Dietary Therapy

What are the parents *actually* doing?

Eric H. Kossoff, MD

Professor, Neurology and Pediatrics

Medical Director, Ketogenic Diet Program

Johns Hopkins Hospital

Baltimore, Maryland USA

GLUT 1 onlus Associazione Italiana

MATTHEW'S FRIENDS • Glut1UK • Ketogenic Dietary Therapies Information • Training • Research • Support Registered Charity No. 1108016

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The State-and-Region Agreement asks for a declaration by Moderators, Speakers, Teachers and Tutors about the frankness of the financing sources and about their relationships with people with commercial interests within the last two years, only if there could be a conflict of interests.
The documents must be available at the Provider offices for at least 5 years.

Conflict of Interests Declaration

Undersigned ___Eric Kossoff MD_____ as:

☐ scientific responsible ☐ moderator ☐ teacher X speaker ☐ tutor

of the event "**1st European Conference on Glut1 Deficiency**"
Milan - Italy, 7th-8th October 2016

Based on Art.. 3.3 about the Conflict of Interests, page 18,19 of the State-and-Region Agreement dated 19 April 2012, managed by **Biomedia n. 148**

Declares

☐ that in the last two years DIDN'T have any relationships about comercial financings with people having conflict of interests in the health field

X that in the last two years HAD relationships about comercial financings with people having conflict of interests in the health field (please specify the names):

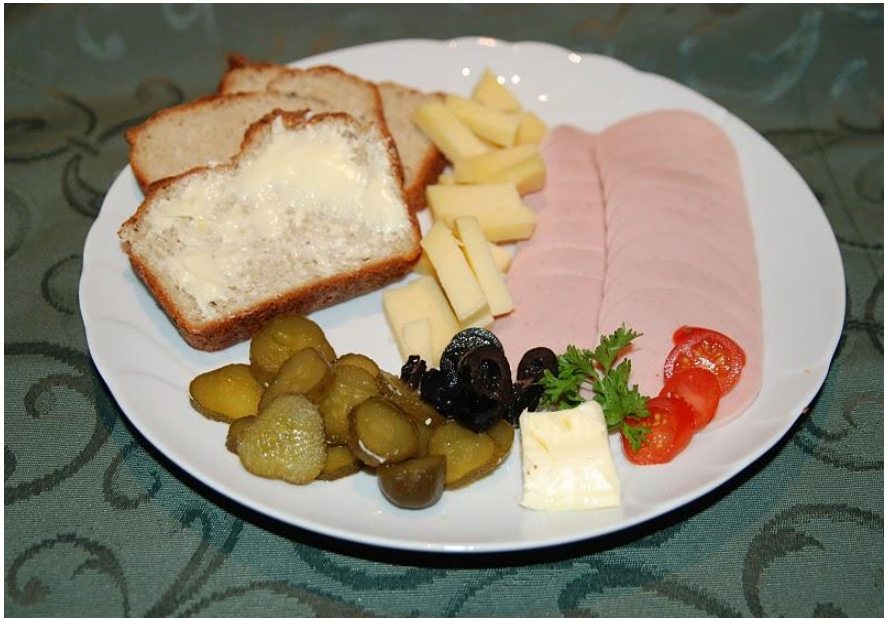
Atkins Nutritionals (Advisory Board)
Nutricia (Consulting)
GW Pharma (Data Safety Monitoring Board)
Demos (Book royalties)

Eur J Pediatr
DOI 10.1007/s00431-016-2765-z

REVIEW

The changing face of dietary therapy for epilepsy

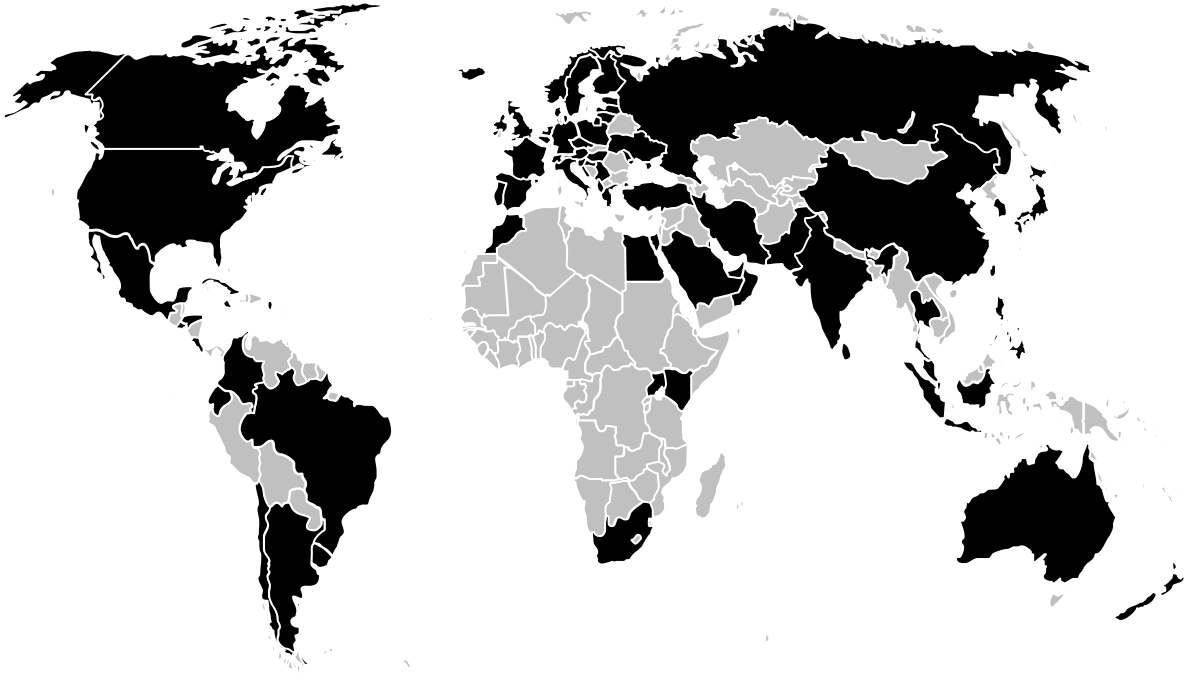
Ludovica Pasca[1] · Valentina De Giorgis[1,2] · Joyce Ann Macasaet[3] · Claudia Trentani[4] · Anna Tagliabue[4] · Pierangelo Veggiotti[1,2]



