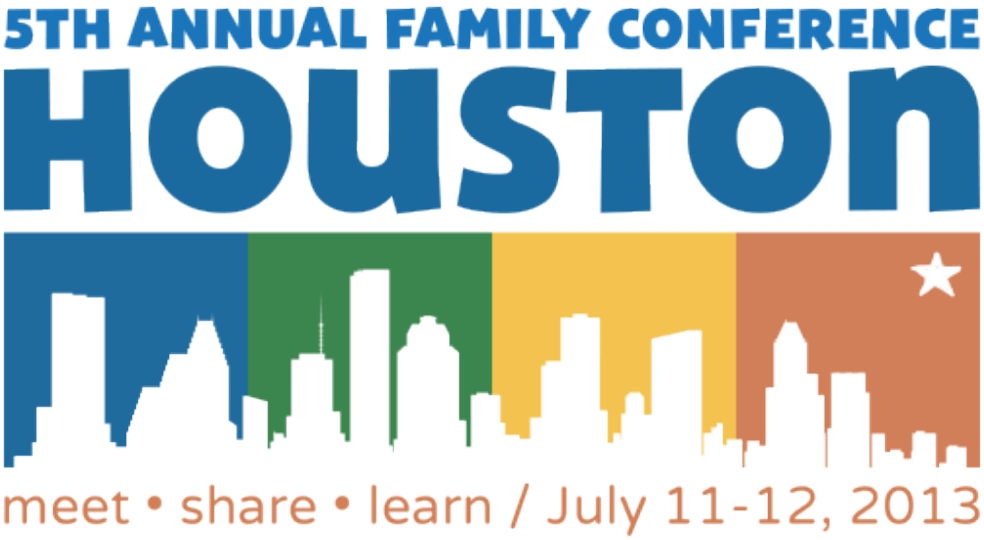
2013 Glut1 Deficiency Foundation Conference Summary Report



gratitude and credit to Kris Engelstad and all the speakers for helping prepare the presentation summaries

Glucose Transporter Type 1 Deficiency Syndrome is regularly referenced using a variety of terms, and these individual summaries were no exception. In the interest of clarity and uniformity, we have used the term Glut1 Deficiency throughout the summary.

Glucose Transporter Type 1 Deficiency Syndrome is also known as: Glut1 Deficiency, G1D, Glut1 DS, Glut-1 DS, Glut1, Glut-1, Glut 1, GLUT1, and De Vivo Disease

Glut1 Deficiency Foundation 2013 Conference Summary

Juan M. Pascual, MD, PhD
Director, Rare Brain Disorders Clinic and Laboratory
Departments of Neurology and Neurotherapeutics, Physiology and Pediatrics
The University of Texas Southwestern Medical Center

Glucose Transporter Type I Deficiency (G1D): The Year in Review and a Look Ahead

In contrast with where we were 5 years ago, today, a researcher or physician can develop an academic career just working on Glut1 Deficiency.

I. Review of the Prior Year

The University of Texas Southwestern Medical Center information:

700 beds
5 Nobel prize recipients.
Is primarily a research institution.
There are over 20 scientists associated with the laboratory.

II. Approach to Glut1 Deficiency and Related disorders

We need to get better at testing for Glut1 Deficiency and other related disorders.
Our main goals are: testing, understanding and treating patients.

III. Accomplishments in 2012-2013

- Lab expands in staff and size
- Staffing and operation of rodent EMU University core facility (Pascual lab)
- 5 new recruits (Kelly, Trent, Tondo, Rajasekaran, Jakkamsett)
- New NIH-funded Departmental clinical research infrastructure (NeuroNEXT)
- Zale-Lipshy University Hospital scheduled to become Neurological Institute
- Children's Medical Center opens inpatient Center for the Neurosciences
- Bruce Beutler, MD, establishes (eventually 1-million) mutant mouse colony
- Triheptanoin (C7) clinical study completed
- Once Upon a Time Foundation Professorship established
- Pascual and Rosenberg (editors): Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease (5th edition; forthcoming)
- We have 3 grants under review by NIH currently (the NIH normally funds only the top 15% of grants)

Our productivity:

- Two new NIH grants
- 10 peer-reviewed articles published in scientific and medical journals since last meeting.
- We have a review on Glut1 Deficiency in "Gene Reviews".
- 2 textbooks being edited and written.
- 8 book chapters were written.
- We have also partnered with the "Office of Rare Disorders" at the NIH.
- Children's Medical Center offers Glut1 Deficiency DNA testing for patients.
- This partnership also involves creating a public information resource as part of this grant. Website: http://childbrainfoundation.org/g1d_pre.html

Main grants

- NIH R01 grant funded (Lu and Pascual) Modulation of brain activity by control of the inspired air
- NIH R01 grant funded: (Pascual) Modulation of neural excitability under energy failure
- NIH R01 grant funded (Lu and Pascual) Normalized functional MRI in human brain disorders
- NIH U10 grant funded: Network for Excellence in Neuroscience Clinical Trials (Department of Neurology and Neurotherapeutics and Pascual)
- NIH U54 grant funded (Pascual; Direct NMR observation of muscle and brain oxidative metabolism) as part of the North American Mitochondrial Disease Consortium (Hirano)
- NIH P41 grant renewed (Pascual; NMR investigation of inborn errors of metabolism) as part of the UT Southwestern Advanced Imaging Research Center (Malloy & Sherry)
- Under review at NIH: U54, R01, U01 grant applications

Main peer-reviewed publications

High-resolution detection of ^{13}C multiplets from the conscious mouse brain by ex vivo NMR spectroscopy.
Marin-Valencia I, Good LB, Ma Q, Jeffrey FM, Malloy CR, Pascual JM *.
J Neurosci Methods. 2012 Jan 15;203(1):50-5. Epub 2011 Sep 17.

2-hydroxyglutarate detection by magnetic resonance spectroscopy in IDH-mutated patients with gliomas.
Choi C, Ganji SK, DeBerardinis RJ, Hatanpaa KJ, Rakheja D, Kovacs Z, Yang XL, Mashimo T, Raisanen JM, Marin-Valencia I, Pascual JM, Madden CJ, Mickey BE, Malloy CR, Bachoo RM, Maher EA.
Nat Med. 2012 Jan 26;18(4):624-9. doi: 10.1038/nm.2682.

Glucose metabolism via the pentose phosphate pathway, glycolysis and Krebs cycle in an orthotopic mouse model of human brain tumors.
Marin-Valencia I, Cho SK, Rakheja D, Hatanpaa KJ, Kapur P, Mashimo T, Jindal A, Vemireddy V, Good LB, Raisanen J, Sun X, Mickey B, Choi C, Takahashi M, Togao O, Pascual JM, Deberardinis RJ, Maher EA, Malloy CR, Bachoo RM.
NMR Biomed. 2012 Oct;25(10):1177-86. doi: 10.1002/nbm.2787. Epub 2012 Mar 1.

Metabolism of [U-(13) C]glucose in human brain tumors in vivo.
Maher EA, Marin-Valencia I, Bachoo RM, Mashimo T, Raisanen J, Hatanpaa KJ, Jindal A, Jeffrey FM, Choi C, Madden C, Mathews D, Pascual JM, Mickey BE, Malloy CR, Deberardinis RJ.
NMR Biomed. 2012 Nov;25(11):1234-44. doi: 10.1002/nbm.2794. Epub 2012 Mar 15.

Analysis of tumor metabolism reveals mitochondrial glucose oxidation in genetically diverse human glioblastomas in the mouse brain in vivo.
Marin-Valencia I, Yang C, Mashimo T, Cho S, Baek H, Yang XL, Rajagopalan KN, Maddie M, Vemireddy V, Zhao Z, Cai L, Good L, Tu BP, Hatanpaa KJ, Mickey BE, Matés JM, Pascual JM, Maher EA, Malloy CR, Deberardinis RJ, Bachoo RM.
Cell Metab. 2012 Jun 6;15(6):827-37.

Effect of hypoxia and hyperoxia on cerebral blood flow, blood oxygenation, and oxidative metabolism.
Xu F, Liu P, Pascual JM, Xiao G, Lu H.
J Cereb Blood Flow Metab. 2012 Oct;32(10):1909-18. doi: 10.1038/jcbfm.2012.93. Epub 2012 Jun 27.

Cortical metabolism in pyruvate dehydrogenase deficiency revealed by ex vivo multiplet (13)C NMR of the adult mouse brain.
Marin-Valencia I, Good LB, Ma Q, Malloy CR, Patel MS, Pascual JM *.
Neurochem Int. 2012 Dec;61(7):1036-43. doi: 10.1016/j.neuint.2012.07.020. Epub 2012 Aug 3.

Glut1 deficiency (G1D): Epilepsy and metabolic dysfunction in a mouse model of the most common human phenotype.
Marin-Valencia I, Good LB, Ma Q, Duarte J, Bottiglieri T, Sinton CM, Heilig CW, Pascual JM *.
Neurobiol Dis. 2012 Oct;48(1):92-101. Epub 2012 Apr 23.

Heptanoate as a neural fuel: energetic and neurotransmitter precursors in normal and glucose transporter I-deficient (G1D) brain.
Marin-Valencia I, Good LB, Ma Q, Malloy CR, Pascual JM *
J Cereb Blood Flow Metab 2013 Feb;33(2):175-182. doi: 10.1038/jcbfm.2012.151. Epub 2012 Oct 17.

Systemic Metabolic Abnormalities in Adult-onset Acid Maltase Deficiency: Beyond Muscle Glycogen Accumulation.
Pascual JM *, Roe CR
JAMA Neurol. 2013 Jun 1;70(6):756-63. doi: 10.1001/jamaneurol.2013.1507

Modeling of brain metabolism and pyruvate compartmentation using $_{13}$C NMR in vivo: caution required.
Jeffrey FM, Marin-Valencia I, Good LB, Shestov AA, Henry PG, Pascual JM, Malloy CR
J Cereb Blood Flow Metab 2013 May 8. doi: 10.1038/jcbfm.2013.67. [Epub ahead of print]

Main books and book chapters

Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease, 5th edition. Pascual JM, Rosenberg RN (editors) Elsevier (Academic Press) Under contract; anticipated publication date 2014.
Principles of progressive and degenerative brain disorders in children, 1st edition. Pascual JM (author) Cambridge University Press Under contract; anticipated publication date 2015
Pascual JM. Disorders of Muscle Excitability, in **Basic Neurochemistry**, 8th edition (2012) (Siegel, George J.; Albers, R. Wayne; Brady, Scott T.; Price, Donald, L., eds.) Philadelphia, Elsevier.
Pascual JM, DiMauro, S. Disorders of the Krebs cycle and of pyruvate metabolism and transport, in **Rudolph's Pediatrics**, 22nd edition (2011) (Rudolph et al, eds.) McGraw-Hill.
Jotterand F, Pascual JM, Sadler, JZ (in press). The Can't and Don't of Psychopathy: Neuroimaging Technologies, Psychopaths and Criminal Responsibility. In: N**euroethics: Issues at the Intersection of Neuroscience and Society**. (J. Giordano, ed.) Cambridge University Press.
Pascual JM (in press). Kernicterus. In: **Encyclopedia of Neurological Sciences**, Second Edition (Michael J. Aminoff and Robert B. Daroff, eds.) Major Reference Works, Elsevier.
Pascual JM (in press). Glut1 haploinsufficiency. In: **Movement Disorders: Genetics and Models**, Second Edition (Mark LeDoux, editor), Elsevier.

