

Modified Atkins diet in GLUT1-DS

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Stéphane Auvin - Disclosures

Clinical trials: Advicenne Pharma, Eisai, UCB pharma, Ultragenyx, Zogenyx

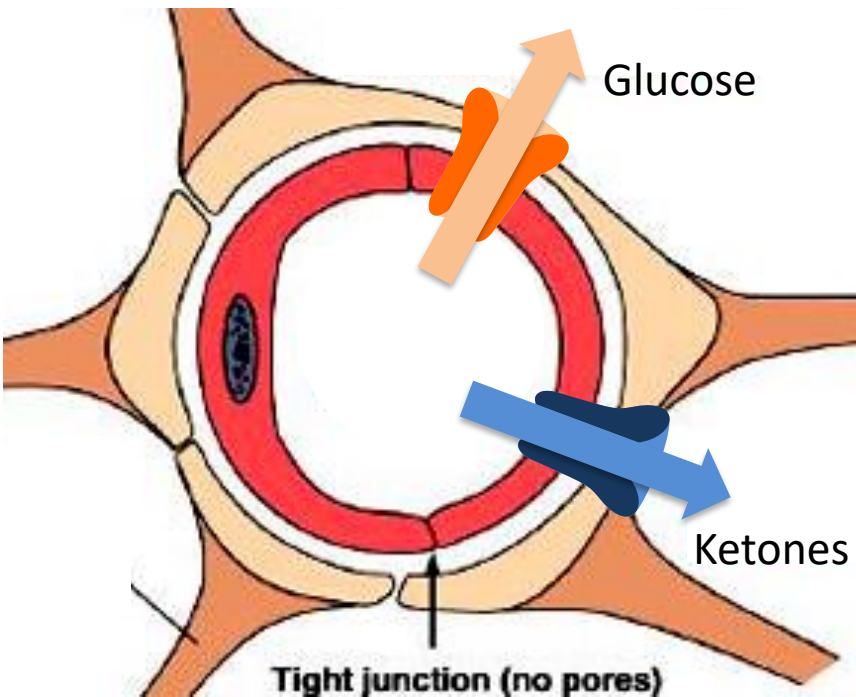
Advice/Expertise: Advicenne Pharma, Biocodex, Eisai, GSK, Novartis, Nutricia, Shire, Servier, Ultragenyx, Zogenyx