4.5 Witloof met mozarella en spek

Ingrediënten:

- 85 gr witloof
- 10 gr mozarella
- 25 gr spek
- 15 gr Becel bakken en braden



☆ 做法：1.將蛋打成蛋液，約用 MCT oil 5g 做蛋皮，

將紅蘿蔔及小黃瓜切條汆燙待用。

2.飯加代糖、醋拌勻。

3.蛋皮包所有材料捲起，切斜塊即可。


NUTRICIA
KetoCal 3:1
NUTRICIA
KetoCal 4:1
Liquigen
KetoCal 4:1 LQ
KetoCal 4:1 LQ


A nutritionally complete, ketogenic supplement
in a 4:1 ratio
KetoKid
Ketogenic Diet Specially Formulated For Epilepsy
Natural Vanilla Flavour
Sugar Free
Enriched with DHA & EPA
Gluten Free
Lactose Free
Net Wt 200g


KetoGEN
4:1 ratio product
Medical Food


KETOGENIC DIET
HEALTH CARE DRINKS
Net:250ml


CAMBROOKE
THERAPEUTICS
KetoVie
4:1
chocolate
LIQUID
CAMBROOKE
THERAPEUTICS
KetoVie
4:1
vanilla
LIQUID


Microlipid
3 FL OZ (88.7 mL)


SOL CARB
When extra calories are needed.
Pour un apport supplémentaire
en calories.


SAMPLE
日清 MCT
パウダー
たんぱく質ゼロ
加えるだけで
エネルギーアップ
(764kcal/100g) 250g


RCF
Free Carbohydrate Free
SOY FORMULA BASE WITH IRON
Concentrated Liquid
13 FL OZ (384 mL)


