

# GLUT1 Transporter Deficiency Syndrome Conference

## Summary Report

Louisville, Kentucky

### July 15, 2010

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[our most sincere appreciation and gratitude to Kris Engelstad for preparing and sharing the contents of this report](#)



## “Clinical Research”

### Clinical Research

There are 3 components to clinical research

- 1) Recruitment- getting patients for studies.
- 2) Intervention- what is the treatment?
- 3) Outcomes- need some outcome measures that are meaningful

Oversight of the clinical study by several groups:

- 1) The institution where the study is done- Institutional Review Board (IRB)
- 2) FDA
- 3) Funding agency
- 4) National Institute of Health- NIH

### Recruitment

Need a good amount of patients to have a trial

Need to know who are the patients? Where are they? How do we find them?

There are guidelines to which patients are eligible- we need to see patients who are already diagnosed with Glut1 DS- so that we don't need to find the patients.

There are plans in the works for an International Patient Registry- this is patient family driven and private (confidential) and includes patients name, mutation type, contact information.

Having larger numbers of patients helps with identifying special concerns- i.e. if a symptom is rare, but there are a lot of patients, a small group of patients with that symptom can be found.

Recruitment requires that patients should have a known mutation that causes Glut1 DS

We can't always find a mutation and some patients haven't had genetic testing.

We will partner w/ the NIH to perform genetic testing- not free but hopefully at lower cost

DNA testing is happening all over (eg. Texas and New York)

Intervention- how do we choose treatments to test?

- 1) Need to be sure that the treatment is safe
- 2) Need to try something that has been proven to work in some situation that might also apply to Glut1 DS
- 3) Needs to be a rational reason- can't try something that you don't know how it works or how it influences the biochemistry of Glut1 DS.

We need to test treatments on the mouse and do laboratory testing. There are 4 mouse models of Glut-1 DS. It is unlikely that some treatment will come to us by chance- most likely by laboratory research. We are just beginning to do this work.

What is a good treatment?

- 1) Knowing how it works
- 2) Knowing whether it is safe
- 3) The ketogenic diet is not the total answer to Glut1 DS- because it doesn't address the cognitive issues.

### Outcomes- how do we judge improvement?

- 1) With brain MRI/MRS we can look at metabolism but this isn't easy. There is no easy way to check brain metabolism—brain MRI is a good measure but it is complicated.
- 2) How do we rate spasticity?
- 3) Seizure activity can be measured relatively easily.
- 4) Cognitive testing can be performed

### Patients/parents signing documents for a research study:

- 1) Consent-the consent describes what the patient will be doing and the risks. It also gives contact information. It should be read.
- 2) Signing Consent  
Means that you are making a commitment to the research.  
Signs away some of your private information.  
25% of people who attend trials don't complete the study.
- 3) HIPPA- Health information Portability and Accountability Act.

### Clinical Trials

Funding- clinical trials are expensive!!! They take a lot of time from all research staff. The patient registry will help in this process. At some point in clinical trials we may see 100 patients for a study so we need a community of patients and researchers. We need to continue establishing a mechanism to communicate with each other and with the doctors.

### Using the internet as your source of information

The docs don't look at the internet and it can be used erroneously to give wrong advice. Be careful with what is on the internet- the information isn't always correct.

### Funding

Funding-how do you help? Talk to your representatives, they are there to serve you. We always need funding. Have a meeting with them. Legislation is passed from pressure by the people. People need to be organized and be part of a national Glut-1 DS organization. Everyone can help. The organization should be patient driven, and non-profit. The group needs an agenda and needs to be energized. The conditions that get the funds are those who have patient advocacy groups that are well organized. The condition of Glut-1 DS is potentially treatable and is one of the better known metabolic diseases. There needs to be a unified front, i.e. physicians working with the parent groups. There are potentially 250 to 300 patients with Glut-1 DS at this time.

Funding is based on how long it takes to answer a question. The NIH will fund laboratory research, generally 5 years at approx. 1.2 million dollars. Clinical trials are about as expensive, but the researchers are trying to do research with what money they have and then will return to the NIH to try to justify being given more money. Getting funding also requires that there is some evidence that the treatment works.

Research on brain metabolism- we have new technology that we did not have before to evaluate brain metabolism. We need this basic research to learn about Glut-1 DS and it can often also apply to our knowledge of brain function.

### Genetic Testing

Genetic testing for Glut1 DS about to become more available. Most of the time we can identify the mutation with a gene test. About 5-15% of the time we can't find the mutation- we believe it is there but can't find it. Sometimes patients have pieces of the GLUT1 gene missing that weren't evident before. Finding a mutation helps assess risk for future offspring, also confirms a diagnosis. Right now, insurance may or may not pay for the genetic testing and the cost may be over \$1,000. Previously, the physicians have been paying for it.

Shotgun sequencing- look at a bunch of genes at one time (*genetic sequencing*)- may be possible to also include Glut-1 DS at some time. There needs to be a benefit to cost ratio in establishing funding for this type of test. No company/government wants to pay for testing if so few patients have this disorder, thus a patient database is important to determine really how many patients with Glut-1 DS are there.