Lectures: Advicenne Pharma, Biocodex, Eisai, Novartis, Nutricia, Shire

Physiological condition

Regular food intake

Balanced energetic level in the brain

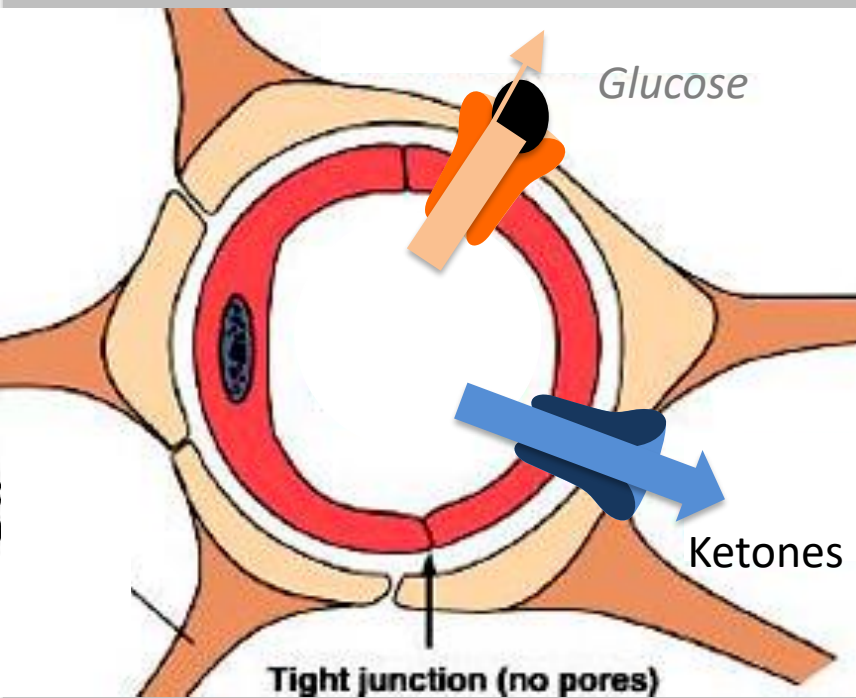


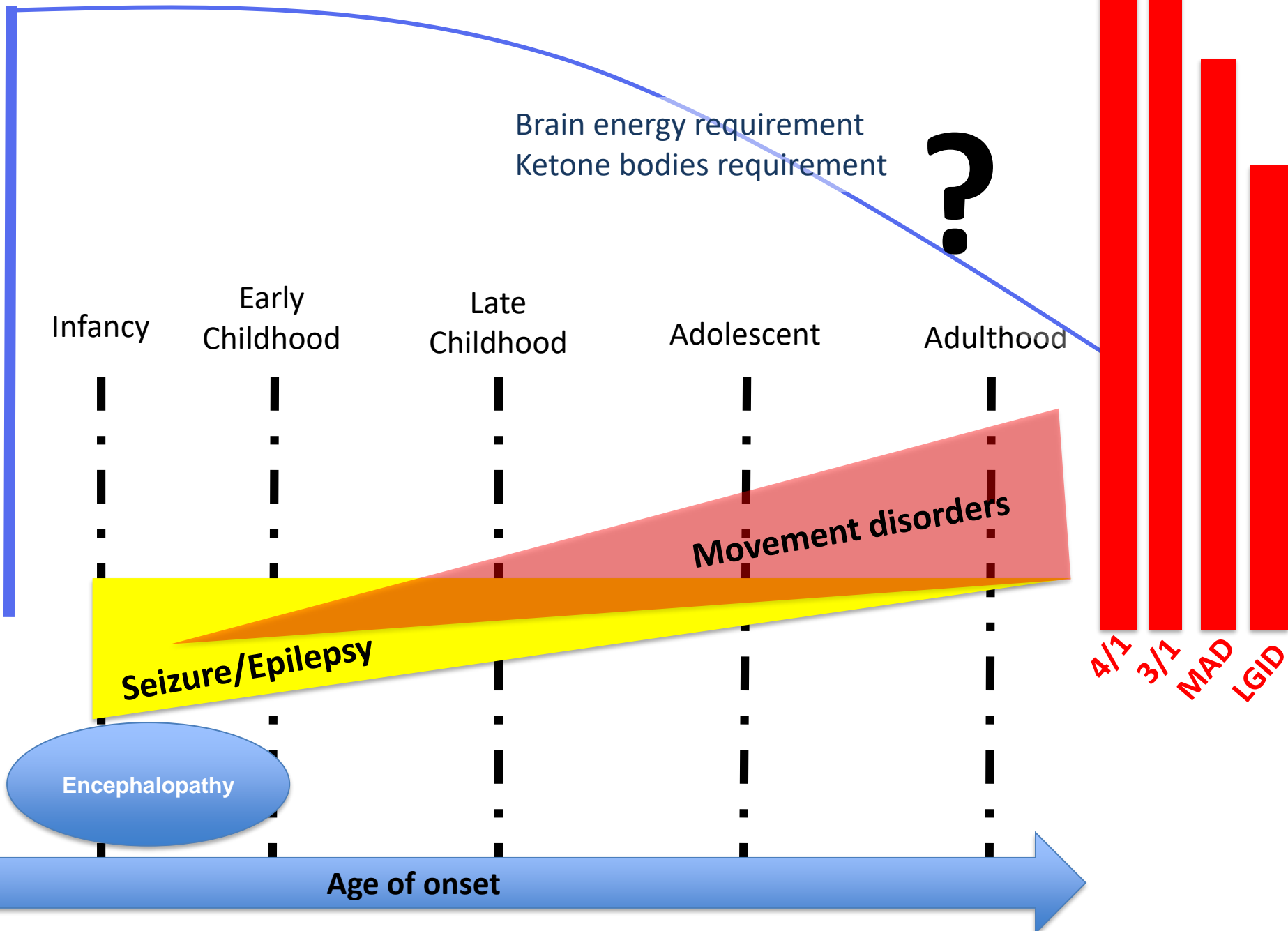
GLUT1-DS

Regular food intake: inadequate energetic brain level

Ketone bodies used as an alternative 'fuel'

Adapted Ketone bodies level ?





Use of modified Atkins Diet?

- Ketogenic diet considered as gold standard
- Japan (questionnaire to Ped Neurol) **Fujii et al. 2016**
 - 39 patients: 31 KD > 1 month
 - N=17 (55%) on MAD, N=11 (35%) on classic KD, 3 on MCT
 - B-OHB: MAD 2.5 mM (0.75–4.1), KD 1.7 mM (0.23–3.5), MCT 2.6 mM (1.5–3.0)
- USA (families) **Kass et al. 2016**
 - 92 families (98% on dietary therapies).
 - 59 classic KD, 29 MAD, 4 MCT, 2 LGI.
 - Seizure-free younger on average (8.2 vs. 11.6 years, $p = 0.01$)
 - Seizure-free slightly younger at GLUT1DS diagnosis (3.8 vs. 5.3 years, $p = 0.05$)
 - KD/MCT Diets vs. MAD/LGIT (74% vs. 63%, $p = 0.30$)

Methods

- Retrospective observational study
- Pediatric Neurology at Robert Debré Children's Hospital, Paris, France.
- Completeness of data by 3 local databases (Pediatric neurology department, Neurophysiology Department, Dieticians)
- May 31, 2008 to June 1, 2015. Patients that discontinued MAD for at least 1 month were excluded.