Namyang
KETONIA
180 mL

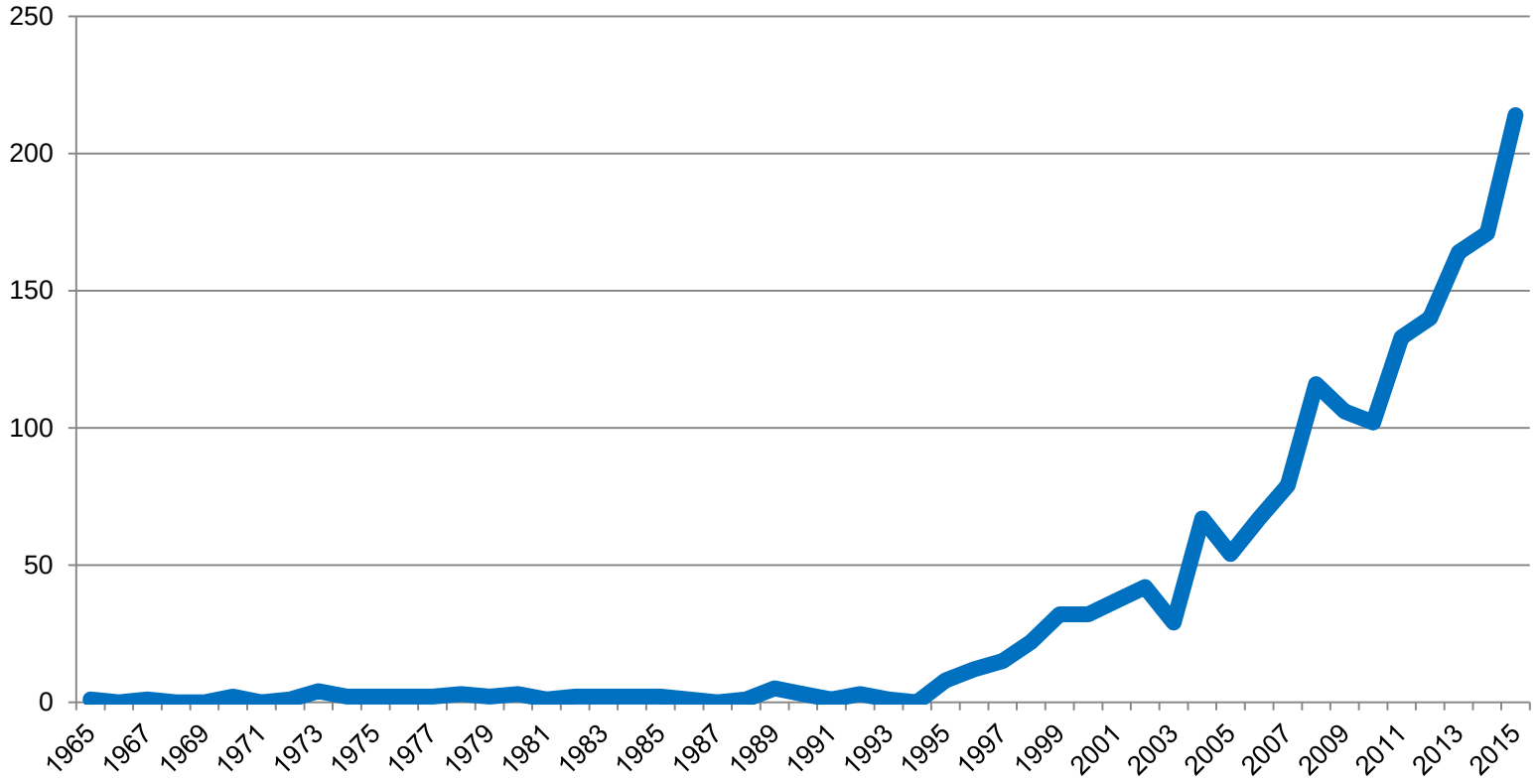

MEIJI
特殊ミルク
No.817-B
ケトンフォーミュラ


KetoVOLVE
4:1 Ratio Powder
Medical Food

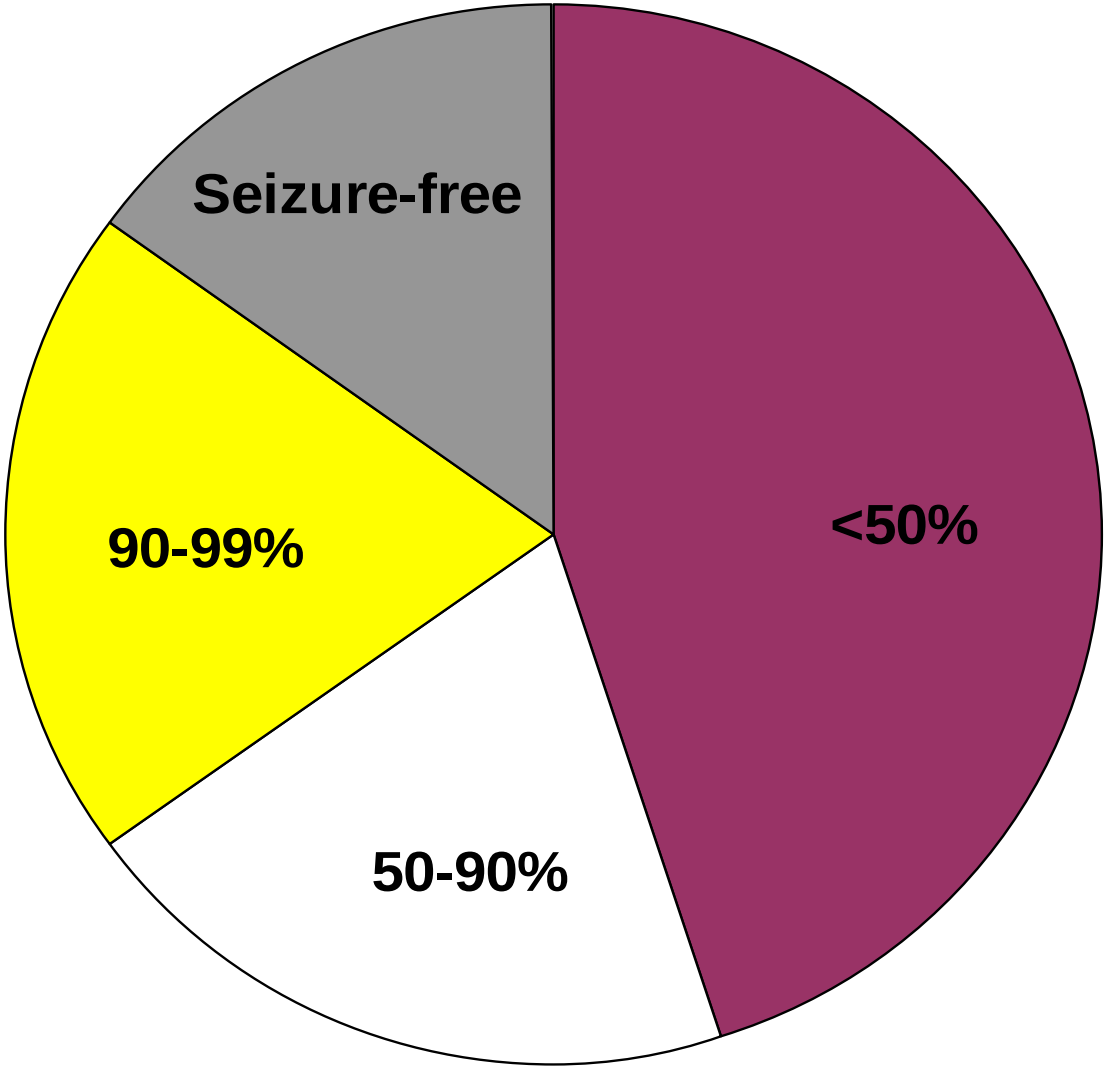

carb
zero


beta
quik

Ketogenic Diet Studies Published



6-Month Seizure Reduction from Ketogenic Diet



BRIEF COMMUNICATION

A blinded, crossover study of the efficacy of the ketogenic diet

*John M. Freeman, *Eileen P.G. Vining, *Eric H. Kossoff, *Paula L. Pyzik, *Xiaobu Ye, and †Steven N. Goodman

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

FULL-LENGTH ORIGINAL RESEARCH

Use of the modified Atkins diet for treatment of refractory childhood epilepsy: A randomized controlled trial

*[1]Suvasini Sharma, *[2]Naveen Sankhyan, *Sheffali Gulati, and †Anuja Agarwala

Acta Neurologica Scandinavica

Acta Neurol Scand DOI: 10.1111/ane.12592

ACTA NEUROLOGICA SCANDINAVICA

A randomized controlled trial of the ketogenic diet in refractory childhood epilepsy

Lambrechts DAJE, de Kinderen RJA, Vles JSH, de Louw AJA, Aldenkamp AP, Majoie HJM. A randomized controlled trial of the ketogenic diet in refractory childhood epilepsy.
Acta Neurol Scand: DOI: 10.1111/ane.12592.

D. A. J. E. Lambrechts[1], R. J. A. de Kinderen[2,3,4], J. S. H. Vles[1,2,5], A. J. A. de Louw[1,6], A. P. Aldenkamp[2,5,6,7], H. J. M. Majoie[1,2,5,8]

Ketogenic diet and other dietary treatments for epilepsy (Review)

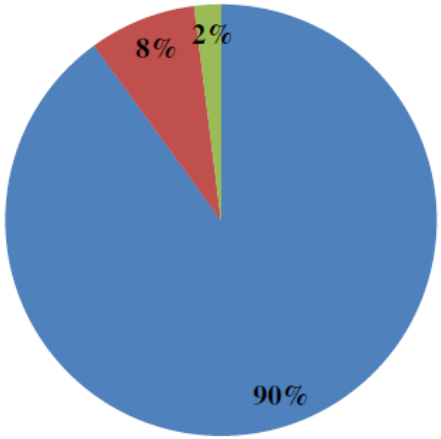
Levy RG, Cooper PN, Giri P, Pulman J

2012

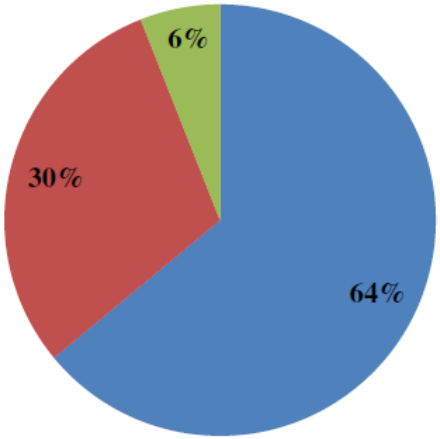
"These studies suggest that in children, the ketogenic diet results in short to medium term benefits in seizure control, the effects of which are comparable to modern antiepileptic drugs."