#### Is new born screening (NBS) for Glut-1 DS a possibility?

Not at this time- there is no easy chemical to test for Glut-1 DS that would allow for NBS. Most diseases have some chemical marker that is abnormal upon mass spectrometry (*a type of laboratory testing*). The quickest and easiest thing to test is the DNA genetic sequencing - but it is very expensive. The physicians believe that there are a lot more patients with Glut-1 DS out there. We generally think of patients with Glut-1 DS as having seizures, but patients with Glut-1 DS have alternating hemiplegia, chorea, etc. It is possible that patients have less severe symptoms only such as: developmental delay without seizures. There are genetic databases out there for patients with seizures, it is possible to get some of them and test for Glut-1 DS to see if they might have Glut1 DS. This costs money, but it should be done.

#### Treatments

Not all treatments for a disorder work for every patient. The animal work is important but mice don't always respond to the treatments in the same way. A well characterized group of patients is required to test a treatment. The NIH needs to have a real strong reason to give money for research in a treatment option. The NIH won't give out money without data on animal and patient studies.

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## “Glut1 Deficiency Syndrome: From the beginning to now and beyond 2010”

### Normal Growth and Development

Newborns heads are proportionally larger than older children and adults.

The brain is growing dramatically in size until about 4 years of age.

The need for glucose is greatest during these early years. The need for glucose slows down at about 10 years of age.

Many patients with Glut-1 DS have microcephaly (*small size head*).

### What is developmental encephalopathy?

There are 3 neurological domains: cognitive (learning and memory), behavior, movement. Impairments in any of these three domains is considered developmental encephalopathy. We can evaluate all three of these domains in our research with Glut-1 DS.

We use the Columbia Neurological Score (CNS) to assess overall neurological function. It is a scored exam of several different neurological functions (balance, movement, reflexes, etc). A perfect score is 76, with Glut-1 patients scoring anywhere from the 40's to 76. Reduced scores in the CNS exam are associated in many patients with reduced cognitive ability.

### What neurological domains are affected by Glut-1?

Many neurological domains are not affected by Glut1 DS, such as the cranial nerves (hearing, vision, etc) but other neurological domains are affected by Glut1 DS, such as balance and speech.

### Glut-1 Deficiency Syndrome

Glut-1 DS was discovered by Dr. De Vivo in 1991. There has been a common phenotype (*set of symptoms*) to most patients with Glut1 DS. This is: early onset of seizures that do not respond to anti-seizure medications, low spinal fluid glucose, motor problems and cognitive issues. Nearly all patients with Glut1 DS have low spinal fluid glucose - which is also known as hypoglychorrhachia. We now see patients with Glut-1 DS that have a slightly different set of symptoms and some patients who don't even have seizures. This makes diagnosing Glut1 DS a bit more difficult. To date, over 100 different GLUT1 gene mutations have been reported in the literature. We expect that even more will be found in the future. Most mutations are spontaneous, which means that the mutation started with the patient. However, these mutations can be passed from the patient to his/her offspring. Each child of a patient with Glut-1 has a 50% chance of inheriting the mutation that his/her parent with Glut1 DS has. This is known as autosomal dominant inheritance.

### What is the diagnostic gold standard for Glut-1?

How is the disease of Glut1 DS diagnosed? The referring doctor usually identifies symptoms of the disease (or just notes that something is wrong with a patient-usually seizures) and then performs a spinal tap to see what the CSF glucose is. If the CSF glucose is low the patient's blood (and the parents) is sent to Columbia University for a red blood cell glucose uptake assay. Most, but not all, patients with Glut-1 DS have low red blood cell glucose uptake.

### Mice with Glut-1 DS

In our laboratory, we have mice with Glut1 DS and we can test them for many different things such as: motor function or reflexes, both of which are neurological functions. We already know that these mice perform more poorly than mice without Glut1 DS. It has also been shown that their head size is smaller than mice without Glut1 DS. We can also try different drugs or diet on them in the laboratory to see if their neurological functions improve.

## “New Studies in Glut-1 Deficiency Syndrome”

The problem in Glut1 DS is that there isn't enough glucose going into the brain. Glucose is made of carbon, hydrogen and oxygen molecules.

There is a lot of research that needs to be done to be able to treat Glut1 DS more effectively. Technology needs to be created and this ultimately involves testing in people, comprehending the disease better and creating treatments. These are 3 goals of the Dr. Pascual laboratory.

We need to partner with NIH to commercialize testing and we need to create a website and provide information on how to obtain genetic testing.

### When DNA testing is negative:

5-15% of patients who look like they have Glut1 DS are gene mutation negative. We need to probe the gene more and are establishing means to do so. Finding a mutation is important to the doctors and the families because it certifies that the patient has Glut-1 DS.

Evaluating brain metabolism as an alternative to DNA testing is another way to establish the diagnosis.