Main conference presentations

Acute and Chronic Effects of Glucose on Brain Metabolism. Feng Xu, Peiying Liu, Hanzhang Lu, Juan Pascual, Xuchen Zhang (2012) **18th Annual Meeting of the Organization for Human Brain Mapping**. June 10-14,Beijing, China
Acute and chronic effects of glucose on brain metabolism in glucose transporter deficiency syndrome. Xuchen Zhang, Juan Pascual (2012). **49th Annual Medical Student Research Forum**, UT Southwestern Medical Center
Oxidation Of Acetate In Human Orthotopic Glioblastoma Tumor Model Is Reminiscent Of Normal Astrocytes. Tomoyuki Mashimo, Kumar Pichumani,Vamsidhara Vemireddy, Kimmo Hatanpaa, Daniel Sutherland, Isaac Marin-Valencia, Juan Pascual, Ralph Deberardinis, Craig Malloy, Elizabeth Maher, Robert Bachoo (2012). **Innovations in Cancer Prevention and Research Conference**, Cancer Prevention and Research Institute of Texas, Austin, TX
Chemotherapy Resistant, Dormant Glioblastoma Cells Exhibit Persistent Oxidative Metabolism. Tomoyuki Mashimo, Kumar Pichumani,Vamsidhara Vemireddy, Kimmo Hatanpaa, Daniel Sutherland, Isaac Marin-Valencia, Juan Pascual, Ralph Deberardinis, Craig Malloy, Robert Bachoo, Elizabeth Maher (2012). **Innovations in Cancer Prevention and Research Conference**, Cancer Prevention and Research Institute of Texas, Austin, TX
Synaptic excitation-inhibition imbalance in glucose transporter I deficiency (G1D) and first treatment of its associated human epilepsy with triheptanoin. Juan M. Pascual, Levi B. Good, Peiying Liu, Isaac Marin-Valencia, Qian Ma, Dorothy Kelly, Mireia Tondo, Jason Park, Ana Hernandez, Xuchen Zhang, Craig R. Malloy, Peter Stavinoha, Hanzhang Lu (2013). **Curing the Epilepsies 2013: Pathways Forward**. National Institute of Neurological Disorders and Stroke, Bethesda, MD
Diagnostic yield of targeted panels of seizure genes Wang, J. Gotway, G., Pascual, J. Park, J. (2013). **Society for Pediatric Pathology meeting**. Salt Lake City, UT

IV. PET Scans

What can be learned from PET?
PET/MRI involves the injection of radioactive glucose. Then we wait 1 hour to measure radioactivity arising from the head. In Glut1 Deficiency, the measurement of the thalamus is low for glucose accumulation. The basal ganglia are about 170% of normal accumulation. Thus, Glut1 Deficiency is a selective regional disease. We don't know why this is a regional disease. Why is this not the case and can this be utilized for better treatment development? We don't see generalized problems in patients; we see certain things (seizures, etc), but Glut1 Deficiency is a fairly selective problem; thus brain glucose deficiency isn't global.

The nervous system relies on a precise balance between activation and inhibition. Brain energy metabolism is abnormal in Glut1 Deficiency and this leads to imbalanced neuronal excitation/inhibition.

V. EEG , MRI and brain neuronal activity

We can't conduct studies that involve the analysis of brain tissue with people.
However, Glut1 Deficiency mice can have an EEG and also other types of useful testing.
We can put labeled glucose into the brain through an IV catheter or into the mouse through a neck IV and follow brain metabolism in Glut1 Deficiency.
The brain's network is causing the seizure.
In patients we see spike-waves in the EEG. This happens often or, for some people, most of the day.
It also happens in mice with Glut1 Deficiency.
What is the minimum number of brain components needed to produce the spike waves? That would be the thalamus and the cerebral cortex.
If you add glucose then the spike and wave goes away (becomes normal).
Our Glut1 Deficiency mice also exhibit these findings, making them a useful research tool.

Glut1 Deficiency mice establish ketosis by themselves. The have high ketones in blood and can make twice the amount of normal ketones. However, we cannot become highly ketotic on a regular diet; we need a ketogenic diet and an expert to teach us.

One problem with glucose metabolism is that glucose generates neurotransmitters. Therefore, neural transmission may be abnormal in the brain, leading to epilepsy.

We have been able to isolate a single cerebral cortex Glut1 Deficiency neuron from the mouse.
Brain neurons have a baseline activity. Abnormal neuronal activity is ongoing all of the time in Glut1 Deficiency.
In Glut1 Deficiency, there is an imbalance of neuron activity. Normally, some of the neurons inhibit and some excite (signal to other neurons).
Inhibition is lower than excitation in Glut1 Deficiency: There is low excitation, but even lower inhibition
The thalamus is responsible for relaying messages to the various sections of the brain.
It is a pacemaker that is firing all of the time in Glut1 Deficiency.

In Glut1 Deficiency, if we shock the thalamus minimally with a small electrical current it will continue to fire.
Normally, if we shock the thalamus, it will calm down quickly.
Therefore, we think that the thalamus acts as a pacemaker in Glut1 Deficiency and is implicated in the spike-wave EEG abnormalities typical of many patients.
The goal of our research is to find out what alters these pacemakers.
Maybe there is a downstream target that we can influence as a treatment option.
Maybe not and we just need to fix the glucose problem.

<u>Caution</u>: C7 oil is just one research option. It would be premature or naïve to think that this is the solution to Glut1 Deficiency without further solid laboratory research, as Glut1 Deficiency is not a well-understood disorder. Better treatments, as usual, will come from more and better laboratory research. We are the only lab and clinic using C7 in Glut1 Deficiency and are pleased to be well ahead on our understanding on how it works and on how human research on C7 and related options should be conducted, but we should be under no illusion that this is ready for broad testing or use.

We have also uncovered many potential new treatment targets in the course of this research- but we are not sure yet of which ones are going to work best.

If we run a functional MRI at the same time as the patient has seizures you can analyze increased blood flow across brain regions. You have specific brain sections that that are responsible for seizure activity.

What makes a brain section different than the other sections?
In Glut1 Deficiency, in addition to having increased metabolism during seizure, there is deactivation in other areas during seizure. This is a network phenomenon.

We have developed a way of putting chemical "labels" (tracers) into a brain, and we can see where the labels go during brain metabolism.
We can look at each atom of, for example, the glutamate molecule.
We can see how glucose is converted into glutamate and we can trace this back to metabolism.
Labeled glucose is metabolized into glutamate, and this into glutamine etc.
What we can do with this?
We can look at the metabolism of a potential treatment such as triphetanoin using the C13 label.
We can give triheptanoin, but thought it would be safer if we first knew what the tripheptanoin does to the brain: How does it get into the brain? What does it do? How is it metabolized?

The conclusion is that, in the mouse brain it seems to do what it is supposed to do, as Dr. Charles Roe, who has a lot of experience in this area, predicted many years ago.

VI. <u>Clinical trials</u>

What is a rare disease?
Are the other diseases that are more common better treated than rare diseases?

Cancer, multiple sclerosis, and Alzheimer's disease are not doing better than Glut1 Deficiency in terms of treatment.
We shouldn't think that Glut1 Deficiency research will not get funds just because it is rare.
Many disorders, even more common ones, have no cures.
What is the limiting factor?

- Not enough patients? Not really. Increasing the number of patients may not help that much if the underlying science is not sufficiently strong.
- We don't know enough about brain metabolism and Glut1 Deficiency? Yes, this is the key issue.
- Is there too much regulatory framework for clinical trials? Not really. We embrace rigorous regulation (usually by the FDA and the IRB) to minimize chances of mishaps.
- Reduction of worthless data is one of the approaches, together with generating better knowledge.

What concerns are important in a clinical trial?
What is in the consent document?
Who owns the data (the researcher or someone else)?
Who has oversight? The regulatory bodies including the IRB and the government, or others?
Will my insurance pay for a new treatment if the trial is successful?
Are all negative data reported?
How is treatment efficacy determined?
Who profits and why does it matter?
Where does the buck stop if there is a problem? (Who is responsible for a clinical trial?)

Keep always two ethical principles in mind:

1. Everything that we do as researchers (and individuals) should be justifiable as if it was to become a universal law.
2. People are ends in themselves and not means to something.

Treatment efficacy- how do we determine if a treatment works?
Outcomes research:

1. A primary outcome measure, ideally, directly relates to the disease process.
2. A secondary outcome measure uses something not so directly related to the disease process.
3. A surrogate outcome measure is used when there are poor primary and secondary outcome measures.

All are used in clinical trials. However, we want to find things that make a difference to the patient; not to the surrogate outcomes. The outcome should be important to the patient; in other words, does it make the patient function better?

Many of us think that the fact that we are dealing with a rare disease should not allow us to use a surrogate outcome in lieu of (or as a shortcut for) a better efficacy measure. If anything, the scientific understanding and treatment development behind rare diseases should be just as (if not more) stringent (i.e., convincing) than it is for other more common diseases. Saving time by taking regulatory shortcuts for drug development and marketing (rather than conducting better laboratory research), is a fallacy in which some may see profit, but which concerns us.

Who is in charge? Who is liable? If something goes well everyone gains.
If something goes wrong? Foremost, the patient suffers the consequences and second, the physician pays a price as well.
Further questions: Who owns the data? Who is the financial sponsor of the clinical trial? What is their ultimate objective?

Therefore, clinical trial consents need to be read carefully.

If we think that a trial does not make sense for the patient (for example, when the evidence is already convincing), we will not do the trial out of ethical concerns for those who may receive a placebo.

What is C7 oil? It is a castor bean oil derivative used in the food and cosmetic industries.
It costs ~$400 for a 50 pound keg of odorless, tasteless C7.
Why should we try C7?

1. Because there are limitations to the ketogenic diet.
2. Because all the experience with food-grade C7 (including ours in Glut1 Deficiency) indicates that it is an affordable, safe medical food with potential to benefit patients.