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|--------------------------|----------|----------|----------|-----------------|----------|---------------------|---------------------|-----------------|-----------|----------------|
| Sex | F | M | F | F | M | F | F | M | F | M |
| Age | 14m | 21m | 4y 6m | 6y 5m | 7y 6m | 9y 5m | 14y 7m | 14y 10m | 16y 4m | 18y 5m |
| First symptoms | 2m | 9m | 6m | 3y | 2y 7m | 3y | 9m | 4y | 6m | 4m |
| Age at diagnosis | 4m | 13m | 8m | 4y11 | 3y10m | 4y 6m | 12y | 11y | 16y | 8y |
| Sz type | - | Abs | - | Abs | - | Abs/FS | Abs | GTC | Abs/FS | Abs/GTC |
| Mvt D | AEM | - | AEM | - | CM | - | PMD | PMD | AEM | AEM |
| Gait | - | - | - | - | - | - | - | - | - | - |
| Ataxia | - | - | - | - | + | + | + | - | + | + |
| Spasticity | - | - | - | - | - | + | + | - | + | + |
| Hypotonia | + | - | + | - | - | - | - | + | + | + |
| Dystonia | + | - | - | - | + | - | + | - | + | + |
| Lang delay | - | - | - | - | - | - | - | - | - | - |
| Dyspraxia | - | - | - | - | - | - | - | + | - | - |
| ID | S | Mild | N | N | N | Mod. | S | N | S | Mod. |
| AED (before diet) | - | ESM | - | VPA/ ESM/LTG | - | VPA/LTG /LEV/ESM | VPA/ ESM/ LTG | LEV/C LB/SUL | NA | PB/CBZ /VGB |
| CSF glucose | 2.2 | 1.8 | 1.9 | 2.1 | 1.8 | 1.48 | 1.9 | 2.2 | 2.2 | 2.1 |
| Ratio | 0.47 | 0.38 | 0.39 | 0.45 | 0.4 | 0.3 | 0.34 | 0.45 | 0.41 | 0.43 |