### DNA probes for mutations in the GLUT1 gene located on chromosome 1.

Each person has 2 copies of the GLUT1 gene. Patients can have a mutation (change in DNA) or pieces of DNA missing. We have 100-200 different probes on glut-1 gene (*a probe is a way of identifying whether a piece of DNA is missing within a gene, the more probes you have the better you can see if some part of the GLUT1 gene is missing*). Both are considered genetic testing.

A new technology had been created that can look at 250 different genes that commonly cause epilepsy. This technology uses a Microchip and only requires a drop of blood from the patient. It is called the “epilepsy-neurological micro array” it is commercially available and would look for missing pieces of genes.

### Timeline for research in Glut-1 DS

Compared to other diseases with energy metabolism defects, much more is known about Glut1 DS. We know a lot about Glut1 DS yet many things are still unknown.

We need to understand parts of the brain better and also to understand brain metabolism more. This would include electrical neuronal circuits.

Our lab has 4-5 different kinds of mice with the disease of Glut-1 DS. To do research, glucose is labeled with magnetic carbon atoms. This not only labels glucose but also everything else downstream-i.e in glucose metabolism or the breakdown of glucose into smaller units. Each chemical that is formed from the originally labeled glucose molecule will also be labeled with the magnetic “marker”.

We also look at brain metabolism.

Neurotransmitters can be evaluated- we know most of what they are.

One mechanism causing epilepsy is an imbalance by excitation and inhibit in brain. We need to discover what laws cover this system and how this interacts with glucose.

Glucose is converted into neurotransmitters- in mice we know how quickly glucose interacts with these transmitters.

How do we do this in humans? Through MRI, which is safe, non invasive, and can be repeated. We are not looking at size, shape of brain. We want to look at brain metabolism, i.e. brain signals in MRI also contain chemistry (not just size/shape). We can look at neurotransmitters.

We can also look at oxygen use by brain. Oxygen use is a signal of brain metabolism-i.e the brain uses oxygen in the process of using glucose. So that, if less glucose is used, less oxygen is also used. Thus we can use oxygen as a signal of brain glucose use which in turn could be used as treatment efficacy (*i.e a treatment drug works if more glucose is used which is evaluated by the use of oxygen*). The question is: does oxygen consumption increase with treatment? We can modify MRI waves to look at different brain functions/chemicals. We can identify things not seen before, e.g we can see fat inside of cells.

Our lab partners with the NIH (National Institute of Health).

We have looked at brain tissues. For any patients who have had brain surgery the lab obtained brain tissue. We applied MRI to brain tissue to evaluate brain tissue chemistry. We can also look at a patient's brain using the MRI to see chemicals.

We have performed brain studies using the pig and received overwhelming data from the pig. In this case, the pig received glucose with a "marker" so that we can see what happens to the glucose.

Patients with brain tumors have been given labeled glucose and then we get tissues from the surgery to run in MRI machine. We can see what happens to brain metabolism with the labeled glucose.

In the future, we will do this, without taking a piece of brain out, by using labeled glucose and MRI's. We have worked out much of the mechanism of glucose metabolism. Knowing this we can try to find something else to treat the patients with besides just the ketogenic diet.

#### Our Research Plans:

Try the labeled glucose and MRI techniques in patients-it is safe.

Use alternative fuels to treat Glut-1 DS and check whether they are effective by using MRI.

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## “The Role of Anapleurotic Therapy in Inherited Metabolic Disorders”

*Background on Energy Production by Kris Engelstad:*

*The food that we eat is primarily made up of carbohydrates (pasta, fruit, sugars), fat (butter, oils), and protein (meats, grains). These three types of food are broken down into other chemicals, resulting in energy (ATP) formation (along with other substances). This is a complicated process called “catabolism” and many different substances are made along the way. The process utilizes the Citric Acid Cycle-“CAC” (also called the Tricarboxylic Acid Cycle-“TCA”) which is in the cell and Oxidative Phosphorylation (in the mitochondria portion of the cell) to produce all of these substances.*

*Glucose (from carbohydrates) made from the breakdown of food is transported into the brain by the Glut-1 Transporter. When glucose gets into the brain it is made into energy (ATP) through the elaborate chemical process of catabolism which uses the CAC/TCA and Oxidative phosphorylation. This energy/ATP fuels the brain and allows it to work properly. With the use of the ketogenic diet, a similar process occurs, however it is ketones (rather than glucose) that crosses the blood brain barrier and is used to make energy/ATP through the CAC/TCA cycle.*

*The term “Metabolism” means getting energy from food. The term Inborn Errors of Metabolism is a generic term meaning that something went wrong in the process of breaking down food into other substances with the end result of energy production. It isn't that the stomach can't break down food into smaller units, but rather that chemicals in the blood are missing thus the process can't work properly. In Glut-1 DS, metabolism (and the production of ATP) isn't working optimally because glucose isn't being transported into the brain in sufficient amounts, thus reduced energy/ATP is produced in the brain. Glut1 DS is considered an Inborn Error of Metabolism.*

*Anapleurotic Therapy is a term that simply means that instead of adding glucose or ketones to the system, we are adding back one of the intermediate substances in metabolism to produce the end result which is energy/ATP. In this case that substance is triheptanoin. Triheptanoin is able to cross the blood brain barrier and enter the catabolism/metabolism process which should result in the production of energy/ATP.*

### Dr. Roe's Presentation

The recognition on inborn errors of metabolism started around 1960's and three disorders were known at that time.