Four Different Diets Today

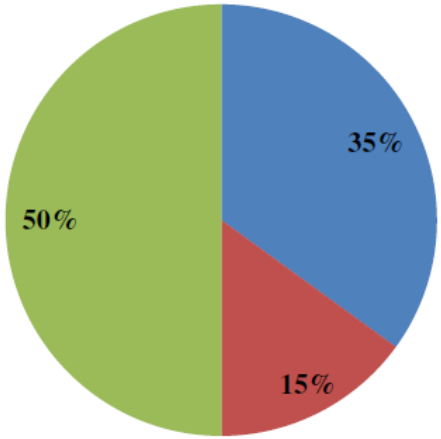
1. Classic ketogenic diet 1921
2. Medium chain triglyceride diet 1970
3. *Modified Atkins Diet* 2003
4. Low Glycemic Index Treatment 2005



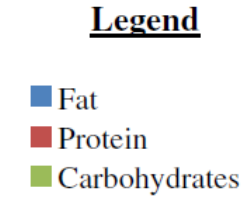
Ketogenic Diet



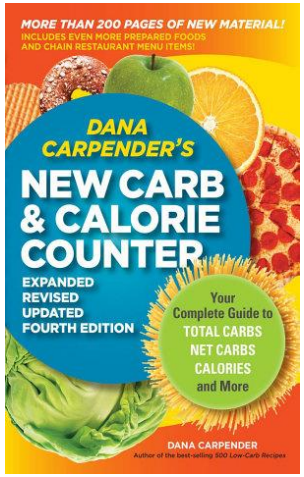
Modified Atkins Diet



Standard Diet



- No calorie or fluid restriction
- No hospital admission
- No fasting
- No weighing of foods on gram scales
  - *15-20 grams carbohydrate/day*



Cochrane Library

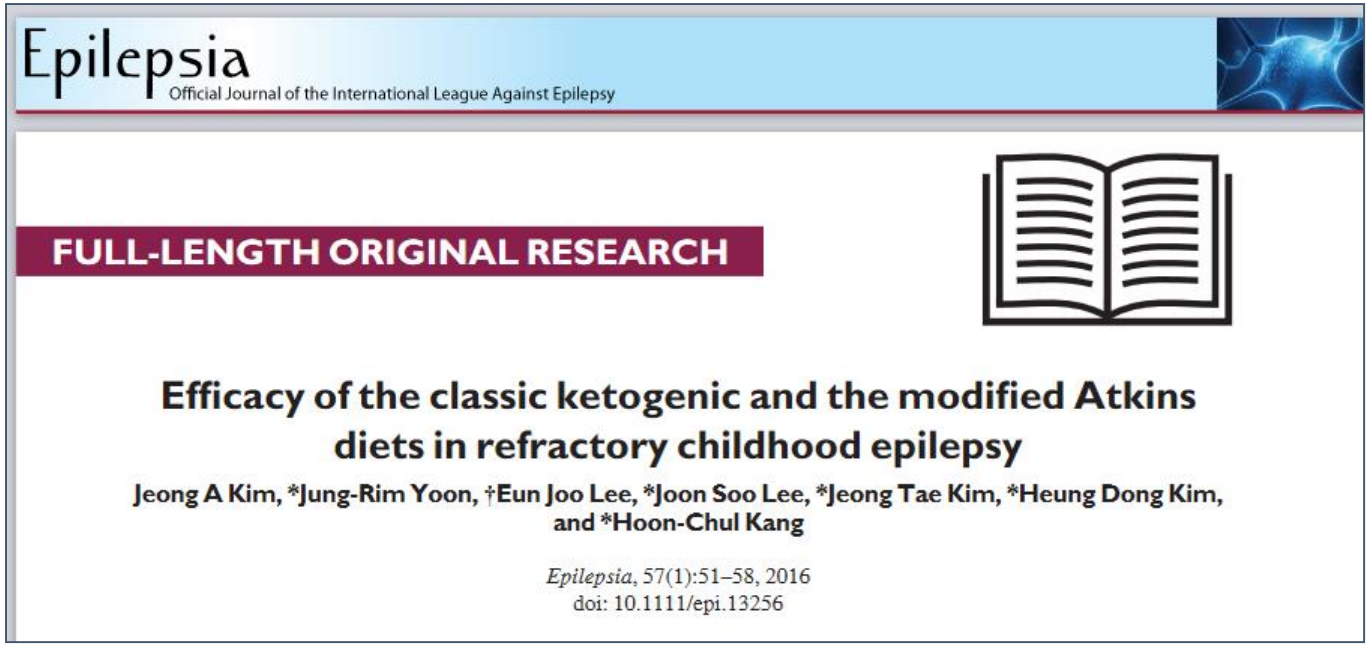
Cochrane Database of Systematic Reviews

Ketogenic diet and other dietary treatments for epilepsy (Review)

Martin K, Jackson CF, Levy RG, Cooper PN

February 2016

"Other more palatable but related diets, such as the modified Atkins KD, may have a similar effect on seizure control as classical KD but this assumption requires more investigation"



Epilepsia
Official Journal of the International League Against Epilepsy

FULL-LENGTH ORIGINAL RESEARCH

Efficacy of the classic ketogenic and the modified Atkins diets in refractory childhood epilepsy

Jeong A Kim, *Jung-Rim Yoon, †Eun Joo Lee, *Joon Soo Lee, *Jeong Tae Kim, *Heung Dong Kim, and *Hoon-Chul Kang

Epilepsia, 57(1):51–58, 2016
doi: 10.1111/epi.13256

51 KD vs. 53 MAD

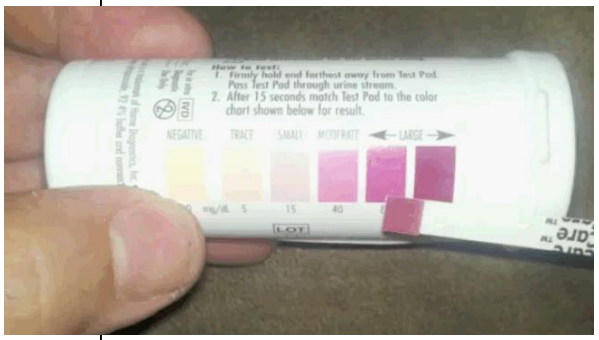
Similar efficacy and better tolerability with MAD

“The MAD might be considered as the primary choice…”