VII. What are we going to do next year?

A. Standard of care document.
B. Glut1 Deficiency registry.
C. G1DCIC: the Glut1 Deficiency Clinical Investigation Consortium will be established.

The Glut1 Deficiency standard of care document is a set of guidelines for the diagnosis and the treatment of G1D.
There will be a physician document and family format document.
There will be free access to all.

The Glut1 Deficiency registry is a UT Southwestern project which is partially funded by Glut1 Deficiency Foundation.
We could assess the following with the registry:
Clinical symptoms of Glut1 Deficiency
DNA/genetic mutation data
What are patients being given for symptoms?
We could get a worldwide headcount of patients with Glut1 Deficiency.
What have patients tried? What is working for them?

The Glut1 Deficiency Clinical Research Consortium is an international clinical trials network.
Several academic institutions, with expertise and interest in G1D, will participate.

There will be as few a commercial links as possible (i.e. financial interests will generally not be welcome).
We want to publish all data as raw data, and this must be accessible to others.
The goals include: education, advocacy, engagement with medical research agencies (NIH, FDA) and the Congress.
This is a true academic consortium: There is no role for extra profit by researchers or commercial interests and such entities and individuals will not be eligible for inclusion.
Why are patient interests best served when potential profits and commercial interests are restrained?

Several references (among hundreds) speak to this issue:

Nature Neuroscience 6, 1001 (2003)
Editorial policies on financial disclosure
Michael F Jacobson & Virginia A Sharpe
We read with interest the recent article[1] in the *New York Times* reporting on undisclosed financial ties in a *Nature Neuroscience* review article on treatments for mood disorders[2]. According to the *Times* article, *Nature*'s policy permitted the author of the review to remain silent about his patent and other significant financial interests in treatments praised in his review.

Canadian Medical Association journal 171(12): 1451–1453 (2004)
Excess in the pharmaceutical industry
Marcia Angell
The main point about excess in the pharmaceutical industry is how much there is of it. Here I can touch on only a few specifics about this altogether over-the-top business.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC534578/

Prof. Dr. med. Jörg Klepper
Children's Hospital Aschaffenburg
Aschaffenburg, Germany

Clinical Studies in Glut1 Deficiency Syndrome

I. Glut1 Deficiency History

Glut1 Deficiency is a success story.
Dr. De Vivo described the first two patients in 1991.
Glut1 Deficiency has a clear pathomechanism, is easy to diagnose, and there is an effective treatment.
We now know of over 300 patients.

Glucose enters brain through the blood brain barrier.
If deprived of glucose our bodies will use fat to make ketones for energy. Ketone production takes place in the liver.
Ketones enter the brain through another transporter (MCT1); not through the Glut1 transporter .
Ketones allow the brain to run on a different "fuel".

The diagnostic criteria for Glut1 Deficiency is: low CSF glucose, normal to low CSF lactate, mutations in the SLC2A1 gene.
Glut1 Deficiency is a worldwide disease.
There are four European groups: Netherlands, Germany, UK and Italy
In the USA the sites are with Dr.'s De Vivo and Pascual.

Glut1 Deficiency is a rare disease with a complex clinical presentation and a heterogenous genetic background.

II. What have we learned in following patients?

We know some things about the long term course of patients on the ketogenic diet.
There are several groups following people over time (reports by Dr.'s Klepper, Pascual, and De Vivo)
Some patients do not carry mutations in the SLC2A1 gene (reports by Dr.'s Klepper and Scheffner).
Triheptanoin may be an option for treatment (Dr. Pascual)

III. What have we learned about the ketogenic diet?

What can we learn from the ketogenic diet?
Glut1 Deficiency and PDH deficiency are types of disorders that use the ketogenic diet. The disorders are rare.

There are 1300 references in the medical literature about the ketogenic diet.
The diet was initially used for intractable epilepsy.
About 5 years ago the modified ketogenic diet was initiated.
The ketogenic diet has been tried for many different diseases.

In 2008 there was international consensus on the ketogenic diet.
There are several types of ketogenic diets today.
The basic idea is to lower the dietary ratio to make it more palatable.

Is there a difference in using the diet for Glut1 Deficiency as opposed to intractable epilepsy?
The dietary ratio of 4:1 is ok for kids, not for infants. Adults are not likely to want to use it.
The 3:1 ratio is ok for infants and children but adults may not want to use it.
The Modified Atkins Diet (MAD) is not for infants, but is ok for kids and adults.
The low glycemic diet should not be used for anyone with Glut1 Deficiency.

We have long term follow-up of some patients using the ketogenic diet.
We have been following patients for up to 14 years.
Some adverse effects include: overshooting ketosis lethargy, hypoglycemia, dehydration, GI, loss of ketosis, constipation, renal stones, slowed growth.

Adverse effects could also include atherosclerosis. We ask ourselves if these children will grow up with this.

If the patient has elevated cholesterol levels there are the following therapeutic options:

- use formula instead of a solid ketogenic diet
- use a lower ketogenic ratio or increase MCT content of diet
- apply carnitine
- increase polyunsaturated fatty acids (PUFAs)

An adverse effect of the keto diet can also be hyperlipidemia.
We are missing the long term data on the ketogenic diet. We have 2 patients followed for 9 years. The triglycerides went down, cholesterol went up in 1 patient and down in 1 patient.
We aren't that worried about it.

IV. Genetics and Glut1 Deficiency

We know of some patients without genetic mutations in the SLC2A1 gene.
Most patients have missense mutations (changes in a single nucleotide).

The Human Genome Project decoded our genome. Maybe there are other genes associated with the function of the SLC2A1 gene.

Professor Hans Scheffer at the Nijmegen Genetic Institute in the Netherlands is looking at all of the genes in the human genome to see if another gene might be interacting with the SLC2A1 gene and causing Glut1 Deficiency (next-generation sequencing).

A lot can happen on the way to produce a functional transporter. It is possible that other genes are involved in the process of making a functional transporter. These things include: 1) Making the Glut1 protein, 2) Transportation of the protein to the cell membrane, 3)Storage in intracellular pools, and 4)All intracellular mechanisms might be impaired which could cause Glut1 Deficiency but no genetic mutation in the SLC2A1 gene.

V. Diets and Co-Factors

Alpha lipoic acid (ALA) is a natural body organic acid. It is a co-enzyme in energy metabolism. It is an antioxidant that has been used for several different disorders. There is laboratory data published in 1994 that indicates that ALA improves glucose transport in muscle cells.
DCD suggests using ALA but without convincing evidence that it works.

Triheptanoin is an artificial ketone body. It enters the brain and converts to energy.

Ketone esters, as presented by Dr. D'Agostino, are high energy ketones that induce sustained ketosis.

What else should we do? There are many glucose transporters in the brain. We do not know how this concert of transporters is impaired in the brain in Glut1 Deficiency.

We need to learn why the ketogenic diet works? We have mice with Glut1 Deficiency and there is such a lot we can do with them! We can feed them diets and drugs, put them in MRI-machines, test them for ataxia and behavior, and finally sacrifice them and look at the Glut1 transporter in tissues.

Glut1 protein is present in other tissues such as: the placenta, heart, retina, and muscle. However in some of these tissues we also have other glucose transporters. We might have to look at the retina over time.

Newborn screening for Glut1 Deficiency would be helpful to find the children who need treatment early. Currently we have no idea how to screen newborns for Glut1 Deficiency.

Diamox (acetazolamide) is being used in Glut1 Deficiency. There are isolated reports that it can help with movement disorders. There are 6 patients described to date in 5 papers. There is a wide age range in the reported patients; all carry different SLC2A1 mutations. Dystonia onset and frequency of movement disorders is variable. Diamox was used at various doses and follow-up is varied. Diamox helped in 5 patients and not in 1 patient. To evaluate Diamox we would need a clinical trial. That might be difficult to do as the best trial would include patients with the same genetic mutation. Likewise, 9 patients with the R126C mutation have been described. Their basic data varies, such as the CSF/Blood ratio or seizure onset.

VI. We need a clinical classification system for Glut1 Deficiency

It would be useful to classify patients clinically. Mullen et al in 2010 presented a neurological classification of Glut1 Deficiency patients which included: 1) Developmental delay, 2) Epilepsy, 3) movement disorder and a combination of 2) and 3).

Pearson et al in 2013, published a classification system that involves the same 3 groups.

The proposal is: why not just classify them as Glut1 Deficiency type 1-4, with 4 being variants such as PED or stomatin-deficient cryohydrocytosis?
Additionally, the presence of SLC2A1-mutations could be indicated by (+ / -) in each patient.

VII. Clinical Studies

We have clinical studies up and running on:

1) Ketogenic diet
2) Long term follow-up with several groups around the world
3) SLC2A1 negative mutations
4) Novel compounds

What should we evaluate in additional clinical studies?

- Glut1 in other tissues
- Newborn screening
- Drugs: anti-epileptic drugs and Diamox
- Clinical classification

To answer these questions multicenter studies will be needed. Here we need the support of patient support groups. Currently in Europe we know of support groups in Germany, The UK, Italy, the Netherlands. There is also a group in Japan.

Dr. Eric Kossoff, MD
Associate Professor of Neurology and Pediatrics
Medical Director, Ketogenic Diet Center
Johns Hopkins Hospital

Advances in the Ketogenic Diet

I. The history of the ketogenic diet is rich in turning points.

1921- A high fat/low carbohydrate diet known as the ketogenic diet was initiated in Rochester, MN. The KD mimics starvation and was one of the most popular treatments of epilepsy for children and adults.
1994 The Charlie Foundation was created.
1994-present There was an increase in publications about the ketogenic diet in the medical literature.
2008 The first International Ketogenic Diet Conference was held in Phoenix.
2008 Consensus group publication on the ketogenic diet in Epilepsia
2013 The ketogenic diet is popular and noted in the media frequently. It is available nearly everywhere now.

II. What is new in dietary therapy in 2013?

For the "classic" ketogenic diet in years past…:

90% of the calories are fat.
The 4:1 ratio is standard. This is the ratio is fat grams to carbs and protein grams combined.
Fluid and calorie intake is limited.
Foods are weighed.
The diet is typically started in the hospital with a brief fasting period.
Involves intensive dietician involvement.
No cheating.

In 2013, things are different. We are seeing a variety of foods that can be made in a ketogenic fashion, such as: ketogenic sushi, ketogenic ice cream, waffles, and Indian food. There are a lot of amazing recipes out there.