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| Mvt D | AEM | - | AEM | - | CM | - | PMD | PMD | AEM | AEM |
| Gait | - | - | - | - | - | - | - | - | - | - |
| Ataxia | - | - | - | - | + | + | + | - | + | + |
| Spasticity | - | - | - | - | - | + | + | - | + | + |
| Hypotonia | + | - | + | - | - | - | - | + | + | + |
| Dystonia | + | - | - | - | + | - | + | - | + | + |
| Lang delay | - | - | - | - | - | - | - | - | - | - |
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| Mvt D | AEM | - | AEM | - | CM | - | PMD | PMD | AEM | AEM |
| Gait | - | - | - | - | - | - | - | - | - | - |
| Ataxia | - | - | - | - | + | + | + | - | + | + |
| Spasticity | - | - | - | - | - | + | + | - | + | + |
| Hypotonia | + | - | + | - | - | - | - | + | + | + |
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| Ataxia | - | - | - | - | + | + | + | - | + | + |
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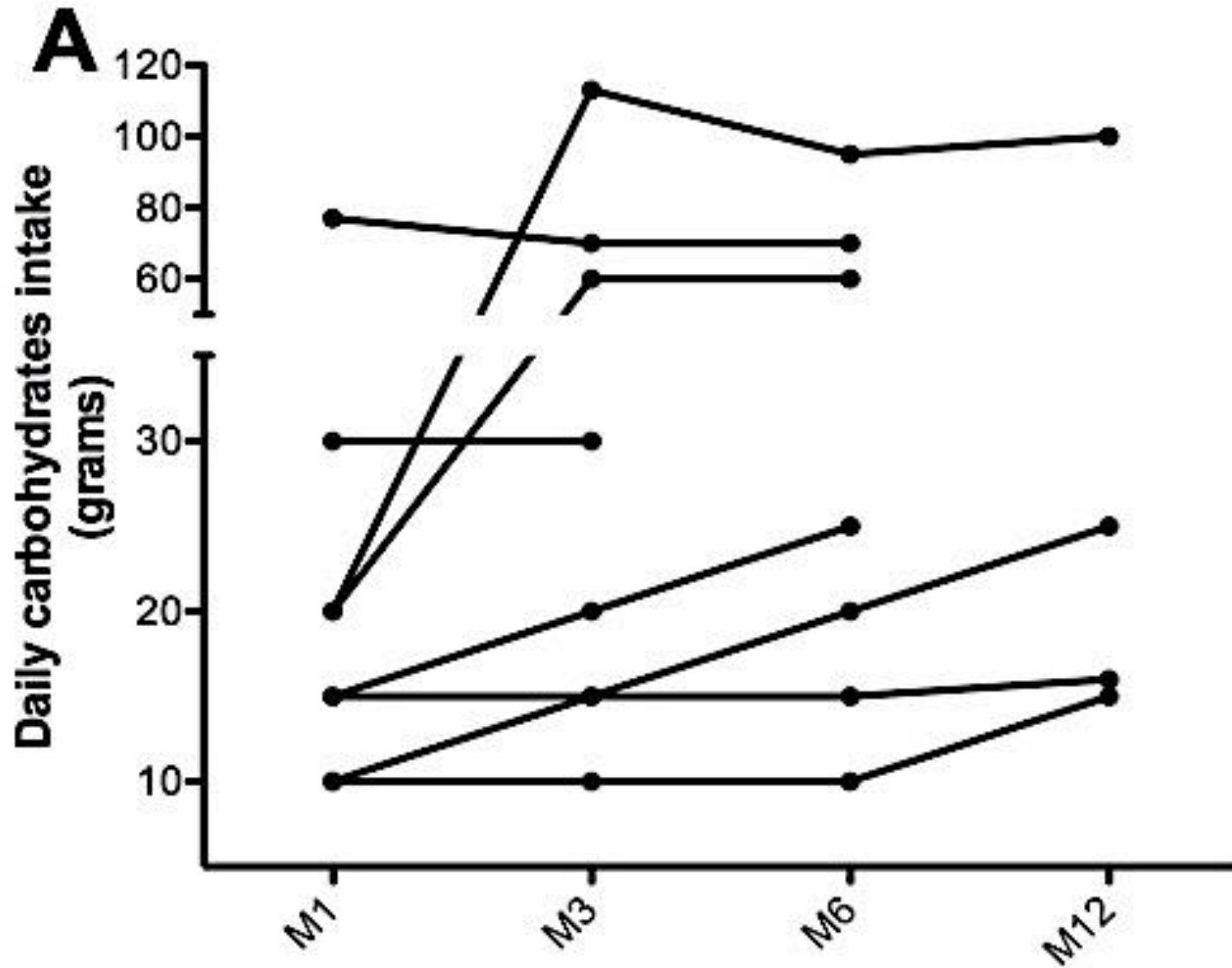
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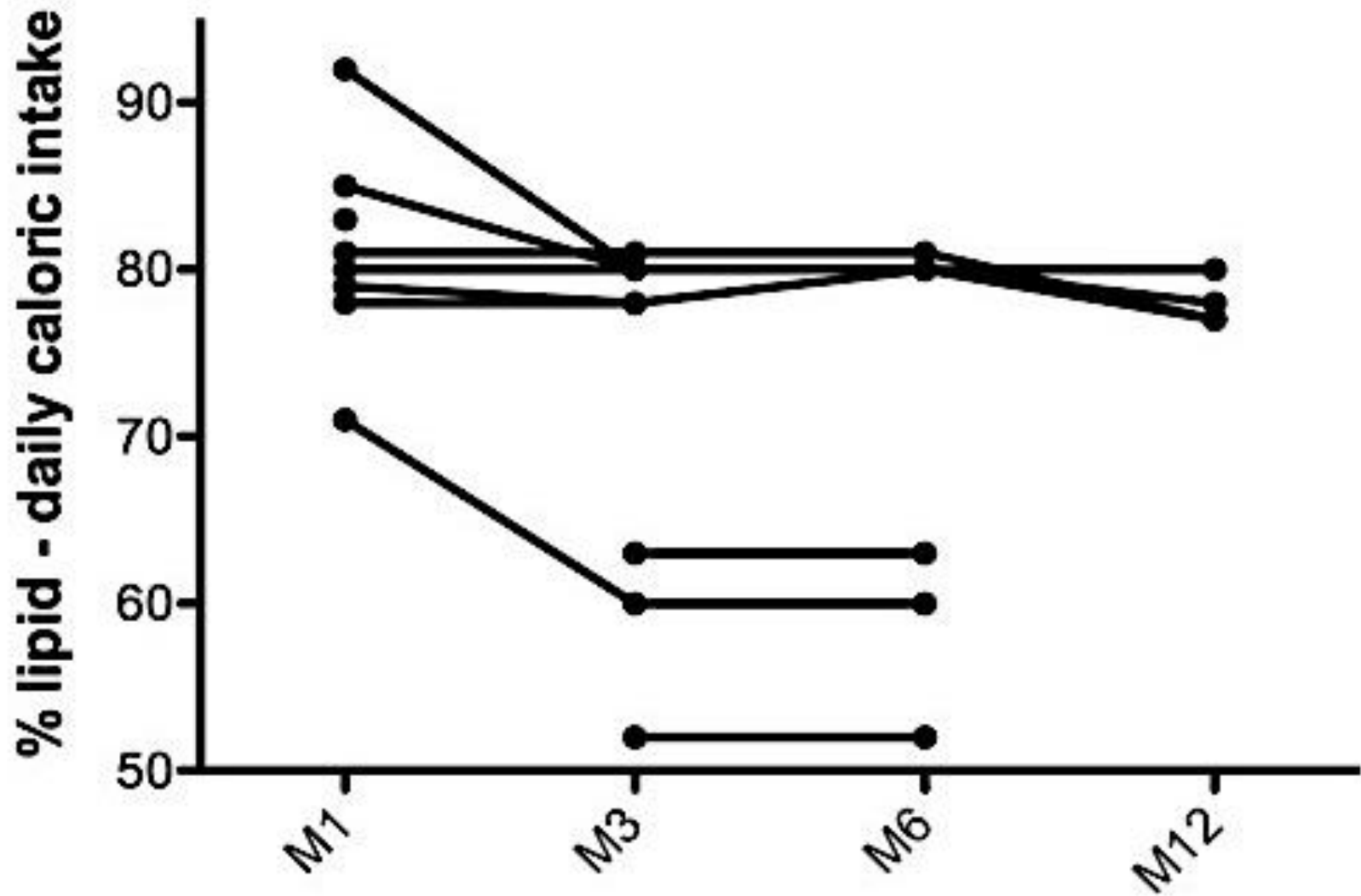
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| Ataxia | - | - | - | - | + | + | + | - | + | + |
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| Hypotonia | + | - | + | - | - | - | - | + | + | + |
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| Ataxia | - | - | - | - | + | + | + | - | + | + |
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| Hypotonia | + | - | + | - | - | - | - | + | + | + |
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Our 'Modified Atkins diet'