Ketogenic Diet

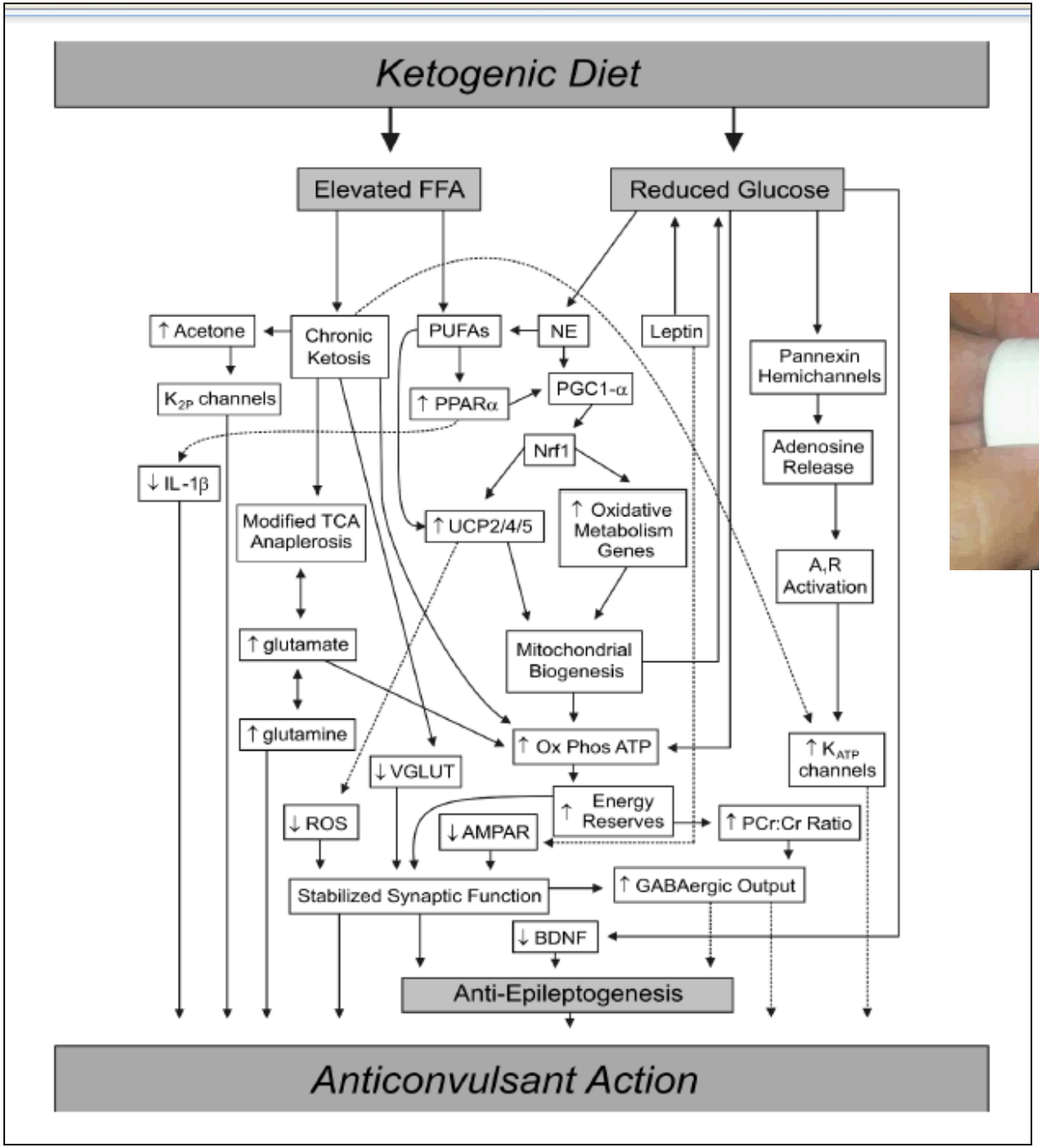
Elevated FFA

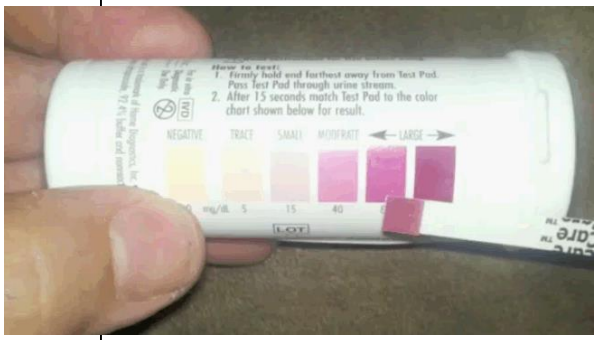
Chronic Ketosis



Masino & Rho 2012

Anticonvulsant Action





Masino & Rho 2012

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

Table 1. Epilepsy syndromes and conditions in which the KD has been reported as particularly beneficial

Probable benefit (at least two publications)
Glucose transporter protein 1 (GLUT-1) deficiency
Pyruvate dehydrogenase deficiency (PDHD)
Myoclonic-astatic epilepsy (Doose syndrome)
Tuberous sclerosis complex
Rett syndrome
Severe myoclonic epilepsy of infancy (Dravet syndrome)
Infantile spasms
Children receiving only formula (infants or enterally fed patients)
Suggestion of benefit (one case report or series)
Selected mitochondrial disorders
Glycogenosis type V
Landau-Kleffner syndrome
Lafora body disease
Subacute sclerosing panencephalitis (SSPE)

Kossoff *Epilepsia* 2009

Glut1 Deficiency Foundation

5TH ANNUAL FAMILY CONFERENCE

HOUSTON

meet • share • learn / July 11-12, 2013

GLUT1 and Dietary Therapies: 3 Key Questions

1. Is the MAD = KD?

2. What happens at puberty (and adulthood) on diets?

3. Does the level of ketosis matter?

“Pro” Argument

- GLUT1 deficiency syndrome has been historically reported as a “brain energy failure” condition
- Theoretically, higher ketosis would improve the situation
- At an early age, it would be logical to provide high quality and quantity fuel
  - Especially for cognition?
- Anecdotal reports of KD > MAD

“Con” Argument

- Anecdotal reports (and patient emails) of high ketones but persistent seizures and other issues
- MAD works for GLUT1
  - Many families reported switching diets successfully
- “the original concept that brain energy failure is reversible by means of a 3:1 or 4:1 KD apparently is far too simplistic. There is more to Glut1 deficiency syndrome than just cerebral energy failure” – Klepper *JCN* 2013

Glut1 Deficiency Foundation

2015 Conference

ORLANDO

meet • share • learn

Family Program July 6-7 | Professional Program July 8

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Pediatric Neurology and Epilepsy

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Eric H. Kossoff, M.D.

