, safe?
Needs further data- metabolic pathway in brain uncertain.

**Ketone esters:** high energy ketones: sustained ketosis for several hours in animal studies
- need further scientific data.
Medication management:

Typically no changes for at least 3 months into the diet.


*Coman et al: J Paed Child Health, 2006*

8 patients: rapid and significant sz control with KD,

4/8 weaned off AEDs
Klepper et al, Neuropediatrics 2005

15 children: all on KD, 2-5.5 years F/U
10/15 seizure free on KD alone
2/15: sz recurred, treated with ETX
1/15: sz improved but not seizure free

Long term: no change in neurological function
no deterioration, but gains made with ongoing development and learning
Difficult to be conclusive:
- Diet rarely continued if no seizure reduction
- Not given to well children
- AED reduction improves behaviour and sedation levels
- Improvement seen related to sz reduction/AED reduction?

Nordli and De Vivo (2001) - infants
- 60% improved attention
- 55% improved social skills
- 59% better activity level

Pulsifer et al (2001) prospective study
- Improvements in attention and social functioning
- Mean seizure freq reduced from 25 to 2 a day
TOLERABILITY OF KD

- Side effect profile same as KD in epilepsy
- Needs vitamin supplements with classical KD

Main concerns:
- Renal stones
- Growth
- Hypercholesterolemia: reduce ratio
  - use of PUFA
  - formula rather than solid ketofoods?
GLUT1 GENE TESTING UK

- Sheffield
- Glasgow: Duncan Guthrie lab
- Leeds

Whole gene sequencing
Testing for known mutations in the family
Prenatal diagnosis
£ 200-350

**BPNSU survey findings: 28 cases over 2 years reported**

70% still did not receive KD!
GLUT1-DIET CONCLUSIONS

- Epilepsies and KD: ketosis less relevant?
- All varieties of KD effective.
- GLUT1DS: epilepsy related to energy failure.
- Ketosis probably more relevant
- **Hence classical KD favoured**
- Keep at least until adolescence.
- Consider ‘novel’ diets if tolerance/compliance issues.
- No data re MCT and LGI diet-not recommended
- Needs joint input with keto-dietician and neurologist.
Thank you.

Questions?