Treatment options for inborn errors of metabolism are to remove the precursor to the chemical that can't be broken down (*if substance A is turned into substance B and an enzyme needed to do so is missing, then A can't turn into B and the concentration of A will increase - this can cause clinical symptoms - the treatment is not to have the production of A in the first place*).

Options to treat inborn errors of metabolism have expanded recently.

As molecular understanding grew scientists discovered another treatment possibility, that is, to prevent the disease (genetic option) and maybe gene replacement.

Some questions that researchers ask themselves about these disorders:

Why are there phenotypic (*symptoms*) differences between kids with the same disorder?

How does the metabolism of one organ affect the metabolism of another organ?

Is there something wrong with energy metabolism? This is true of many of the inborn errors of metabolism.

## Energy Failure

Not getting glucose into the brain effectively to use in oxidative metabolism.

There is a need to stop looking for preventing blocks, but rather how to get energy into brain ( *i.e treating inborn errors of metabolism isn't just looking at why A can't turn into B, but also things such as energy failure, such as in Glut1DS, in which there isn't enough of A [glucose] to begin with*).

We need an odd chain carbon fatty acid to use for therapy. Researchers can think about using different chain lengths and evaluate what is more or less effective as a treatment. This process involved using anapleurotic therapy.

In theory, for any metabolic disturbance where there is a compromise in ATP production- anapleurotic therapy could be used to treat patients.

## Caloric reserves for energy production in an adult:

If a person is fasting he/she will use reserve calories.

Fat represents 85% of reserve and the rest is protein and glycogen (storage form of complex carbohydrates in muscle and liver).

The liver takes glucose and forms glycogen.

When a child is acutely ill, glycogen (energy reserved in the liver) will be released.

In the fasting state:

Protein can be made to Amino acids (blood) which then can make energy (*a person who is fasting will eventually use muscle to make energy if food is severely limited*).

Fatty acids in bloods can be used to make energy (*many people try to lose weight by fasting which utilizes fat reserves to make energy*). In the ketogenic diet, fatty acids are broken down (categorized) which makes ketone bodies. The liver provides ketones and glucose for brain function as a reserve calorie source from foods that we eat. In fasting- the attempts to make energy is poor.

If the pathways that turn food into energy are blocked problems occur. It is like a chain reaction. If energy/ATP is reduced, different substances are produced that further "clog the system" making the whole production of energy even more disabled. Reduced ATP increases AMP which turns on an enzyme that phosphorylates other enzymes (rendering them inactive). These other enzymes are normally responsible for the process of catabolization. If you can raise the ATP level then you can stop the phosphorylation and the destruction of other substances necessary for the process to work. This is important for the field of Glut1 DS.

Chemicals made, when this system isn't working, that change the acid base balance within mitochondria which further down-regulates mitochondria function and thus less ATP is made (ATP is made in the mitochondria from the byproducts of the breakdown of glucose and/or fatty acids).

## Anapleurotic therapy

Anapleurotic therapy is "re-filling the citric acid cycle" for its normal function of making ATP (energy). When the citric acid cycle is suppressed- gluconeogenesis is also suppressed.

Three anapleurotic substances are available and triheptanoin is one of them.

Triheptanoin - should provide substrate for ATP production (TCA cycle) and shut down the phosphorylation process.

## Triheptanoin (7 carbon molecule)

Will be given at 30-35% of total caloric intake of diet

Triheptanoin makes a 5 carbon chemical that can be used in TCA cycle

Makes acetyl Co A and propionyl Co A goes into CAC (citric acid cycle)

This results in energy/ATP production

It can also make ketone bodies - taken up by every other organ system and similar breakdown with the eventual production of ATP.

Triheptanoin was used in a study with an inborn error of metabolism (The disorder was in fatty acid oxidation metabolism - Not Glut-1 DS) and it showed clinical benefits. The benefits were:

Mortality was reduced

Glucose homeostasis was restored to normal

Improved muscle strength

Reduction of muscle breakdown

#### Triheptanoin overview:

Odd carbon number triglyceride

Stimulates CAC and enhances ATP production

Won't be a silver bullet- but should be better than ketogenic diet

Virtually no odd carbon fatty acids available in nature.

Triheptanoin is made from the Castrol oil, a 7 and an 11 carbon acid- the 7 carbon is split and makes a 5 carbon substance.

It is made in Germany.

It has been used in butter for many years in Europe and is thought to be safe.