GLUT1 Ketogenic Diet Survey

Participation in this survey is completely voluntary. No names will be recorded and no individual information will be shared.

1. What diet is your child receiving currently? (Circle)
   KETOGENIC DIET MODIFIED ATKINS DIET LOW GLYCEMIC INDEX TX NONE
2. If your child is no longer receiving any of these diets, please state why it was stopped (or why it was not started)? (Leave blank if still on a diet)
   _____
   _____
   _____
   _____
3. My child is a BOY / GIRL (circle)
4. How old is your child now? _____years__
5. When was GLUT1 Deficiency syndrome diagnosed? _____years
6. How old was your child when the diet was started? _____years__
   How long has your child been on the diet? _____
7. KETOGENIC DIET INFORMATION
   Current Ratio? 4:1 3:1 2:1 Higher than 4:1
   Did your child fast when the diet was started? YES / NO
   Was your child admitted to the hospital? YES / NO
8. Has your ketogenic diet center discussed coming off the diet ever? YES / NO
   - If no, have they specifically said it's a lifelong treatment? YES / NO
   - Do you plan to take your child off ever? YES / NO / NOT SURE
9. Has your ketogenic diet center discussed transitioning to the MAD? YES / NO
10. Have you ever switched from KD to MAD (or LGIT)? YES / NO. If yes, please provide details:
    _____
    _____
11. Do you check ketones through (circle all that apply): URINE / BLOOD / NEITHER
12. Do you see a relationship between seizures and ketones? YES / NO / NOT SURE / (NO SEIZURES)
13. Do you see a relationship between learning/behavior/movement (circle) and ketones? YES / NO / NOT SURE
14. If your child has reached puberty, did you see a change in ketones when puberty came? YES / NO. Was there a change in seizures? YES / NO
15. Is your child on any extra ketogenic diet supplements? (please circle any that apply)
    Carnitine
    Extra oils (C7, MCT, etc)
    Polycitra/Cytra K
    Other: _____
16. Is your child on antiseizure medications? YES / NO. If yes, which ones?
    _____
17. Compared to before the diet, how much better are seizures now? (Circle)
    100% gone (seizure-free)
    90-99% gone (once in a while)
    50-90% better (improved, but still frequent)
    0-50% improved (really not better – we're thinking of coming off)
18. Have there been any side effects related to the diet? If so, please describe:
    _____
19. Have you discovered any tricks to allow your child to be successful on the diet for long periods that you'd like to share?
    _____
20. Any additional comments you'd like to add about your families' experience with the ketogenic diet?
    _____
    _____
    _____

Thank you for your participation in this survey!
We will share the results at the next GLUT1 Deficiency Foundation meeting!

Eric Kossoff MD

Glenna Steele

Glut1 Deficiency Foundation

www.G1DFoundation.org

Seizure 35 (2016) 83–87

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Use of dietary therapies amongst patients with GLUT1 deficiency syndrome

Hannah R. Kass [a], S. Parrish Winesett [b], Stacey K. Bessone [b], Zahava Turner [c], Eric H. Kossoff [c,*]

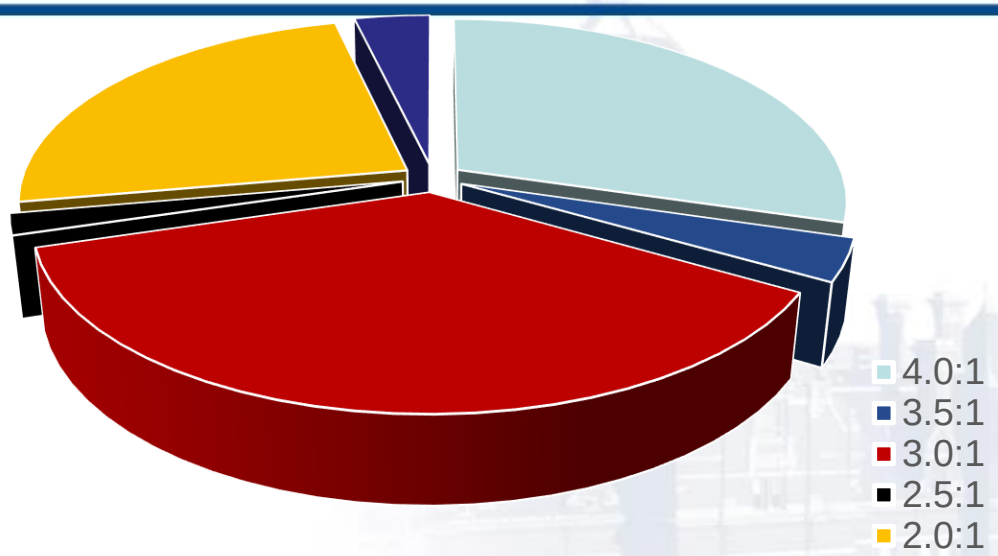
[a] University of Mary Washington, Fredericksburg, VA, USA
[b] Johns Hopkins All Children's Hospital, St. Petersburg, FL, USA
[c] Johns Hopkins Hospital, Baltimore, MD, USA

Results: Overall

- 92 families completed the survey
  - 55% at the Orlando meeting
- Current age: 1-24 years (mean: 9.9 years)
  - GLUT1 diagnosis: 0.1 – 18 years (mean 4.8 years)
- 90 had been treated with diet therapy

Results: Wide Range of Diets!