- No fasting period in the in-patient department
- No caloric restriction
- Proteins: 30-35% of caloric intake
- Initially 10-15g of carbohydrates daily initially
- After clinical improvement, allowed to increase carbohydrates by 5 g/day at intervals of at least 1 month, up to a maximum of 10% of caloric intake per day.
- In most patients, we allowed a maximum of 40g of carbohydrates if tolerated.





| | | Patients | | | | | | | | | |
|---------------------------|--------------------|---------------|--------------------|--------------------|---------------|--------------------|---------------|---------------|---------------|---------------|---------------|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Age at diet start | | 3y 10m | 13m | 8m | 4y 11m | 8y | 4y6m / 8y3m | 12y | 11y | 16y | 8y / 12y |
| Type of diet | | MAD | MAD | MAD | MAD | MAD | KD/MAD | MAD | MAD | MAD | KD/MAD |
| Duration of MAD treatment | | 11m | 11m | 4y | 1y10m | 3y9m | 15m | 2y6m | 3y | 6m | 6y |
| Seizure type | | 0 | 0 | 0 | Absences | 0 | 0/FS | 0 | ↓GTC | 0 | 0 |
| MAD M1 | MD | Free of MD | 0 | Free of MD | 0 | Free of MD | 0 | Free of MD | ↓PMD | Free of MD | Free of MD |
| | Antiepileptic drug | 0 | ESM | 0 | VPA/ESM/LTG | 0 | VPA/LTG | VPA | VPA/CLB | 0 | 0 |
| | CGI | Much improved | Very much improved | Very much improved | Much improved | Very much improved | Much improved | Much improved | Much improved | Mini improved | Much improved |
| MAD M3 | Seizure type | 0 | 0 | 0 | Absences | | 0/↓FS | ↓Absences | 0 | 0 | 0 |
| | MD | Free of MD | 0 | Free of MD | 0 | | 0 | Free of MD | Free of MD | Free of MD | Free of MD |
| | Antiepileptic drug | 0 | ESM | 0 | VPA/LTG | | LTG/ESM | ↑VPA | VPA | 0 | 0 |
| | CGI | Much improved | Very much improved | Very much improved | Much improved | | Much improved | Mini improved | Much improved | Mini improved | Much improved |
| MAD M6 | Seizure type | 0 | 0 | 0 | Absences | | 0/↓FS | ↑Absences | 0 | | 0 |
| | MD | Free of MD | 0 | Free of MD | 0 | | 0 | Free of MD | →PMD | | Free of MD |
| | Antiepileptic drug | 0 | 0 | 0 | VPA/↑LTG | | LTG/ESM | ESM | SUL | | 0 |
| | CGI | Much improved | Very much improved | Very much improved | Min improved | | Much improved | Mini | Mini | | Much improved |
| MAD M12 | Seizure type | | | 0 | Absences | | 0/↓FS | →Absences | 0 | | 0 |
| | Movement disorder | | | Free of MD | 0 | | 0 | Free of MD | →PMD | | Free of MD |
| | Antiepileptic drug | | | 0 | ↑VPA/LTG | | LTG/ESM | ESM/LTG | SUL | | 0 |
| | CGI | | | Very much improved | No change | | Much improved | Mini | Mini | | Much improved |