For infants the child can use one of the infant formulas. Various formulas are available in the world and the ketogenic diet is no longer just a USA diet; there are centers all over the world. However, many regions in the world do not have the ketogenic diet; we need to expand out to the much of the rest of the world. We do not have to fast at the diet initiation. Fasting "jump starts" the diet but maybe not so important in the long run. Many other places do not fast and the patients do fine.
Day to day management is less reliant on ketone measurements.
Adjust calorie ratio and fluids for growth and hunger- NOT for seizure control.
An online ketone calculator can be found at: www.Ketocalculator.com

Other possibly easier diets in use include:
- MCT oil
- Low glycemic index treatment
- Modified Atkins diet

III. Modified Atkins Diet (MAD)

The MAD diet was created by parents initially who realized you didn't have to be so strict with the classic ketogenic diet after many years. It was then formally created at Johns Hopkins in 2001.
You don't need to be as strict with the MAD diet and it is still high fat (64-65% fat) but the big difference is still protein, as more protein is allowed which can help with hunger and growth.
No weighing foods, no fasting, no fluid, no calorie restriction.
The MAD diet is easier to teach patients in clinic (takes about an hour)
Many parents go on the diet also to lose weight.
There are foods available in the grocery stores that can be used in the MAD diet.

MAD has been around for about 10 years, so we know a lot about it. Over 400 children in 30 studies have been reported in the literature.
Similar to the ketogenic diet, ½ of children with seizures respond with at least 50% seizure reduction. We are starting to get good long term data of the diet.
After 12 months of use, the results are maintained.
Side effects of the MAD diet include constipation, weight loss, and higher cholesterol levels – but probably better than the ketogenic diet

IV. New ideas and uses in 2013

If you give fatty acids the liver makes ketones which cross the blood brain barrier. Ketones include betahydroxybutyrate, acetoacetate, and acetone. Scientists who evaluate the ketogenic diet are looking into why the diet works. We are learning that the reason the diet works for different patients can be different. Most ketogenic diet experts now believe that ketosis shows that you are on the diet, but it is like a blood level – not critical for seizure control.

Carson's (a patient at the Ketogenic Diet Center) story shows how we are trying to get the idea out that the ketogenic diet can be tried first rather than anti-epileptic medications. She had new onset infantile spasms and was started on the diet before steroids and it worked. They have set up a foundation – www.carsonharrisfoundation.org In patients with new onset infantile spasms it has been successful in 10 of 24 cases.

Other exciting epilepsy uses of the ketogenic diet in 2013 include:
Less "severe" epilepsy- absence "petit mal" and juvenile myoclonic epilepsy.
More "severe" epilepsy also- status epilepticus.

The diets can be started by feeding tube also.

Ketogenic/MAD diet also tried for many other neurological conditions (it is possibly even helpful for cancer). We are working on trying to get other professionals interested in ketogenic diet.

V. What is new with diets for Glut1 Deficiency?

Questions that we need to address for the Glut1 Deficiency families include:

1. Do the level of ketones matter? In regular cases of epilepsy the ketone levels maybe don't matter so much. Is that true for Glut1 Deficiency?
2. Can we use the novel diets such as low glycemic (not so much), MCT diet (ok), MAD possibly.
3. Can we use the MAD diet for children with Glut1 Deficiency and then switch to the ketogenic diet if needed? Maybe. Can we use the MAD diet for adolescents with Glut1 Deficiency who become tired of dietary therapy?
4. Should the diets be used for the non-epileptic forms of Glut1 Deficiency? (such as movement disorders) If a patient is on the MAD diet, would their cognition improve more if switched to the ketogenic diet?

Are high ketones better than low ketones?
Pro-arguments for why high ketones might be better:
Theoretically higher ketones would improve the function and "fuel" for Glut1 Deficiency.
At an early age it would be logical to provide high quality and quantity fuel.
There are anecdotal reports that the KD is better than the MAD in Glut1 Deficiency.

Con arguments for why high ketones aren't necessary:
There is no proof in the literature of kids who have done better on KD than MAD diet.
MAD works for Glut1 Deficiency (many reports now, especially in the past 2 years).
Some patients with high ketones are still having seizures and other issues – some with no ketones are seizure-free...
The concept that brain energy failure is reversible by a means of a 3:1 or 4:1 diet is far too simplistic (quote from Dr. Klepper's review)

VI. Why should we consider MAD for Glut1 Deficiency?

Side effects of ketogenic diet can include: constipation, weight loss, vitamin deficiency, acidosis, kidney stones, growth slowing, high cholesterol, pancreatitis, and cardiomyopathy

Long term use (> 6 yrs) can cause kidney stones (25%), bone fractures (21%), 82% with low height and weight. Ketones and acidosis may not be a good thing long-term for bone density and we are evaluating this. Long term use of the ketogenic diet may be a problem for kidneys, but we aren't sure. MAD probably has fewer side effects.

What about switching from KD to MAD diet? If the patient is seizure free he/she has an 80% chance of switching diets without a problem. Thankfully if a patient is switched back to the KD the seizures become under control again if they were in control before the switch.

Do ketones need to be maintained between 4-5mmol/L in a young child? We don't know that a certain range of ketones is important. There is no proof that the range is important. As long as the child is doing well don't worry about being so strict with ketone levels.

Do ketone levels vary throughout the day? Ketones are generally lower in morning and higher in night. We don't worry so much about these fluctuations. The Ketogenic Diet Center at John Hopkins Hospital does not check blood ketones.

What about the use of alpha liopic acid? There is not consensus data on this subject. Most of the consensus group do not use it. This is not a set thing that you have do.

Veronica Hinton, PhD
Associate Professor of Clinical Neuropsychology
Columbia University

Columbia University Research Updates
Natural History of Glut1 Deficiency

I. Glut1 Deficiency - the first 21 years

De Vivo and colleagues identified first two cases in 1991
Recommended ketogenic diet
The first two patients have been followed for over 20 years.
Since the initial recognition:

- The genetic basis has been diagnosed.
- Over 200 cases have been identified.
- The mouse model of Glut1 Deficiency has been established.
- Dr. Pascual and Dr. Klepper were mentored by Dr. De Vivo.

II. Natural History of Glut1 Deficiency

We have followed the natural history of Glut1 Deficiency over time.
Knowing the natural history helps us plan clinical trials.
What happens over time in development?

What happened to the first two cases?
The first diagnosed child is now 24 years old
Stayed on the diet until age 13
Moderate intellectual delay
Lives with parents attends a day program

The second identified individual remains on the ketogenic diet.
Now is 22 years old
Mild intellectual delay
Lives with parents in rural area
Helps out with housework and some childcare of nieces and nephews

We evaluate patients over time with standard tests:
Neurological exam
Cognitive skills
Adaptive behavior

Can examine performance over time to see how they developed

III. The natural history of the first two Glut1 Deficiency patients followed over time.

Neurological exam
The Columbia Neurological Score (CNS):
The CNS has a total possible score of 76 points.
The exam has several subdomains or areas of evaluation.
We looked at three time points over time
Scores for both individuals stayed exactly the same across time
There is no evidence of decline in neurological function over time.
However, the start point (initial CNS score) is lower than in non-affected individuals.

Cognitive evaluation:
We measure receptive vocabulary. This establishes whether patients understand the meaning of certain words. We derive an age standardized score. This is how do they perform compared to other kids their age.

We measured over 6 time points. In two patients with Glut1 Deficiency we see that gains were made in receptive vocabulary over time. There is an increase in the number of items they get correct over time. When we look at age standardized scores across time, we see the scores remain stable. The start point is lower than the general population, but Glut1 Deficiency patients are gaining skills at a comparable rate to non-affected individuals.

We also use a test for spatial understanding. This is a non verbal IQ test.
Both of our initial two individuals improved in "raw data" over time (or the number of correct responses). Patients tend to make gains over time. If we evaluate them according to standardized scores, there is no change over the 6 time points. The start point is lower than the general population, but Glut1 Deficiency patients are gaining skills at a comparable rate to non-affected individuals.

We also have a test that is a simple design copy.
All tests are standardized for the non-affected population.
The first patient improved over time and the second patient had some improvement.
According to age standardized scores, performance remained stable over time.
Again, although performance was lower than the general population, over time it followed the same developmental trajectory as the unaffected population.

We also look at adaptive behavior
Adaptive behavior is a measure of parent report describing what behaviors their child does in areas of Communication, Socialization and Daily Living Skills.
For the two cases, over 4 time points, it looks like there may be some decline over time when compared to normative (non-affected) behavior. Although when just evaluated the patient compared to their initial scores there is no decline. In other words, there is no loss in skills. There is no decline in the number of items that can be accomplished, but they may not made comparable gains as they get older..

IV. The natural history of a larger number of Glut1 Deficiency patients.

What about a larger sample size? We have followed a much larger population of children with Glut1 Deficiency.
I am reporting here on 13 children followed for many years, all of whom were treated with ketogenic diet.
This is a subset of patients from the even larger group that we have been following over time.
Mean follow-up of these 14 children is 11 years after initial assessment.
The ages and severity of Glut1 Deficiency varied at initial evaluation.

Neurological evaluation remained stable over time
CNS scores ranged from severely to minimally affected.
In 13 individuals there was no significant change in CNS over time

Cognitive performance remained stable over time (when compared to general population)
There was no significant change over time in receptive vocabualary and spatial understanding.

In terms of age adjusted scores for the design copy test, we see some declines over time; however no child looses skills when compared to their initial evaluation.

In adaptive behavior when compared to general population, we see no significant changes over time.

What does all of this mean?
Glut1 Deficiency is chronic, non progressive condition
In children on the ketogenic diet:
NO declines are seen in neurological, cognitive and adaptive behavior over time.
Gains are made in that individuals continue to learn and perform better on measures
When compared to general population, children with Glut1 Deficiency follow a similar developmental trajectory as peers.

Good for all families to know there is no expectations of declines over time
Children continue to learn and develop
Knowledge of natural history useful when planning future treatment studies

Jacqueline Montes, PT, EdD, NCS
Physical Therapist, Researcher
Columbia University Medical Center

Clinical Outcome Measures for Glut1 Deficiency

I. Outcome Measures

The definition of an outcome measure is standardized and validated clinical assessment used to evaluate change in the context of a research protocol.

Some important aspects that it must have:

- Easily administered.
- Age appropriate.
- Impose minimal patient burden.
- Multi-site uses must all be able to do the test the same way.
- Disease specific.
- Functionally meaningful.

Other examples of outcome measures:

- Cognitive function tests
- Fatigue questionnaires
- Columbia Neurological score
- These outcome measures can be applied to Glut1 Deficiency and to other disorders.
- 6 Minute Walk Test (6MWT) is an outcome measure.

II. The 6 Minute Walk Test (6MWT)

The 6MWT measures the distance walked around a course in 6 minutes.
It is safe to administer and it is easily administered.
The 6MWT was initially developed for adults for cardiopulmonary disease. It has been widely adopted by other neurological disorders as well as pediatric conditions such as Duchenne Muscular Dystrophy and Spinal Muscular Atrophy.

Our first experience with using the 6MWT in a neurological disorder is with Spinal Muscular Atrophy (SMA). The test performs very well in patients with SMA.