#### Questions researchers ask:

Which diet is better for kids? All kids are different. This is not known at this time.

We need seizure control but also treatment for other effects of Glut1 DS.

#### What stage are we at in using triheptanoin?

Triheptanoin is not yet FDA approved and must be used in the context of a research study. There are 10 years of safety data available.

#### What is the efficiency of crossing the blood brain barrier?

More effective as an anapleurotic agent than the 4 carbon molecules.

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## “Epilepsies in Glut-1 DS”

### Outline of Talk

- 1) Excitation and inhibition
- 2) Energy failure
- 3) Treatments

### 1) Excitation and Inhibition

Definition of a seizure: sudden surge of electrical activity in the brain that usually affects how a person feels or acts within a short time. Many different disorders can cause seizures.

Definition of epilepsy- epilepsy is the tendency towards having seizures. The requirement for calling symptoms “epilepsy” is: “At least 2 seizures on 2 occasions, separated by at least 24 hours”. Additionally, these can’t have been caused by injury or intake of harmful substance. Epilepsy is not a disease itself, but is caused by a number of different diseases

Seizures can look different in one individual and between individuals. For example, they could be emotional responses, behavioral actions, and some seizures are not even noticed.

Seizures can have lots of different manifestations:

- Chewing movements
- Breathing difficulty
- Drooling
- Falling down
- Fluttering of eyelids
- Sensory manifestations such as
- Confusions, black outs, smells, spacing out, fear, panic

[www.epilepsy.com](http://www.epilepsy.com) is a good website to read all about epilepsy.

### 2) Energy Failure

What protects our brains from having seizures?  
All people can have a seizure if the right circumstances prevail.

Excitation and Inhibition

- There are two types of neurons in the brain- inhibitory and excitatory
- Excitatory neurons- amplify the signals (create a signal—like a green light)
- Inhibitory- stops this process (like a stop light)
- We need both for a normal functioning brain

To keep these neurons in balance we need a source of energy - without the energy to keep this in balance seizures can result. In Glut1 DS we don’t have anything to balance out the excitatory neurons, thus seizures are produced. Like a car needs oil and gas to run properly, in Glut1 DS we don’t have the gas (e.g. the brain needs glucose [the gas] to run).

What do the seizures in patients with Glut1 DS look like?

90% of cases start having seizures in infancy- these can be focal (small areas) or large areas of the body. Seizures are variable in Glut-1 DS - can be daily or only once in a while. They can be associated with cognitive difficulties and movement disorders.

Possible manifestations:

- Whole body stiffening
- Brief staring events
- Brief jerk of limb
- Atonic seizures with fall- possibility of injury

There is a lot of variability of seizure types in Glut1 DS and generalized then focal are most common in Glut1 DS.

We see more focal seizures in younger children than older kids  
In children we can see subtle types of seizures also such as small limb jerks.

### 3) Treatments

How do the seizure types respond to seizure medications?

We treat the Glut1 DS seizures by treating the condition of energy failure. Traditional seizure medications are not effective and don't combat the problem of energy failure. Some things can make this energy failure worse, such as caffeine and benzodiazepines.

The ketogenic diet is high in fat and low in carbohydrates which forces body to burn fat which as an alternative fuel source.

Generally the outcome of using ketogenic diet in Glut1 DS is:

- Increased alertness and activity
- Other AED's (anti-epileptic drugs) can usually be withdrawn
- The effect is quick
- The diet should be maintained through puberty

Early diagnosis and treatment are essential - and the diet should be maintained through adolescence

#### Current Project of Dr. Pong

Glut1 DS Epilepsy Project

We want to better define seizure types and there is some evidence that some of the AED's might be useful.

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## “Expanding Glut-1 DS Phenotype and Research”

### Definitions:

Chorea- dancing like movements

Dystonia- abnormal posturing of body part

Paroxysmal- a sudden outburst of emotion or action

Phenotype - a phenotype is comprised of the signs and symptoms of a disease. Generally, there is a set of signs and symptoms that are found a specific disease. For example, patients with Glut-1 DS have low CSF glucose (sign), balance problems (symptom), cognitive issues, seizures, etc. A patient doesn't need to have all of the signs and symptoms to fall under the phenotype of Glut1 DS. This is compared to a “genotype: which is the genetic (DNA) anomaly.

Sign- something that the doctor can see or measure (low CSF glucose).

Symptom- something that the patient says that they have that may or may not be measureable- (eg. headaches, seizures).

## Lecture

### Glut1 DS Signs and Symptoms

What does a doctor evaluate? Signs and symptoms of a disease.

Some signs and symptoms of Glut-1 DS

- 1) Developmental delay
- 2) Decreased head growth
- 3) Low CSF glucose
- 4) Seizures

The signs and symptoms together are called a “phenotype”.

The classic Glut-1 DS phenotype- has all of the following signs and symptoms: seizures, developmental delay, decreased head growth and low CSF glucose.