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| MAD M1 | MD | Free of MD | 0 | Free of MD | 0 | Free of MD | 0 | Free of MD | ↓PMD | Free of MD | Free of MD |
| | Antiepileptic drug | 0 | ESM | 0 | VPA/ESM/LTG | 0 | VPA/LTG | VPA | VPA/CLB | 0 | 0 |
| | CGI | Much improved | Very much improved | Very much improved | Much improved | Very much improved | Much improved | Much improved | Much improved | Mini improved | Much improved |
| MAD M3 | Seizure type | 0 | 0 | 0 | Absences | | 0/↓FS | ↓Absences | 0 | 0 | 0 |
| | MD | Free of MD | 0 | Free of MD | 0 | | 0 | Free of MD | Free of MD | Free of MD | Free of MD |
| | Antiepileptic drug | 0 | ESM | 0 | VPA/LTG | | LTG/ESM | ↑VPA | VPA | 0 | 0 |
| | CGI | Much improved | Very much improved | Very much improved | Much improved | | Much improved | Mini improved | Much improved | Mini improved | Much improved |
| MAD M6 | Seizure type | 0 | 0 | 0 | Absences | | 0/↓FS | ↑Absences | 0 | | 0 |
| | MD | Free of MD | 0 | Free of MD | 0 | | 0 | Free of MD | →PMD | | Free of MD |
| | Antiepileptic drug | 0 | 0 | 0 | VPA/↑LTG | | LTG/ESM | ESM | SUL | | 0 |
| | CGI | Much improved | Very much improved | Very much improved | Min improved | | Much improved | Mini | Mini | | Much improved |
| MAD M12 | Seizure type | | | 0 | Absences | | 0/↓FS | →Absences | 0 | | 0 |
| | Movement disorder | | | Free of MD | 0 | | 0 | Free of MD | →PMD | | Free of MD |
| | Antiepileptic drug | | | 0 | ↑VPA/LTG | | LTG/ESM | ESM/LTG | SUL | | 0 |
| | CGI | | | Very much improved | No change | | Much improved | Mini | Mini | | Much improved |

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| MAD M1 | Seizure type | 0 | 0 | 0 | Absences | 0 | 0/FS | 0 | ↓GTC | 0 | 0 |
| | MD | Free of MD | 0 | Free of MD | 0 | Free of MD | 0 | Free of MD | ↓PMD | Free of MD | Free of MD |
| | Antiepileptic drug | 0 | ESM | 0 | VPA/ESM/LTG | 0 | VPA/LTG | VPA | VPA/CLB | 0 | 0 |
| | CGI | Much improved | Very much improved | Very much improved | Much improved | Very much improved | Much improved | Much improved | Much improved | Mini improved | Much improved |
| MAD M3 | Seizure type | 0 | 0 | 0 | Absences | | 0/↓FS | ↓Absences | 0 | 0 | 0 |
| | MD | Free of MD | 0 | Free of MD | 0 | | 0 | Free of MD | Free of MD | Free of MD | Free of MD |
| | Antiepileptic drug | 0 | ESM | 0 | VPA/LTG | | LTG/ESM | ↑VPA | VPA | 0 | 0 |
| | CGI | Much improved | Very much improved | Very much improved | Much improved | | Much improved | Mini improved | Much improved | Mini improved | Much improved |
| MAD M6 | Seizure type | 0 | 0 | 0 | Absences | | 0/↓FS | ↑Absences | 0 | | 0 |
| | MD | Free of MD | 0 | Free of MD | 0 | | 0 | Free of MD | →PMD | | Free of MD |
| | Antiepileptic drug | 0 | 0 | 0 | VPA/↑LTG | | LTG/ESM | ESM | SUL | | 0 |
| | CGI | Much improved | Very much improved | Very much improved | Min improved | | Much improved | Mini | Mini | | Much improved |
| MAD M12 | Seizure type | | | 0 | Absences | | 0 | →Absences | 0 | | 0 |
| | Movement disorder | | | Free of MD | 0 | | 0 | Free of MD | →PMD | | Free of MD |
| | Antiepileptic drug | | | 0 | ↑VPA/LTG | | LTG/ESM | ESM/LTG | SUL | | 0 |
| | CGI | | | Very much improved | No change | | Much improved | Mini | Mini | | Much improved |