The 6MWT measures physiological fatigue in SMA patients. In SMA we see a 17% change in velocity between the first and last the last minute walked.

What is fatigue- a common symptom in many neurological conditions. There are 2 general types of fatigue.

Physiological fatigue is a decline in 1 or more aspects of performance during continuous performance of a prolonged task

Experienced or Perceived fatigue- is a subjective symptom and can be defined as an overwhelming sense of tiredness or exhaustion

Experienced fatigue is a symptom in many different disorders where there is weakness.

We have shown fatigue in SMA, but not in DMD, myasthenia gravis, mitochondrial disorders, or Glut1 Deficiency.

Mitochondrial disorders and Glut1 Deficiency are both energy failure syndromes.

All of the patients have weakness, but not all have fatigue.
Only SMA had measurable fatigue.
We look at percent predicted walking distance to determine weakness.
All groups have a variable amount of weakness.
SMA only has physiological fatigue that was related to weakness.

III. The 6MWT in patients with Glut1 Deficiency

Glut1 Deficiency we looked at the percent of predicted walking distance.
We tested 14 patients.
Mean predicted distance walked is 55% of what is predicted for their age, gender and height.
.
There was no measurable fatigue (difference in distance walked between first to the last minute).

In Glut1 Deficiency the distance walked on the 6MWT is associated with the CNS score.
The relevant domains in the CNS score were gait and balance; which is more important than the domain of muscle strength and tone.
The stance and gait domain was also highly correlated with distance walked.
Strength is not correlated with distance walked.

IV. Gait Analysis

In SMA patients we used the "Gait Analysis"; which provides a lot of information on spatial and temporal parameters of gait.

We see fatigue with SMA patients and the decline of performance is related to change in stride length. Stride is the length is the distance from one heel strike to the next time that same heel strikes.

In 8 Glut1 Deficiency patients studied with gait analysis, the velocity, cadence, base of support, and stride length did not change over time. Nor did time spent in double support; or how much time you spend with 2 feet on the floor. A higher the number indicates worse balance.

Glut1 Deficiency patients compared to controls walked slower, took fewer steps per minute, smaller steps, and spend a lot more time in double support.

Summary of 6MWT and gait analysis for Glut-1 DS:
Percent time spent in double support is a measure of balance. This is increased in Glut1 Deficiency
Stance and gait is related to 6WMT.
The CNS score is a measure of disease severity.

All of these things can be measures of Glut1 Deficiency severity.

Summary of 6MWT and gait analysis for Glut1 Deficiency:
Percent time spent in double support is a measure of balance. This is increased in Glut1 Deficiency.
Stance and gait is related to 6WMT.
The CNS score is a measure of disease severity.

All of these things can be measures of Glut1 Deficiency severity.

V. Other motor function tests

Another outcome measure that could be used for Glut1 Deficiency is the "Gross Motor Function Measure (GMFM)".

The GMFM was originally designed for kids with cerebral palsy.
It assesses function over 5 domains and can be used in lower function to higher functioning patients.

It is burdensome as it can take up to 45 minutes.
It includes both dynamic and static items.
It can be used to evaluate motor function in non-ambulatory patients.
It can be performed in children as young as 2 years of age.

To summarize:
Cognitive and adaptive function improves in Glut1 Deficiency patients; but are stable compared to non-affected patients.
The 6MWT is an informative measure of balance, walking ability, and endurance.
GMFM may have a role in clinical trials for Glut1 Deficiency.
Our overall goal is to improve quality of life in patients with Glut1 Deficiency.

Cigdem Inan Akman, MD
Director of Pediatric Epilepsy
Associate Professor of Clinical Neurology and Pediatrics
Division of Child Neurology
Columbia University Medical Center

Seizures and Epilepsy Diagnosis in Glut1 Deficiency

Glut1 Deficiency is a genetic syndrome linked to SLC2A1 gene (Solute carrier family 2 member 1 gene), located in Chromosome 1, 1p34.2. Glut1 protein is the product of this gene function. Glut1 protein has a unique role for glucose transport across blood brain barrier. The alteration in this gene results in Glut1 protein reduction, therefore causes decreasing glucose transport across the blood brain barrier.

In 1991 , Dr De Vivo and his colleagues described 2 infants with seizures, deceleration in head growth, abnormal movements or spasticity with low CSF glucose level. These clinical and biochemical features led to the diagnosis of Glut1 Deficiency. Since then, the clinical features including seizures, developmental delay, microcephaly, abnormal movements such as ataxia, spasticity, dystonia, and dyskinesia are acknowledged as the cardinal features of Glut1 Deficiency.

Clinical features of seizures: Clinical presentation of seizures varies in children with Glut1 Deficiency. Seizures can be reported with obvious clinical manifestations such as clonic movements, muscle jolt, or blank staring episodes. Clinical events with limpness, change in color, change in breathing and head nods can be also seen during the infancy in Glut1 Deficiency. These subtle clinical features may not be brought to the medical attention and often delay the diagnosis of seizures. Majority of the children (90%) presents with seizures within the first 12 months of age, and the mean age of seizure onset is around 8 months. Rarely seizure onset can be seen beyond 18 months of age. Multiple seizures can be reported in the same individual or within the same family, including generalized tonic clonic, absence, myoclonic, and complex partial seizures. Tonic seizures are seen less often. Infantile spasms and epileptic spasms, one of the most severe forms of infantile seizures, have been reported only in few patients.

Epilepsy syndromes: Based on the seizure types and EEG findings, various epilepsy syndromes are identified in patients with Glut1 Deficiency. The clinical spectrum of epilepsy diagnosis expands from mild to severe spectrum. One of the most common types of childhood epilepsy syndromes, such as childhood absence epilepsy, juvenile absence epilepsy and juvenile myoclonic epilepsy have been reported in Glut1 Deficiency and represent the mild spectrum. Approximately 10% of children with early onset childhood absence epilepsy (earlier than 4 years of age) may have Glut1 Deficiency. On the contrary, refractory generalized epilepsy, myoclonic astatic epilepsy and intractable infantile seizures suggest the severe spectrum of epilepsy syndromes in Glut1 Deficiency. It is also reported that the clinical course of seizures, age of onset, seizure types and EEG findings may vary within the same family of individuals received the diagnosis of Glut1 Deficiency.

EEG findings: Baseline EEG activity often shows generalized slowing. Spikes discharges are seen frequently including focal or generalized spike discharges. The slowing of EEG activity and spike discharges often improve following meal or consumption of carbohydrate enriched diet. Approximately 17% of patients may have normal EEG findings. Rapid improvement of EEG findings can be seen with the administration of ketogenic diet within days.

Treatment of seizures: Ketogenic diet is the most effective treatment for the cardinal symptoms of this genetic syndrome. Seizure freedom can be reached in the majority (67%) of the children and 60% may have seizure freedom within the first week of the treatment. Rarely seizure freedom can occur with non-diet treatment (8% of children), with the treatment of antiepileptic drugs. However, antiepileptic drugs have limited role for the treatment of seizures in Glut1 Deficiency. Depakote or phenobarbital require special attention and caution which may potentially increase seizures. The medication such as acetozolimide, topiramate, zonisamide which may potentiate acidosis may have a role to improve seizure control.

Clinical course: Despite the stormy clinical course with frequent seizures and refractoriness to the initial treatment; seizures may subside over time and may be seen sporadically in late teenage years or in early adulthood.

Stacey K. Bessone RD, LD/N
All Children's Hospital
Johns Hopkins Medicine

Ketogenic Diet: Best Practices

Objectives

1. Understand an example of the general guidelines of diet initiation for the Ketogenic diet
2. Understand an example of the guidelines of diet initiation for the Modified Atkins diet.
3. Have knowledge of guidelines for outpatient follow up.
4. Be able to recognize and address common challenges of the Ketogenic and MAD diet.
5. Add creativity to meals
6. Find current resources useful for diet follow up.

Mechanism of Action

- On the Ketogenic diet the brain uses ketones (a bi-product of fat metabolism generated in the liver) as its source of fuel instead of glucose.
- This avoids relying on the use of glucose transporter type I for glucose uptake into the brain.

Background

- Classical Ketogenic Diet
  - Primary Diet used at ACH/JH
  - Ratios of 4:1 and 3:1
  - Requires inpatient initiation

- Modified Atkins Diet
  - -10 to 15 grams Carbohydrate per day
  - Initiated outpatient

Classical Ketogenic Diet

- Initial Nutrition Evaluation outpatient
  - Nutrition evaluation and plan for diet initiation, instructions on obtaining supplies and schedule admission.
- Four day admission inpatient
- Educational classes
  - Includes treating hypoglycemia, sick day procedures, medications.
- Demonstration of weighing food and formula preparation

Monitoring Inpatient

- Baseline Lab work
  - CMP, CBC, Fasting Lipid Profile, Carnitine levels, Vitamin D, Selenium
- Supplements
  - Vitamin and mineral, Cytra-K Crystals
- Meal Plan/Formula Recipe
  - Includes instructions, Calories, Protein and fluid goals

Home Monitoring

- Ketone checks AM and PM
- Blood glucose checks 2 times/day,
  - 2 hours before or after a meal or feed, for 1 week then discontinue
- Seizure/Symptom diary

Modified Atkins Diet

- Initiated Outpatient
  - Nutrition Evaluation and Instruction
    - -Diet guidelines
    - References, Atkins carb counter
  - Baseline Labs
    - Lipid profile, CBC, CMP, Vitamin D
  - Supplements- Vitamin/mineral

Monitoring

- Check ketones after 3 days
- After ketosis obtained, check ketones 2 times/week
- Weekly weights

Follow Up Outpatient Visits

- Ketogenic Diet
  - 1 week to 1 month after discharge
    - lab work obtained- CMP, Beta Hydroxybutyrate
  - Additional visits determined with minimum every 6 months
- Modified Atkins
  - 1 month after initiation, then as determined by doctor, minimum every 6 months

Evaluation at Outpatient Visit

Items to Address:
- weight/height, Recipe/meal plan, supplements and fluids
- Goals (patient and Medical staff)
- Are they being met? If not why?
- (Eating out, school, meal creativity)

Challenges of the Ketogenic and Modified Atkins Diets
Elevated Cholesterol and Lipids

Lab work checked every 6 months - Some increase in levels acceptable

Recommendations:
- Add Carnitine
- Increase use of MCT or Coconut oil
- Add Fish oil supplements
- Lower ratio

Weight Changes

- Excessive Weight Gain
  - Adjust calories 5% to 10%
  - Decrease snacks
  - Cheating
- Weight Loss
  - Adjust Calories 5% to 10%
  - Increase snacks
  - Lower Ratio

Breakthrough Symptoms/Seizures

Items to Address
- Compliance
- Medication changes, Food product Changes, Other Products (scale broken, toothpaste, lip balm)
- Increase Ratio
- Decrease Ratio- better compliance

Vitamin and Mineral and Other Deficiencies

- Vitamin D- Bruising, hair loss, Increased infections, lethargy
- Selenium- Hair loss, Cardiac complications
- Thiamin – optic neuropathy
- Iron- Lethargy, Bruising
- Carnitine- Lab work confirmed
- Zinc- Poor Growth, Lethargy

Hospital/ER Visits

- Dextrose free IV
- Medications-low carb/carb free
- Identifies for Ketogenic diet (medical record, bracelet, allergy note)
- Bring scale, formula and food
- Letter

Diet Maintenance
G tube feeds

- Carb and Protein by mouth
- MCT oil through G tube

Transitioning to Eating by Mouth

- Provide calorie total per meal
- Provide calorie total per oz. of formula
- TF- Food intake = Adjusted tube feed
- Work towards replacing a meal

Transitioning from Classical Ketogenic Diet to Modified Atkins

- Evaluate total Carbohydrate intake per day on Ketogenic Diet
- Roll total daily carbs into Modified Atkins
- For example: Patient on 9 Grams Carb per day on keto diet will go to 9 grams a day on MAD removing restrictions of calorie and portion control.