- KD – 59
- MAD – 29
- MCT – 4
- LGIT – 2



- Switching was common! 27% changed diets during their treatment.
- Many started with KD and changed to MAD

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Seizure Reduction Overall

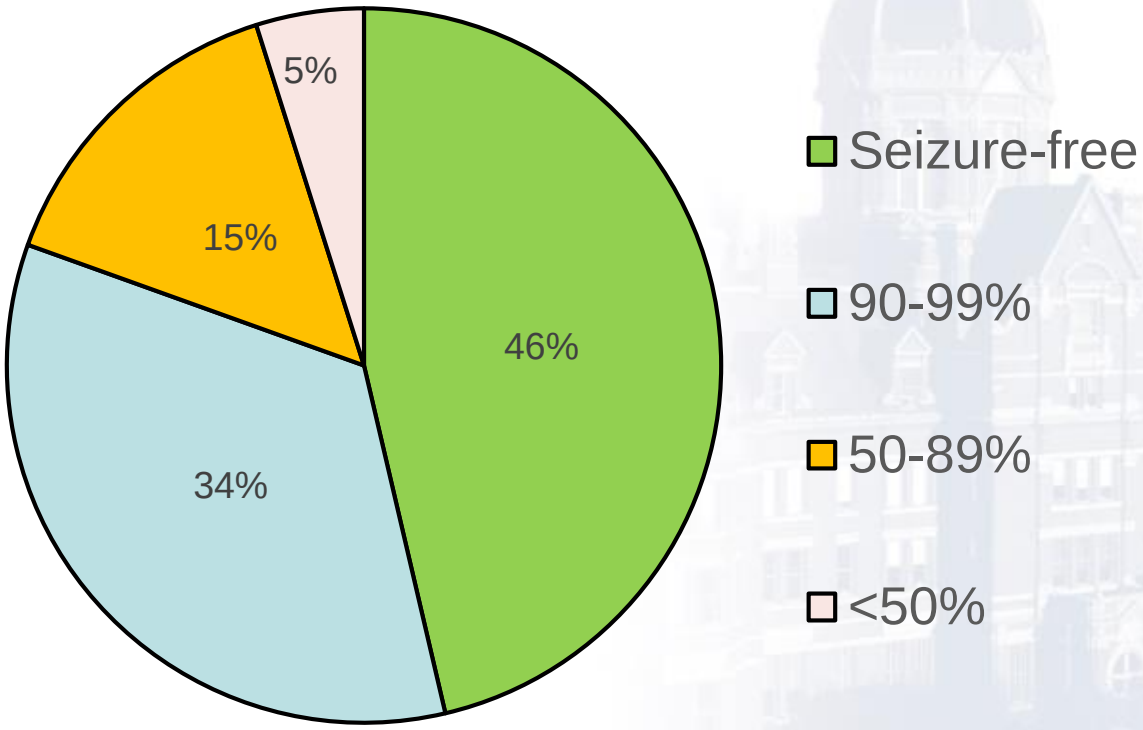

Table 1
Factors correlated with presence of reported seizure freedom.

Factor	Presence ($n=38$)	Absence ($n=46$)	p value
Mean age at GLUT1 diagnosis (years), (SD)	3.8 (3.5)	5.3 (3.4)	0.05
Mean age at diet onset (years), (SD)	4.0 (3.6)	5.0 (3.5)	0.22
Mean current age (years), (SD)	8.2 (5.7)	11.6 (5.2)	0.01
KD/MCT currently	28 (74%)	29 (63%)	0.30
4:1 KD	5 (13%)	11 (24%)	0.21
Checking blood ketones	22 (58%)	25 (54%)	0.74
Fasted at diet onset	17 (45%)	20 (43%)	0.91
Gender (female)	19 (50%)	23 (50%)	1.00
On anticonvulsants?	5 (13%)	26 (57%)	<0.001
Survey collected at GLUT1DF meeting?	19 (50%)	24 (52%)	0.84
On carnitine?	23 (61%)	25 (54%)	0.57

Table 1
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On carnitine?	23 (61%)	25 (54%)	0.57

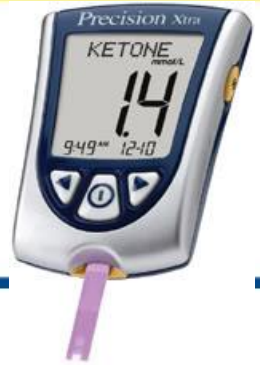
Results: Concurrent Medications

- 32 (36%) were on medications
  - Wide variety: levetiracetam (8), acetazolamide (6), lamotrigine (6), ethosuximide (4)
- Only 1 with valproate, zero on phenobarbital
- Many were on “extra” supplementation
  - Carnitine (52), oral citrates (25), MCT oil (20)

Results: Other Diet Benefits

- 76 of 76 had improvement in abnormal movements and/or cognition
  - 84% “much” better

Results: Ketones



- Varied monitoring
  - 34% only blood BOH, 34% only urine, 21% both, 11% neither
- 44/66 (67%) reported a correlation with ketones and seizures
- No difference in seizure freedom in those who checked blood vs. urine ketones

Results: Puberty

- 22 had reached (or finished) puberty
  - 14 (64%) reported a “change” in seizure frequency
  - 11 (50%) had a drop in ketosis

Results: Side Effects

- Side effects *reported* were common, but not overly problematic

- Constipation (24)
- Weight loss or hunger (6)
- Gastroesophageal reflux (5)
- Kidney stones (2)
- Acidosis (2)
- Elevated cholesterol (1)

Results: Discontinuation?

- Mean diet duration: 5.6 years
  - Range: 1 month - 20 years
  - 3 had stopped

- 8 (9%) planned to come off diet
- 22 (24%) said they had no plans to
- 60 (67%) were unsure

Conclusions

- The results from this survey suggest families are implementing and switching between various ketogenic diets
  - Incredible creativity
- Outcomes are outstanding regardless for extended periods of time
  - Great for seizures (and movements…)
  - 2/3 of patients without medications

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Conclusions

- Day-by-day monitoring, drugs, and supplements are also variable
- Further study needed:
  - Puberty
  - Discontinuation?
  - Correlation with ketosis
- The future…
  - Long-term outcomes
  - Adults with GLUT1…and…

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Ketogenic Diet in Glut 1 Deficiency Syndrome through the Life Cycle: Pregnancy to Neonate to Toddler

Jennifer Kramer MS RD, Noelle Carr RD CSP
Lisa Smith MD, Mandy Harris MD
Indiana University Health