| | | Patients | | | | | | | | | |
|---------------------------|--------------------|---------------|--------------------|--------------------|---------------|--------------------|---------------|---------------|---------------|---------------|---------------|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Age at diet start | | 3y 10m | 13m | 8m | 4y 11m | 8y | 4y6m / 8y3m | 12y | 11y | 16y | 8y / 12y |
| Type of diet | | MAD | MAD | MAD | MAD | MAD | KD/MAD | MAD | MAD | MAD | KD/MAD |
| Duration of MAD treatment | | 11m | 11m | 4y | 1y10m | 3y9m | 15m | 2y6m | 3y | 6m | 6y |
| MAD M1 | Seizure type | 0 | 0 | 0 | Absences | 0 | 0/FS | 0 | ↓GTC | 0 | 0 |
| | MD | Free of MD | 0 | Free of MD | 0 | Free of MD | 0 | Free of MD | ↓PMD | Free of MD | Free of MD |
| | Antiepileptic drug | 0 | ESM | 0 | VPA/ESM/LTG | 0 | VPA/LTG | VPA | VPA/CLB | 0 | 0 |
| | CGI | Much improved | Very much improved | Very much improved | Much improved | Very much improved | Much improved | Much improved | Much improved | Mini improved | Much improved |
| MAD M3 | Seizure type | 0 | 0 | 0 | Absences | | 0/↓FS | ↓Absences | 0 | 0 | 0 |
| | MD | Free of MD | 0 | Free of MD | 0 | | 0 | Free of MD | Free of MD | Free of MD | Free of MD |
| | Antiepileptic drug | 0 | ESM | 0 | VPA/LTG | | LTG/ESM | ↑VPA | VPA | 0 | 0 |
| | CGI | Much improved | Very much improved | Very much improved | Much improved | | Much improved | Mini improved | Much improved | Mini improved | Much improved |
| MAD M6 | Seizure type | 0 | 0 | 0 | Absences | | 0/↓FS | ↑Absences | 0 | | 0 |
| | MD | Free of MD | 0 | Free of MD | 0 | | 0 | Free of MD | →PMD | | Free of MD |
| | Antiepileptic drug | 0 | 0 | 0 | VPA/↑LTG | | LTG/ESM | ESM | SUL | | 0 |
| | CGI | Much improved | Very much improved | Very much improved | Min improved | | Much improved | Mini | Mini | | Much improved |
| MAD M12 | Seizure type | | | 0 | Absences | | 0 | →Absences | 0 | | 0 |
| | Movement disorder | | | Free of MD | 0 | | 0 | Free of MD | →PMD | | Free of MD |
| | Antiepileptic drug | | | 0 | ↑VPA/LTG | | LTG/ESM | ESM/LTG | SUL | | 0 |
| | CGI | | | Very much improved | No change | | Much improved | Mini | Mini | | Much improved |

| | | Patients | | | | | | | | | |
|---------------------------|--------------------|---------------|--------------------|--------------------|---------------|--------------------|---------------|---------------|---------------|---------------|---------------|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Age at diet start | | 3y 10m | 13m | 8m | 4y 11m | 8y | 4y6m / 8y3m | 12y | 11y | 16y | 8y / 12y |
| Type of diet | | MAD | MAD | MAD | MAD | MAD | KD/MAD | MAD | MAD | MAD | KD/MAD |
| Duration of MAD treatment | | 11m | 11m | 4y | 1y10m | 3y9m | 15m | 2y6m | 3y | 6m | 6y |
| Seizure type | | 0 | 0 | 0 | Absences | 0 | 0/FS | 0 | ↓GTC | 0 | 0 |
| MAD M1 | MD | Free of MD | 0 | Free of MD | 0 | Free of MD | 0 | Free of MD | ↓PMD | Free of MD | Free of MD |
| | Antiepileptic drug | 0 | ESM | 0 | VPA/ESM/LTG | 0 | VPA/LTG | VPA | VPA/CLB | 0 | 0 |
| | CGI | Much improved | Very much improved | Very much improved | Much improved | Very much improved | Much improved | Much improved | Much improved | Mini improved | Much improved |
| MAD M3 | Seizure type | 0 | 0 | 0 | Absences | | 0/↓FS | ↓Absences | 0 | 0 | 0 |
| | MD | Free of MD | 0 | Free of MD | 0 | | 0 | Free of MD | Free of MD | Free of MD | Free of MD |
| | Antiepileptic drug | 0 | ESM | 0 | VPA/LTG | | LTG/ESM | ↑VPA | VPA | 0 | 0 |
| | CGI | Much improved | Very much improved | Very much improved | Much improved | | Much improved | Mini improved | Much improved | Mini improved | Much improved |
| MAD M6 | Seizure type | 0 | 0 | 0 | Absences | | 0/↓FS | ↑Absences | 0 | | 0 |
| | MD | Free of MD | 0 | Free of MD | 0 | | 0 | Free of MD | →PMD | | Free of MD |
| | Antiepileptic drug | 0 | 0 | 0 | VPA/↑LTG | | LTG/ESM | ESM | SUL | | 0 |
| | CGI | Much improved | Very much improved | Very much improved | Min improved | | Much improved | Mini | Mini | | Much improved |
| MAD M12 | Seizure type | | | 0 | Absences | | 0/↓FS | →Absences | 0 | | 0 |
| | Movement disorder | | | Free of MD | 0 | | 0 | Free of MD | →PMD | | Free of MD |
| | Antiepileptic drug | | | 0 | ↑VPA/LTG | | LTG/ESM | ESM/LTG | SUL | | 0 |
| | CGI | | | Very much improved | No change | | Much improved | Mini | Mini | | Much improved |