Resources

- Keto Cookbook
- TheCharlieFoundation.com
- The Ketogenic Diet Book
- Atkins.com
- Atkinsforseizures.com

Interesting Fat Sources

- Avocado oil
- Walnut oil
- Grape seed oil
- Coconut oil

Staying on Target

- Seasonal Menus
- Make eating out possible
- Work with your dietitian on goals
- Change Menus Often
- Recruit other around you to participate!
    - Low inflammation
    - Better weight control and satiety

Diet Modifications

- Gluten Free
    - Strict at 4:1
- Low Lactose
    - Heavy cream, cheese and sour cream are low in lactose or could be avoided
- Vegetarian- Lacto-Ovo possible at 3:1 or 2:1
- Low Sodium- limit processed foods

Summary

The Ketogenic and Modified Atkins diet can provide effective treatment for Glut1 Deficiency as well as other known medical diagnosis. With proper follow up, monitoring and some creativity it can become a lifestyle, NOT A DIET, and can provide that best quality of life possible for patients and their families.

Dominic D'Agostino, PhD
Assistant Professor Department of Molecular Pharmacology and Physiology
Morsani College of Medicine University of South Florida

Therapeutic Ketosis with Ketone Esters for Seizure Disorders

For the past 12 years, our laboratory has been funded by the Office of Naval Research (ONR) to solve a number of physiological problems related to military diving during missions of attack, defense or submarine rescue. Navy SEALS perform dive operations using a closed circuit rebreather using 100% oxygen to dive longer at a given depth and avoiding decompression sickness (the bends).

One problem with breathing oxygen at hyperbaric pressure is the potential for Central Nervous System Oxygen Toxicity (CNS-OT), which triggers tonic-clonic seizures (i.e., *Grand Mal* seizures). Evidence suggests that CNS-OT results from excess reactive oxygen species (ROS) and impaired brain glucose metabolism and occurs with no warning and is often fatal.

The main goal of our ONR-funded research at the Hyperbaric Biomedical Laboratory at University of South Florida is develop an anti-seizure mitigation strategies to preserve brain energy metabolism under the environmental stress associated with CNS-OT. Our laboratory recently demonstrated that administration of ketone ester (acetoacetate diester) in rats fed a standard diet induced rapid and sustained therapeutic ketosis in rats (ketones > 5 mmol/L) that lasted over 4 hrs and significantly delayed the onset of CNS-OT seizures (Figure 1).

Many seizure disorders and neurological disorders are linked pathophysiologically to energy dysregulation, and ketone esters represent an innovative strategy to normalize aberrant energy metabolism associated with these disorders. Recent evidence suggest that oral consumption of ketone esters is safe in humans (2) and may provide therapeutic effects by virtue of enhanced bioenergetics associated with ketone metabolism. Ketone esters may represent the sought-after "ketogenic diet in a pill", especially if future experiments can demonstrate efficacy in other models of seizures and metabolic disorders like Glut1 Deficiency.

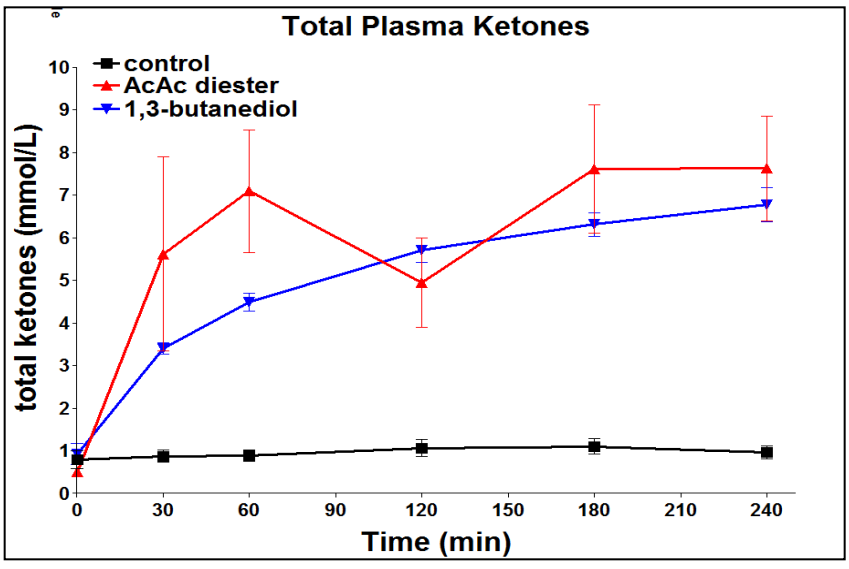
Reference

1. D'Agostino DP, Pilla R, Held HE, Landon CS, Puchowicz M, Brunengraber H, Ari, C, Arnold P, Dean JB. Therapeutic ketosis with ketone ester delays central nervous system oxygen toxicity seizures in rats. *Am J Physiol Regul Integr Comp Physiol.* 2013 May 15;304(10):R829-36.

2. Clarke K, Tchabanenko K, Pawlosky R, Carter E, Todd King M, Musa-Veloso K, Ho M, Roberts A, Robertson J, Vanitallie TB, Veech RL. Kinetics, safety and tolerability of (R)-3-hydroxybutyl (R)-3-hydroxybutyrate in healthy adult subjects. *Regul Toxicol Pharmacol.* 2012 Aug;63(3):401-8.

Methods to Induce Sustained Therapeutic Ketosis

Ketones Levels (mM)	Side Effects
Ketogenic Diet (1-3 mM)	noncompliance
MCT oil (1-2 mM)	GI side effects
Ketone Esters (any level)	**None reported**
1,3-Butanediol	**None Reported**
BHB Balanced Mineral Salts	**None Reported**



Note: this summary is intended to be integrated with Dr. Dominic D'Agostino's summary.

Raffaele Pilla, PhD, PharmD, Doctor Europaeus
Department of Molecular Pharmacology and Physiology
Morsani College of Medicine
University of South Florida

Ketone Ester in Two Models of Chemoconvulsant Rat and Upcoming Project on Cancer Patients

Background

For the past 12 years, our laboratory has been funded from the American Navy, notably from the Office of Naval Research (ONR). This special section of the US Navy aims to solve a number of physiological problems related to military diving during missions of attack, defense or submarine rescue.

Normally, we breathe a gas mixed grossly composed of 21% oxygen and 79% nitrogen. The only element we metabolize is clearly the oxygen, whereas the nitrogen falls under the definition of "inert gas". When we breathe at surface, and thus at a barometric pressure of 1 atmosphere absolute (ATA), nitrogen does not constitute a problem, as it is simply not assimilated by the lungs. However, when we compress a certain amount of air and trap it into a scuba tank, and then we dive at depths of over 12 meters, nitrogen starts to become a serious issue for a couple of reasons. Reason #1 is that nitrogen can cause what is defined as *nitrogen narcosis*, which manifests itself under form of "drunkenness". Some anecdotal reports state that divers with nitrogen narcosis sometimes try to give their regulator to the fish. Whether these stories are true or false, a subject in nitrogen narcosis tends to act recklessly, he/she would not care about his/her diving buddy's safety, as well as about his/hers. Reason # 2 why nitrogen could cause problems is that if a diver, after descending deeper than 18 meters, does not take his/her time to do a correct safety stop at about 15 feet of depth during his/her ascent, there might be a high risk of bends, which are caused by massive accumulation of nitrogen in the joints and then result in sharp pain, which only intense hyperbaric chamber treatments would be able to solve. However, nitrogen can be even more dangerous and could accumulate in spinal bones and paralyze the diver, or in proximity of the optic nerve, causing blindness. In order to prevent all this, the solution seemed to be to increase the percentage of oxygen in the tank, at the expenses of nitrogen. Nowadays, navy seals dive using 100% oxygen (and thus, no nitrogen at all) in their tanks. This allows them to dive longer at a given depth and be safer on their way back to surface.

However, it has been found that an excess of breathed oxygen can cause a problem of another nature, which goes under the name of Central Nervous System Oxygen Toxicity (CNS-OT). This syndrome is enhanced by a steep production of reactive oxygen species (ROS), also known as free radicals, that can cause the onset of epileptic-like seizures (i.e., *Grand Mal* seizures). When such a seizure attack happens at depth, chances for the diver to survive become poor. In fact, the US navy experiences a high number of deaths in the past 25 years.

At University of South Florida (USF), we are part of the ONR network and work to find out how to solve these issues. In particular we have been working on how to predict the onset of CNS-OT seizures and how to prevent them from happening.

In order to study these phenomena we have surgically implanted radio-telemetry devices in rats. These devices allowed us to record in real time electroencephalogram, electrocardiogram, electromyogram, core body temperature and physical activity. After the implant, we mimicked a navy seal's dive using a hyperbaric chamber, in which we exposed the rats to hyperbaric oxygen.

We were able to record all the physiological parameters mentioned above before, during and after the onset of CNS-OT seizure. What we found out was that 5 to 8 minutes before the onset of seizures, tidal volume (breathing depth/capacity) and respiratory frequency significantly increased, thus providing a clear physiological sign that predicts convulsions.

In addition, in order to induce neuroprotection to the brain, we preconditioned our animals to different gas mixes at different mild pressures before the deep dives, and found out that the best treatment, to get the best protection against seizures, was to expose the rats to high altitude flights (16,000 feet) for three times before exposing them to a deep dive. Apparently there is a major barometric pressure effect acting on their neuronal plasticity, and reducing at the same time the ROS production. The mechanisms behind this phenomenon still have to be elucidated, but we are close to providing more evidence. These findings could be applied in the future in the prevention of different types of seizures (not only CNS-OT seizures).