Mother

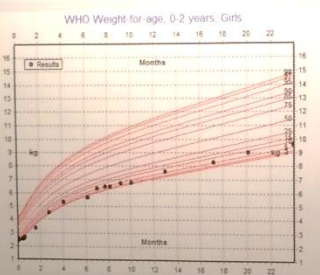
- Mother was diagnosed with Glut 1 DS at age 18. Her symptoms prior to diagnosis included migraines, dyskinesia since age 3, mild cognitive delay, and ataxia. She has been on modified Atkins diet since diagnosis.
- Mother's diagnosis included lumbar puncture (CSF glucose 38, serum glucose 101, ratio 0.37), genetic testing, normal MRI, normal 24 hour EEG
- Mother's mutation: SLC2A1 c377G>A with Amino Acid Change pARG 126His
- She was followed every 3-6 months by neurologist and dietitian. Her dyskinesia, ataxia, and migraines were under control and academics greatly improved (honor roll).
- Began college one year after diagnosis and began struggling with depression and anxiety and started Trazadone and Zoloft. She was again having some dystonic movements, headaches, and presented with anemia, and low blood ketone levels at a follow up ketogenic diet/neurology visit. She was started on iron therapy (added 325 mg FeSO4, continued basic multivitamin with minerals (18 mg iron), and high fat, low carb (20 g restriction) diet modifications were reinforced.
- She visited her primary care doctor in Feb 2014 for follow up of anxiety, depression, and anemia. She had a 20 pound weight gain with a subsequent positive pregnancy test followed by ultrasound documenting estimated 25-28 week gestation.

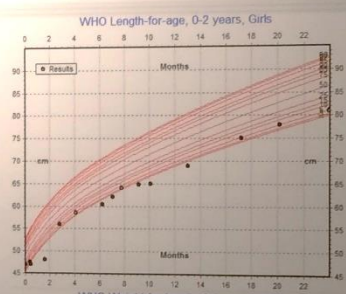
Pregnancy Management

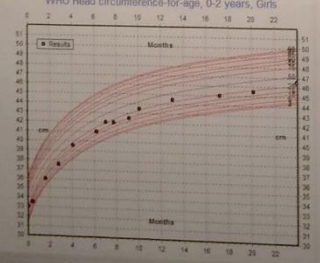
- No medical literature available, medical team consulted with Dr. Darryl DeVivo.
- Low carb (<20 g), high fat modified Atkins diet was maintained
- OB performed ultrasounds every 2 weeks and bi weekly non stress tests beginning at 32 weeks gestation– results were consistently normal
- Medications and supplements:
  - Caltrate 1200 mg, Colace prn, Zofran 4 mg prn, Zoloft 100 mg, Levocarnitine 500 mg TID, Prenatal multivitamin, Ferrous Sulfate 325 mg, Trazadone – weaned when pregnancy confirmed at 28 weeks
- Low free carnitine of 15 at 28 weeks and continued low at 37 weeks with level of 16 despite carnitine supplementation
- Declined amniocentesis and any prenatal testing for Glut 1 deficiency of the infant
- Planned induction to optimize coordination of care with OB, NICU, nutrition, and neurology – born at 39 weeks + 4 days

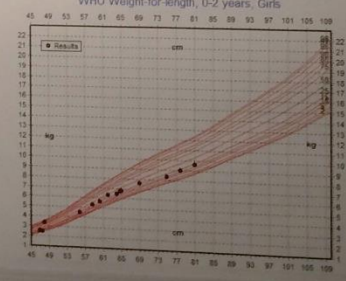
Pregnancy Concerns

- late prenatal care
- Glut 1 deficiency syndrome
- Low carb, high fat diet
- **Depression, anxiety, and complex social situation surrounding the pregnancy**









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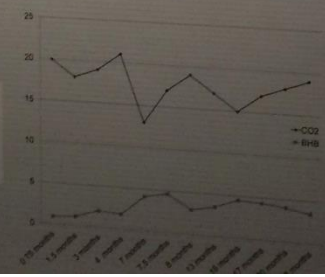
- The authors would also like to thank the families and the children themselves for trusting us to care for them.

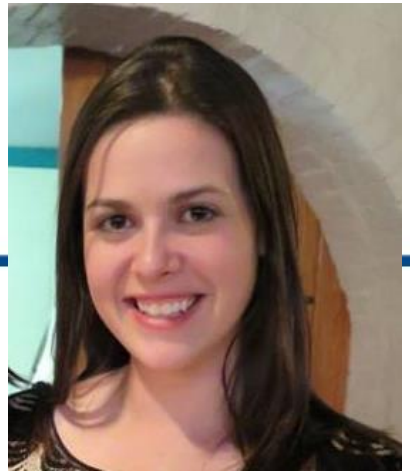


Neonate

- Term Infant Girl (39 weeks +5 days)
- APGARS 7&9, 30 minutes of skin to skin time, and then taken to NICU for observation for <12 hours due to known 50% risk of Glut 1 deficiency syndrome, meconium stained fluid, neurological exam normal, briefly required blow by oxygen.
- Initial blood glucose <40 mg/dL but increased to >60 with feeding.
- Mother declined lumbar puncture at birth
- Cord blood targeted gene analysis sent after delivery
- Social – infant was placed for open adoption
- Nutrition–fed donor breast milk at ~110 kcal/kg due to potential protective properties and high fat content until diagnosis could be determined.
- Infant discharged home on day of life 2 with adoptive parents
- Day of Life 12 – follow up with neurology, elected to do a lumbar puncture since genetic testing still pending and not expected for 2 more weeks; CSF glucose 28, serum glucose 85 with ratio of 0.32 (normal ratio 0.65).
- Day of Life 13 – admitted to NICU for initiation of ketogenic diet with presumed diagnosis of Glut 1 deficiency (cord blood results confirmed shortly after admission)
  - Normal EEG during
  - Discharged home after 3 days on 2:1 ratio 120 cal/kg with Gerber Good Start Gentle and Ketocal 4:1 powder, 20 cal/ounce + 0.5 ml Poly vi Sol with Iron
  - Low ratio chosen due to mother's mild phenotype and no neurological concerns of infant

First Two Years of Life

- Has met all developmental milestones appropriately, normal neurological exam
- Complications:
  - Slow but consistent growth trends:
    - Weight for age: 5-10%ile
    - Length for age: 2-5%ile
    - Wt/Lt ratio: 10-25%ile
    - OFC: 25%ile
  - Labs:
    - CO2: 15-19
    - Uric Acid: 6.6-7.6
    - Nephrocalcinosis – followed by Peds Nephrology and managed with 3 mEq/kg bicarbonate with goal of CO2>20
    - BHB: consistently 3-5 mmol/L after 6 months of age
  - Feeding:
    - Difficulty accepting solids; began offering at 5-6 months of age
    - Referred for feeding



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