| | | Patients | | | | | | | | | |
|---------------------------|--------------------|---------------|--------------------|--------------------|---------------|--------------------|---------------|---------------|---------------|---------------|---------------|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Age at diet start | | 3y 10m | 13m | 8m | 4y 11m | 8y | 4y6m / 8y3m | 12y | 11y | 16y | 8y / 12y |
| Type of diet | | MAD | MAD | MAD | MAD | MAD | KD/MAD | MAD | MAD | MAD | KD/MAD |
| Duration of MAD treatment | | 11m | 11m | 4y | 1y10m | 3y9m | 15m | 2y6m | 3y | 6m | 6y |
| Seizure type | | 0 | 0 | 0 | Absences | 0 | 0/FS | 0 | ↓GTC | 0 | 0 |
| MAD M1 | MD | Free of MD | 0 | Free of MD | 0 | Free of MD | 0 | Free of MD | ↓PMD | Free of MD | Free of MD |
| | Antiepileptic drug | 0 | ESM | 0 | VPA/ESM/LTG | 0 | VPA/LTG | VPA | VPA/CLB | 0 | 0 |
| | CGI | Much improved | Very much improved | Very much improved | Much improved | Very much improved | Much improved | Much improved | Much improved | Mini | Much improved |
| MAD M3 | Seizure type | 0 | 0 | 0 | Absences | | 0/↓FS | ↓Absences | 0 | 0 | 0 |
| | MD | Free of MD | 0 | Free of MD | 0 | | 0 | Free of MD | Free of MD | Free of MD | Free of MD |
| | Antiepileptic drug | 0 | ESM | 0 | VPA/LTG | | LTG/ESM | ↑VPA | VPA | 0 | 0 |
| | CGI | Much improved | Very much improved | Very much improved | Much improved | | Much improved | Mini improved | Much improved | Mini improved | Much improved |
| MAD M6 | Seizure type | 0 | 0 | 0 | Absences | | 0/↓FS | ↑Absences | 0 | | 0 |
| | MD | Free of MD | 0 | Free of MD | 0 | | 0 | Free of MD | →PMD | | Free of MD |
| | Antiepileptic drug | 0 | 0 | 0 | VPA/↑LTG | | LTG/ESM | ESM | SUL | | 0 |
| | CGI | Much improved | Very much improved | Very much improved | Min improved | | Much improved | Mini | Mini | | Much improved |
| MAD M12 | Seizure type | | | 0 | Absences | | 0/↓FS | →Absences | 0 | | 0 |
| | Movement disorder | | | Free of MD | 0 | | 0 | Free of MD | →PMD | | Free of MD |
| | Antiepileptic drug | | | 0 | ↑VPA/LTG | | LTG/ESM | ESM/LTG | SUL | | 0 |
| | CGI | | | Very much | No change | | Much improved | Mini | Mini | | Much |

Discussion

- Already 20 patients reported in the literature
- Mostly case reports
 - Including 6 patients Mov Disorders
- Mostly seizure free on MAD (62-69% with KD)
- Also effective on MD (41% with KD)

Leen et al. 2010
Pong et al. 2012

Discussion

- 2 patients were switch from KD to MAD
 - No change in neurological symptoms
 - Growth
 - Physical activity
 - Fatigue

Discussion

- Various level of ketosis by KD, MAD, MCT
- How to conduct the diet?
- What is the ketosis requirement in each patient?
- Always have in mind the possibility to switch to KD (symptoms / development)

Conclusion

- MAD seems to have similar efficacy than KD on Sz and MAD
- KD should be offered in non-responder to MAD
- Most important point remains diagnosis delay
- Interest to have a diet than can be keep for the long-term
- Need to be further studied
- Same cognitive outcome?????

How to address the cognitive issue?

- The inclusion criteria will be:
 - GLUT1-DS diagnosis (clinical history + CSF)
 - Diagnosis delay <1y (first symptom to diagnosis)
 - MAD duration for at least 2 years (possible to include patient initially on KD but duration MAD > duration KD)
 - Age > or = 6-year-old and Age < 18-year-old

Evaluation of cognition by WISC

Merci pour votre attention

DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY

ORIGINAL ARTICLE

Use of modified Atkins diet in glucose transporter type 1 deficiency syndrome

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