Currently, there are two new projects we are working on, and both are going to happen in Italy.

Project #1: University of Salerno, Italy
Director: Dr. Giangennaro Coppola
Collaborators: Dr. Raffaele Pilla, Dr. Andrea Viggiano
Background: Pentylenethrazole (PTZ), also known as Metrazol, Pentetrazol, Pentamethylenetetrazol and Cardiazol, is a powerful circulatory and respiratory stimulant and high doses of it cause convulsions (Meduna et al., 1934). On the other hand, Kainic Acid (KA), found in 1953 on some Japanese seaweed, is a potent neuroexcitatory amino acid used for inducing seizures in animals. It is a neurotoxin that specifically binds kainite receptors and thus it is broadly used for epilepsy studies.
Objectives: We will be testing the anticonvulsant efficacy of orally administered Ketone Ester (KE) and 1,3-Butanediol (BD) using the two established animal models of epilepsy PTZ and KA in male adult Winstar rats.
Experimental plan: We will use 40 male adult Winstar rats (*Rattus Norvegicus*). Rats will be anesthetized with urethane, then implanted with cortical electrodes. Their phemoral vein will be catheterized and rats will be gavaged with KE, BD or water (control). 30 min later, PTZ or KA will be injected i.v., then rats will be sacrificed with a urethane overdose. Blood samples, brains and abdominal organs will be collected for futher ketone bodies analyses. We will calculate the subgroups' latency times to seizure via their electroencephalogram records and blood ketone levels at the moment of PTZ and KA administration will be monitored.

Group I (KE)				Group II (BD)			
Control		Treated		Control		Treated	
PTZ	KA	PTZ	KA	PTZ	KA	PTZ	KA
5	5	5	5	5	5	5	5

Project #2: Service of Oncology, Hospital Fatebenefratelli, Benevento, Italy
Director: Dr. Antonio Febbraro
Collaborators: Dr. Raffaele Pilla, Dr. Guido
Background: According to the Warburg theory (the Metabolic Theory of Cancer), respiratory insufficiency is the origin of cancer. All other characteristics of cancer arise either directly or indirectly from insufficient respiration. As a consequence, the activation of specific oncogenes cause mitochondrial dysfunction. Notably, about 90 to 95% of cancers are due to environmental factors, whereas 5 to 10% are genetics-related. A number of scientific publications have demonstrated the high correlation between blood glucose and tumor growth (Seyfried et al., *British Journal of Cancer 2003, 89, 1375 – 1382*), as well as the efficacy of a ketogenic diet Vs. a standard diet in prolonging animals' lives during stage 4 cancer (Stafford et al.. *Nutr Metab (Lond). 2010 Sep 10;7:74*). Therefore recently the ketogenic diet (KD), a carbohydrate-restricted diet, has been proposed as alternative approach to fight a number of cancers. Notably, cancer cells have defective mitochondria and cannot metabolize fats. In fact, their primary and sole energy source is represented by carbohydrates. When exogenous carbohydrates and sugars are cut from diet, slowly metabolism shifts from glucose consumption to lipid consumption (from which metabolism ketone bodies are derived). Adopting this system, cancer cells will be isolated and "starved" from their primary nutrients and slowly the tumor mass and effects will decrease. It has also been demonstrated that neurons can alternatively and completely use ketone bodies as an energy source, in absence of glucose (Maurer et al., *BMC Cancer 2011, 11:315*), that a ketogenic diet can improve the quality of life in patients with advanced cancer (Schmitt et al., *Nutrition and Metabolism 2011, 8:54*) and that a KD is very helpful for pediatric oncologic patients (Nebeling et al., *Perspectives in Practice*) and patients with prostate tumor (Freedland et al., *The Prostate 2008, 68:11-19*). In addition, a number of neuronal cancers have been successfully treated with a KD, such as Glioblastoma Multiforme (Seyfried et al., *Brain and Spinal Cord Cancer*), and it has been shown that the association of radiotherapy and KD is highly effective against Malignant Gliomas (Abdelwahab et al., *Plos One 2012*).

Objectives: We will be treating 30 adult patients with cancer from the oncology service at Fatebenefratelli Hospital (15 controls and 15 on a KD), in order to test whether the diet has any beneficial effect on the final outcome of their cancer, after at least 3 months following the diet.
Experimental plan: Only patients in stand-by from chemotherapy will be selected. 15 patients will be kept on a standard diet (control) and another 15 patients will be fed on a KD 4:1 for at least 90 days, according to their personal needs. In addition, patients' diets will be implemented with Omega 3 fats (Fish Factor©, Sigma-tau) and with Ketocuisine (Solace Nutrition©). During and at the end of the study, blood analyses will be run and results will be published on scientific journals under form of clinical study and/or single clinical case reports.

Group I (control)	Group II (KD)
15	15

Liz Donohue
Director, CoRDS
2301 E 60th Street, N
Sioux Falls, SD 57104
(605) 312-6413

Title: Coordination of Rare Diseases at Sanford (CoRDS) Rare Disease Patient Registry

What is CoRDS?

The Coordination of Rare Diseases at Sanford (CoRDS) is a free patient registry for any and all rare diseases. It was developed because access to information and resources about rare diseases presents a challenge to researchers, physicians, patients and their families. By helping individuals with rare and uncommon disorders connect with the researchers who study those disorders, CoRDS can accelerate research and keep families aware of opportunities to participate in research studies or clinical trials. The **purpose** of the CoRDS registry is to facilitate research on rare diseases by providing a resource through which researchers can screen for prospective study participants. In this way, researchers, physicians and patients work together to advance research.

How does CoRDS work?

CoRDS provides a secure way for participants to make their basic medical history known to researchers without compromising their privacy. Individuals who have a diagnosis of a rare disease, an uncommon disease of unknown prevalence, or who are searching for a diagnosis are invited to enroll in CoRDS by filling out the CoRDS Registry Form and then completing the CoRDS Informed Consent Form and Questionnaire. Rare disease researchers from around the world can apply to access the de-identified information collected on the questionnaire. This means that participants' names and contact information remain private, and are only available to CoRDS personnel here at Sanford Research. CoRDS will contact participants on behalf of the researchers to share relevant research opportunities. It is always up to the participant to decide whether or not to participate in any research studies or clinical trials. Participants can also consent to share information with certain Patient Advocacy Groups (PAGs) and/or existing registries that support individuals with rare diseases.

How does CoRDS help rare disease research?

There are approximately 7,000 rare diseases affecting 25 million Americans and 350 million people worldwide. Research into rare diseases is challenging due to a lack of information. CoRDS was established as a resource to bring rare disease patients and researchers together to accelerate research into these orphan diseases.

What is a rare disease?

According to the Rare Disease Act of 2002, a rare disease is one that affects fewer than 200,000 people in the United States. In terms of prevalence, that equates to approximately 1 in 1,500 people. The exact definition of a rare disease changes depending on the country, for example, a rare disease in the United Kingdom affects 1 in 2000 people.

Why would someone want to enroll?

- The CoRDS registry
- Provides individuals an opportunity to be informed of research studies and clinical trials for which they may be eligible
- Provides researchers with a central resource for the identification and more rapid recruitment of potential research participants
- Has the potential accelerate research into rare diseases
- Is of no cost to enroll and does not take long!

What if an individual has already enrolled in a different registry for their rare disorder?

- They can still enroll. CoRDS offers a unique opportunity for individuals affected by rare disorders.
- CoRDS collects information on all rare diseases, and has the ability to collate information based on a disease characteristic or symptom. This helps researchers understand the cause rare diseases and develop treatments.
- The CoRDS Questionnaire is brief and asks simple questions about contact information, diagnosis, test results, and interest in research participation.
- CoRDS personnel will notify participants of research opportunities related to rare disease research.
- Participants update participant information annually to maintain accurate data.

What information does CoRDS collect?

CoRDS collects information about participants through the CoRDS Questionnaire. The questionnaire requests basic contact, demographic, and clinical information and asks if participants have an interest in participating in future research studies. It was designed to be relevant to all rare diseases, as outlined in the NIH Office of Rare Disease Research (ORDR) Common Data Elements.

How does CoRDS collect information?

- CoRDS collects participant information through the CoRDS Questionnaire completed during enrollment. CoRDS provides three convenient enrollment options:
- Online: Sanford Research has developed a secure online portal for participants who prefer to enroll online. To request online enrollment, complete the CoRDS Registry Screening Form and provide an email address. CoRDS personnel will send a unique username and password that can be used to login to the secure online enrollment portal to enroll.
- Mail: Those who prefer to enroll via postal mail can do so by indicating their preference on the CoRDS Registry Form. Please be sure to provide an accurate mailing address and phone number, as CoRDS personnel will send the enrollment documents to the address listed.
- In-Person: Participants can enroll on-site at Glut-1 Conferences. CoRDS has had the pleasure of attending conferences in 2012 and 2013 and will look forward to attending the conference in 2015 in Orlando!

How does CoRDS protect participant information?

Participant privacy and security is very important to CoRDS. The CoRDS registry follows strict guidelines to assure participant information is protected. Federal and state laws also protect participant privacy. All confidential electronic information will be stored in the secure Velos eResearch Clinical Research Management System. Any confidential hard copy information (paper consent forms, questionnaires) will be stored in secure, fireproof cabinets. Every possible effort will be made to maintain confidentiality. In the unlikely event that there is a breach in the database, participants will be notified.

Who can have access to CoRDS?

- CoRDS offers participants three distinct options for sharing information. During enrollment, each individual is asked in which of the following opportunities they would like to participate:
-
- Researchers: The information in CoRDS will be made available to researchers studying rare, uncommon, or undiagnosed disorders if they have obtained approval for their research project from (1) the Institutional Review Board (IRB) at the researcher's institution and (2) the CoRDS Scientific Advisory Board led by Dr. David A. Pearce.
- (An IRB is a group of scientists and laypersons from the community (i.e.: lawyers, clergy, professors) who review proposed research using human subjects. The IRB will review the research to ensure that CoRDS participants' rights are upheld.)

- Other Patient Registries: A subset of de-identified information collected from each profile can be shared with certain other databases. CoRDS shares data with other databases in order to help improve understanding of rare diseases, to avoid the duplication of efforts, and to collaborate with existing research efforts and organizations dedicated to rare diseases.

- Patient Advocacy Groups: Patient advocacy groups (PAGs) representing individuals with rare or uncommon diseases who have partnered with CoRDS may also request access to information in CoRDS that may or may not include participants' names. The PAG will sign an agreement stating that they will not use the information for research purposes. If a participant indicates that they would like their information shared this way, Dr. David A. Pearce and CoRDS personnel will not be held responsible for the use of information by the PAG.