A Glut1 DS diagnosis is generally dependent upon the presence of gene mutations and decreased glucose uptake. We can start with the general phenotype and use the diagnosis to look for other populations of patients who might differ from the classic Glut1 DS phenotype but still have Glut1 DS.

### New Phenotypes

We know of patients with Glut1 DS who don't have the classic phenotype but still have Glut1 DS. So this allows us to think about other sets of symptoms that we see and wonder if they also have Glut1 DS. These symptoms would include:

- 1) Alternating hemiplegia of childhood
- 2) Paroxysmal exercise induced dyskinesia
- 3) Paroxysmal choreoathetosis and spasticity
- 4) Other movement disorders

### Movement disorders

Movement patterns that do not involve seizures

This would include: tics, dystonia, myoclonus, abnormal gait

Dystonia (definition)- abnormal posturing/twisting which could be of any body part (arm, leg, jaw, head)  
Chorea (definition)- dancing movements (patient looks like they are dancing)  
Myoclonus- sudden jerks of body parts (can be due to seizures or not)  
Abnormal walking patterns- e.g. ataxia (walking like a “drunk”), spastic gait- stiffening, apraxia (clumsy- difficulty with motor planning)

Movement disorders are common in Glut1 DS

Percent of each movement disorder found in patients with Glut1 DS

Dystonia- 85%  
Chorea-75%  
Tremor-70%  
Myoclonus in 16%

90% of patients with Glut1 DS have a gait abnormality- ataxia, ataxia and spastic, dystonia

Movement disorders don't have to be constant, as they can be intermittent and can mimic epilepsy.  
If they show up on an EEG they are epileptic.

Paroxysmal movement disorders- intermittent- common in kids with Glut1 DS.

This includes:  
Episodes, weakness, chorea, dystonia, ataxia

Other paroxysmal events found in Glut1 DS patients:

Mood changes- paroxysmal dysphoria  
Emotional changes  
The frequency is variable

Triggers of paroxysmal movement disorders include:

Fatigue (is most common)  
Dietary compliance  
Excitement  
Anything that causes a burden on the patient

Why are movement disorders so common in Glut1 DS?

The brain is important in the production of movement  
The basal ganglia and the thalamus are important for movement  
In addition, the cerebellum and thalamus have low levels of glucose availability with Glut1 DS

The decrease of glucose transport into brain when a patient is subject to additional stress causes a bigger energy drain and these events occur.

The ketogenic diet can help with these episodes.

Expanding the phenotype of Glut1 DS ( i.e What other sets of symptoms could be indicative of Glut-1 DS?)

1) Alternating Hemiplegia of Childhood (AHC)

Alternating hemiplegia of childhood is a symptom of no specific diagnosis.  
Alternating hemiplegia is: weakness on one side of body which can have tonic/dystonic episodes.  
It can also be associated with cognitive impairment and progressive ataxia.  
Patients with this set of symptoms are known but may not diagnosed with a specific disorder.  
Triggers to these events are some of the same ones as those found in Glut1 DS.  
GLUT1 gene mutations have been found in some of these kids even though they have not had seizures.

2) Paroxysmal Exertional Induced Dyskinesia (PED): this is dystonia (abnormal posturing) or chorea (dancing movements) after exercise.

This is a symptom not a disorder. Some GLUT1 gene mutations have been found in these kids. There are several different types of dystonia, some of them may have Glut1 DS.

Dystonia types

DYT1 childhood onset, dystonia in limbs

DYT6

DYT9

DYT18- exercise induced dyskinesia- some may have Glut1 DS

DYT9 age on onset 2-15 yrs, involuntary movement, slurred speech, blurred vision, episodes, triggers exercise, alcohol, ( 1996 paper) Suspected gene in 1996 was on chromosome 1- we are trying to see if there is a GLUT1 mutation.

Dr. J. Pascual described another patient with episodes of chorea who has a diagnosis of Glut1DS.

The Main Point: The classic Glut1 DS phenotype is expanding and finding these other populations of patients will allow these kids to be treated also.

Research Questions:

- 1) What is the size of the population of patients with these other syndromes? There are a few hundred AHC patients. Other population sets are likely a few hundred each. We will find more of the milder cases of Glut1 DS as we look further into other phenotypes.
- 2) Why aren't doctors doing lumbar punctures (LP) as part of the standard of care? LP's are important and we are frustrated that doctors don't do more LP's.
- 3) Scenario: a child is diagnosed with autism and some kids with autism also have seizures. Could any of these patients have Glut1 DS? Autism is not really a feature of Glut1 DS. Autism is not a diagnosis it is a symptom and there are many causes of autism. Autism by itself is not generally a symptom of Glut1. One wouldn't necessarily test for Glut1 DS in an autistic child. Similar to autism not being a diagnosis, cerebral palsy is also not a diagnosis, it is just a description of what the doctor sees.
- 4) In Glut1 DS, the intermediates in the pathways from glucose/fatty acids to ATP are depleted and we need to fill up those pathways. Triheptanoin may help fill up those pathways.
- 5) Why do kids still have symptoms when we are treating them with the ketogenic diet? Triheptanoin has helped in other diseases with issues in skeletal muscles. Although it seems to be beneficial, the diseases are not cured by triheptanoin or the ketogenic diet. Improvements are seen but no cure. We need to look for things that are not normally screened for.

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## “Glut 1 DS Characteristics of Cognition and Behavior”

First:

Please remember that these findings are from GROUP data. The data show what children are “at risk for” if they have the Glut 1 DS diagnosis, but not all children will have every characteristic.

Every individual is unique! Each child needs a thorough clinical neuropsychological evaluation to determine his or her own individual strengths and weaknesses and remediation strategies best suited for his/her profile.

Keeping that in mind, here are 10 Take Home Points & Implications:

- 1. Across children diagnosed with Glut 1 DS there is a wide range of cognitive function. As a group, scores appear to be normally distributed, but are shifted down from general population about 1 ½ to 2 standard deviations.**
  - Some children’s IQ will be in the “normal” range, but most will have scores significantly lower than expected for general population.
  
- 2. Among children with Glut1 DS, receptive language skills are stronger than expressive language skills (regardless of overall level of IQ)**
  - Speech therapy is recommended!
    - Because speech in individuals with GLUT 1 DS tends to be 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
  - For some children augmentative communication devices may be helpful
  
- 3. Among children with Glut1 DS, visual attention to details tends to be weak**
  - These are areas emphasized in academic school work and 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
  - This may be variable throughout the day; there may be “spells” of inattention

#### **4. Among children with Glut1 DS, fine motor skills are weak**

- This is 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

#### **5. There is a definite bias in cognitive processing style. Children use a sequential processing approach preferentially. Use this to your advantage!**

- They are better at seeing the trees, than the forest
- Use teaching strategies that rely on sequential or step-wise approaches to material.
- Teach one thing, then another and another
- Rely on repetition and rote memorization
- Break large assignments into manageable steps
- Consider using organizational strategies similar to those recommended for children with attention deficit disorder
- Explain clearly what the general point or “take home” message is

#### **6. Children with Glut1 DS have difficulty using simultaneous or “whole picture” processing approaches. Be aware of limitations**

- They have difficulty seeing the forest, and tend to focus on the individual trees
- 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

#### **7. Adaptive behavior scores are comparable to scores on cognitive tests**

- There is a wide range of adaptive behavior performance
- Although for some children adaptive scores may fall in the “normal range,” the majority of children with Glut1 DS perform at levels below those expected for their age
- Compared to Daily Living, Communication and Motor Skills, Socialization skills are strengths (across all levels of function)
- Adaptive behavior skills are crucial areas to learn

- Some parents may be reticent to give their children age-appropriate responsibilities in caring for themselves and their home, but having children participate in day-to-day activities and helping them become proficient in self care and household skills will likely increase the child's sense of family and self worth
- Helping children be more independent in caring for themselves will instill greater self confidence and help them achieve more

## **8. Social skills are strengths!!**

- This is not easy to measure, but readily apparent!
- Children with Glut1DS stand out in their “winning personalities”
- Children with Glut1 DS present as delightful, full of charm, empathetic, socially outgoing and have a playful sense of humor.
- Their ability to make friends will serve them well throughout life
- Children with Glut 1 DS should be encouraged to be active in school groups and all social settings, giving them ample opportunities to develop and enjoy warm relationships with others
- This is a remarkable strength and one that is not emphasized as much academically as other skills, yet may well help them in all aspects of their lives

## **9. There are no known aberrant behaviors associated with Glut 1-DS.**

- Although some children may have problem behaviors, there is no consistency observed across the group. There is no evidence of any significant psychopathology associated with the diagnosis.
- Many children with Glut1 DS may have attention difficulties, and these may fluctuate during the course of the day.
- As children mature and gain more insight, some may have adjustment concerns related to living with a developmental disability. These adjustment problems seem similar to those observed in adolescents living with any type of disability and may be responsive to intervention with supportive psychotherapy
- Again, the predominant behavior characteristic associated with Glut1 DS is how cued into others the children are.
- Thus, praise and encouragement are likely the most useful tools in teaching children with Glut-1 DS! They respond very well to positive feedback.

## **10. 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 over time
- Attention is better maintained, allowing for the child to learn more
- Stay in good ketosis!!!

## The Use of the Ketogenic Diet in Glut-1 DS

Glucose normally fuels the brain. In the ketogenic diet, ketones rather than glucose are the source of fuel for the brain. Adequate ketones are reached when the blood beta-hydroxybutyrate ( $\beta$ -OHB) is 4-5 mmol/L.