Who is eligible to enroll in CoRDS?

Any individual with a rare diagnosis, a diagnosis of an uncommon disease with unknown prevalence, or who is searching for a diagnosis is eligible to enroll in CoRDS. A Parent or Legally Authorized Representative (LAR) may enroll affected minors or dependent adults on the participant's behalf.

Unfortunately, CoRDS can only enroll individuals who are fluent in English. CoRDS plans to include different languages in the future, so stay tuned for updates on language capabilities!

Is there a cost to enroll?

No – it is completely free to participate in CoRDS. In addition, CoRDS ensures that it is free for researchers to access the registry, and free for patient advocacy groups to partner with CoRDS. The registry is funded through the Sanford Children's Health Research Center and through a Sanford Health Foundation grant.

How does an individual enroll in CoRDS?

There are two simple steps to enroll in the CoRDS Registry.

- Complete Screening Form: Individuals can begin the enrollment process by completing the CoRDS Registry Form. This step, called "Screening," allows CoRDS personnel to review the individual's eligibility and preferred enrollment method (see How does CoRDS collect information? to learn more about the different options).

- Provide Consent and Complete Questionnaire: CoRDS personnel will contact the individual to complete enrollment via the preferred method indicated on the CoRDS Registry Form. Each individual will be given a copy of the CoRDS Informed Consent Form, and will be asked to read and sign the document to provide consent to participate in CoRDS. CoRDS will then ask the participant to complete the CoRDS Questionnaire, to be stored in the CoRDS Registry.

After enrolling, how will participants be contacted?

After completing enrollment, participants will be contacted by CoRDS when:

An approved researcher would like to share information about a study or trial for which the participant is eligible. CoRDS personnel will contact those individuals on behalf of the researcher and provide them with the information on the study and the contact information for the researcher. At that time, the CoRDS participant is able to decide whether or not they would like to participate in the clinical trial or research study. If interested in participating, the individual will be provided with the contact information necessary to connect with the researcher.

CoRDS requests that all participants update their information annually.

Questions?

The CoRDS team loves to hear from individuals interested in the registry and is happy to answer any questions! More information is also available on our website www.sanfordresearch.org/cords

Veronica J Hinton, PhD
Associate Professor of Clinical Neuropsychology
Columbia University

Cognitive and Behavior Skills in Children with Glut1 Deficiency

Goal 1. Determine characteristics associated with Glut1 Deficiency

We examined:

a. Intellectual Function
    i. There is a wide range across the group and the mean of the group is shifted down from general population about 2 standard deviations
b. Language Ability
    i. Communication difficulties are common
        1. Poor articulation
        2. Dysfluent speech
    ii. Receptive language skills are stronger than expressive skills
    iii. Children understand more than they may seem to judging by their speech limitations
c. Adaptive Behavior, as reported by parents on standardized questionniare
    i. Adaptive behavior composite scores are shifted down from general population
    ii. Social skills are strengths!
d. Behavior
    i. There is no evidence of any characteristic unusual behaviors associated with the disorder
    ii. Poor attention is common
    iii. Behavior concerns are <u>not</u> associated with neurological score, cognitive score, adaptive behavior or age
    iv. Although some children may have problem behaviors, there was no consistency observed across the group
e. Processing Style
    i. Among higher functioning children there is a **primary reliance on using a sequential information processing approach**
    ii. This differs from the general population who use both approaches comparably
    iii. **Holistic and spatial integration** strategies are particularly impaired
    iv. May well be related to diminished energy expenditure of thalamus

Goal 2: To examine relationship of skills with different variables, such neurological function, gender, age

We examined

a. Neurological performance
    i. Cognitive performance is associated with neurological score
b. Age and Gender
    i. There is no association of cognitive performance with age or gender

Goal 3: To examine effects of development over time

c. Cognitive skills
    i. Cognitive Skills remain stable across time
d. Adaptive behavior
    i. Adaptive behavior remains stable across time

Goal 4: To consider implications of findings on how to optimize quality of life

There is a wide range of cognitive function and as a group, scores are shifted down from general population

- Every Individual is unique!
- We present GROUP data, but each child needs a thorough clinical neuropsychological evaluation to determine his or her own individual strengths and weaknesses
- Data show what children are "at risk for" if they have Glut1 Deficiency diagnosis, but not all children will have every characteristic

Receptive language skills are stronger than expressive language skills

- Speech therapy is recommended!
- Because speech is dysfluent and poorly articulated, children may appear to be more impaired than they are. Speech therapy can help children express themselves with more ease.
- Children may be frustrated at times by the difficulties they face getting understood by those who don't know them well

Visual attention to details is weak

- These are areas emphasized in academic school work but can be trained and improved
- Visual search puzzle-games like "spot the difference" in pictures, eye-spy, word search and "Where's Waldo" help train this ability
- Help go over school assignments carefully, step-by-step to help teach your child to focus on details

Fine motor skills are weak

- Another areas emphasized in academic school work – writing and copying
- Physical therapy and occupation therapy can help with this
- Encouraging play with blocks and legos and small items as well as encouraging drawing is recommended
- For some, use of an assistive keyboard may be essential

There is a definite bias in cognitive processing style. Be aware of limitations

- Give extra help when trying to pull together the whole picture
- Talk about stories and what the point is (fables and folktales work well for this!)
- Play with abstract puzzles where the whole is greater than the sum of the parts –work on integrating visual information

There is a definite bias in cognitive processing style. Be aware of limitations

- Give extra help when trying to pull together the whole picture
- Talk about stories and what the point is (fables and folktales work well for this!)
- Play with abstract puzzles where the whole is greater than the sum of the parts –work on integrating visual information

Adaptive behavior scores are comparable to scores on cognitive tests

- These are crucial areas to learn
- Helping children be more independent in caring for themselves will instill greater self-confidence and help them achieve more

Social skills are strengths!!

- Children are delightful and full of charm and empathetic and socially outgoing.
- Their ability to make friends will serve them throughout life
- This is a remarkable strength and one that is not emphasized as much academically as other skills
- Encourage them to be active in school groups and all social settings
- Thus, praise and encouragement are likely the most useful tools in teaching children with Glut1 Deficiency

There are no aberrant behaviors associated with Glut1 Deficiency

- There may be inattention and adjustment concerns related to living with a developmental disability
    - Consider using behavioral interventions that work for children with Attention Deficit Hyperactivity Disorder
    - One suggestion: Taking Charge of ADHD: The Complete, Authoritative Guide for Parents (Revised Edition) by Russell Barkley.
- the predominant behavior characteristic is how cued into others the children are
- Thus, praise and encouragement are likely the most useful tools in teaching children with Glut1 Deficiency

For those children on the diet, normal developmental gains are made over time. There is no evidence of decline!

- Even though the ketogenic diet may not be a "cure," it does help keep children developing and there is no evidence of progressive worsening
- Attention is better maintained, allowing for the child to learn more
- Stay in good ketosis!!!

Eric Kossoff, MD
Associate Professor, Neurology and Pediatrics
Medical Director, Ketogenic Diet Center
Johns Hopkins Hospital

Ketogenic Diet Therapies and Their Applications

In 2013, the ketogenic diet is more popular than ever before. It is available now in nearly every city and almost every country in the world. No longer perceived by most epilepsy specialists as a treatment of last resort, it is used sooner in the treatment of seizures. Glut1 Deficiency has been well-established as one of the true "indications" for the ketogenic diet. For families of children with Glut1 Deficiency, the Internet has become a great resource in order to help get started on the diet promptly.

One big change over the last few decades has been the increased ease of using dietary treatment. Many centers no longer admit or fast during the start of the diet. There are four diets available now: the classic ketogenic diet, the MCT oil diet, the modified Atkins diet, and the low glycemic index treatment (LGIT). All but the LGIT induce serum ketosis, and therefore are potentially appropriate for people with Glut1 Deficiency. Additional details about these diets, how they are started today, and why we choose one over another will be presented during this breakout session.

We are also now living in a time where ketogenic diet side effects are not only well-known, but often preventable. This certainly is important in making the diet safer for children, especially those who have to stay on it for many years, such as those with Glut1 Deficiency. Most researchers are trying to prevent side effects by using supplements. These include Polycitra K, carnitine, selenium, Vitamin D, salt, and amino acids. Long-term side effects of the diet have been described for those on it for over 6 years. They include bone fractures, kidney stones, and decreased growth. For children with Glut1 Deficiency, these side effects need to be closely screened for. Several adults with extremely long ketogenic diet experience (over 20-30 years) have been cared for at our center at Johns Hopkins and their stories will be discussed.

One big concern that many families have, and often lead them to seek second opinions from other ketogenic diet centers, is in regards to "fine tuning" the diet to achieve better seizure control. There are many anecdotal reports of interventions such as calorie reduction, ratio increase, achieving an ideal body weight, and other changes helping to reduce seizures. What is he scientific evidence behind fine tuning? Does it really work? Can it be done for a child with Glut1 Deficiency who has been on the diet for many years?

As our patients with Glut1 Deficiency become adolescents and then eventually adults, many still require ketogenic diet therapy. It is unclear whether a transition to the modified Atkins diet will maintain seizure control even as the diet becomes less restrictive. Similarly unclear is who will continue to provide dietary guidance to these teenagers who are now adults. Most adult neurologists and dietitians are not comfortable with managing adults on ketogenic diets. That is changing, and since August 2010, we have had a very successful Adult Epilepsy Diet Center at Johns Hopkins with an adult dietitian and epileptologist focusing on helping maintain patients on this therapy. As more centers like ours open around the world, there will options for patients who "grow up" on dietary therapy, such as those with Glut1 Deficiency.

Lastly, this breakout session will cover some frequently asked questions by families to me at national meetings and parent support groups. What are important questions you should ask your ketogenic diet team? How can you keep your child motivated, successful, seizure free and safe on dietary therapy?

Summary of KetoCal's Session at Glut1 Deficiency Family Conference 2013:

The KetoCal team discussed the new and renovated products available since last year's meeting and did a cooking demonstration using the new products.

New products:

- KetoCal 4:1 Liquid- Unflavored
- Liquigen, an emulsified MCT oil

Renovated products:

- KetoCal 3:1 powder: Increased Vitamin D, added DHA/ARA
- KetoCal 4:1 powder (coming soon): Increased Vitamin D, improved fat profile, added DHA/ARA, added fiber
- KetoCal 4:1 Liquid Vanilla (August 2013): Increased Vitamin D, improved texture (no more clumping!)

Recipe demonstration:

- KetoCal Potato-less Baked Potato Soup
- KetoCal Creamy Taco Soup
- Liquigen Fudge Popsicle Recipe

Recipes coming soon on myketocal.com and ketocalculator!