### Optimizing $\beta$ -OHB Level

- 1) Monitor blood  $\beta$ -OHB using Precision Xtra monitor (available through Abbott Laboratories)
- 2) Increase the ration of fat to carbohydrate and protein until  $\beta$ -OHB become 4-5
- 3) Maintain the correct total daily calorie intake
  - Avoid obesity
  - Consume adequate calories to ensure linear growth (height)

### Precision Xtra Monitor

- 1) Frequency for checking blood ketone levels
  - During diet initiation phase - check daily
  - Once  $\beta$ -OHB is stable and is between 4-5 (check once a week)
  - Check if child becomes increasingly symptomatic - check level (e.g. More seizures, more ataxic, less focused, etc)
- 2) Purchase cost is approximately \$75 for monitor
  - Ketone strips are approximately \$2-4 per strip
  - Purchase at local pharmacy or online at <http://www.abbott.com>
- 3) Potential coverage through insurance (with letter of medical necessity)
- 4) Calibration solutions come with the kit, or call Abbott Labs.
- 5) Urine ketone sticks are not necessary when using Precision Xtra

### Adjust ratio of fat to carbohydrate + protein

- Infants/young children can become ketotic with lower fat to carb + protein ratios
- Older children and adults need higher fat to carbohydrate + protein ratios
- Work with nutritionist to adjust ratio to fit the patient's requirements

### Maintain the correct total daily calorie intake

- Avoid being overweight - Body Mass Index (BMI)  $\leq 25$   
$$BMI = \frac{\text{weight in pounds} \times 703}{(\text{height in inches})^2}$$
- Provide adequate calories to promote linear growth (height)
- Avoid giving extra calories (even if they are within the pre-calculated ratio)

### Issues with Long Term Ketosis

- 1) Lipid status
  - Cholesterol and triglycerides can become elevated over time if diet contains only saturated fats.
  - Young children - cream and butter for fats
  - Older children - transition from saturated (cream and butter) to polyunsaturated fats (oils - eg. toasted sesame seed, canola, olive, peanut oil)
- 2) Osteoporosis
  - Calcium, phosphorus and vitamin D balance need to avoid osteoporosis.
  - Elemental Calcium Requirements (read label):

0-12 months	250-400mg daily
1-3 years	500mg daily
4-8 years	800mg daily
9-18 years	1300mg daily

- 3) Kidney Stones  
Increased risk of kidney stones in ketotic patients. Prevention of kidney stones:
  - Adequate fluid intake - dark urine means inadequate fluids
  - Correct amount of calcium - previous slide
  - Potassium Citrate 2 meq per kilo/day (optional)
- 2) Burnout - "I am sick of the diet" - affects both patients and caregivers
  - Ask for help
  - Network with other families
  - Be creative with your recipes (but keep the same ratio)

### Supplements

- 1) Complete vitamin and mineral tablet  
One tablet daily of either Scooby Doo Complete (chewable) or Centrum Complete (must contain iron)
- 2) Calcium (as per previous slide)
- 3) L-Carnitine  
L-Carnitine is a nutrient that helps turn fat into energy. Keto diet is deficient in carnitine.  
Dose: 50 mg/kg per day divided into 2-3 doses  
Availability: sugar free liquid or capsules
- 4) Alpha Lipoic Acid  
Alpha lipoic acid has been shown in the laboratory (at very high doses) to normalize glucose by correcting the defect.  
Starting Dose: 10mg/kg/day  
Maintenance dose: increase if well tolerated (gastrointestinal symptoms can occur)
- 5) Selenium  
Selenium level tends to be low in patients on the ketogenic diet.  
Dose: 1 Brazil nut per day or 30-50 mcg/day

### Monitoring General Health

- 1) Have regularly scheduled blood tests:  
CBC, lipid profile, hepatic profile, metabolic panel, calcium, magnesium, phosphorous, selenium, manganese, and betahydroxybutyrate.
  - During initial diet phase (0-6 months) Obtain at 2,4, and 6 months
  - Thereafter obtain every 6 months
- 2) Monitor weight and height every 6 months

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# Diet Demonstration:

parent volunteers

## cooking demonstrations and recipe tasting informal discussions and Q&A

The following recipes and foods will be demonstrated and samples will be available for tasting:

Mac-N-Cheese  
Chocolate Brownies

Flax Bread  
Almond Crackers

Stir Fry Noodles  
Oopsie Rolls

these recipes and many more, along with photos of each, are available at [www.charliefoundation.org](http://www.charliefoundation.org)

### Just the Cheese Frying Cheese:

Glenna Steele

available at: [www.specialcheese.com](http://www.specialcheese.com)

easy, yummy high fat cheese for snacks or meals - tastes a bit like a grilled cheese sandwich

### Hi-maize Milkshake:

Janet Bean and Matt Rizzo

information available at [www.hi-maize.com](http://www.hi-maize.com)

Hi-maize is a dietary fiber containing resistant starch, which means it reduces the glycemic response of foods that contain it. The company has provided lots of literature and free samples for us.

### product sample donations to share:

EZ-Sweetz liquid sucralose

DaVinci Syrups

Just the Cheese Crunchy Baked Cheese Snacks

Hi-maize Resistant Starch

Miracle Noodle (for cooking demonstration)