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Glut1 Deficiency Foundation

Family Conference

8.5 edition - virtually!

FAR APART - TOGETHER AT HEART

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July 23-25, 2021

Conference Summary Report

compiled by:

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and

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Day 1:

30 Years of Glut1 Deficiency

Darryl De Vivo, MD

The highlights as we have come to understand G1DF can be divided into 3 decades:

1st decade:

- Recognize and introduce this rare disease to professionals and the public
- Develop some form of treatment
- Understand the molecular basis of the disease

While the first two cases were in 1991, and it was suspected that there was a defect in the transport of glucose from the blood into the brain, it wasn't until 1998 that it was reported that a mutation in the SLC2A1 gene caused this condition.

The ketogenic diet was introduced in 1991 as the standard of care. Although glucose is the primary fuel for brain metabolism, ketone bodies are alternative fuel to meet the needs of the developing brain.

2nd decade:

- Pathophysiology of the condition
- Developed a mouse model which was published in 2006 that captured well the condition

3rd decade:

- Effort to develop more effective disease modifying treatment, particularly gene therapy
- Realized there was a disturbance in the development of cerebral microvasculature
- The point prevalence of the disease was increasing

Original report in the NEJM in 1991: 2 infants presenting with seizures, developmental delay, decelerated head growth and movement disorder. This has become the classical phenotype in 80-90% of patients.

2 key biomarkers:

- low CSF glucose
- low CSF lactate

Introduced at that time the ketogenic diet therapy (KDT) as the standard of care

Early diagnosis facilitates early treatment. A delay between initial presentation and correct diagnosis creates missed opportunity to treat the patient early with KDT

The course of the disease in first patient diagnosed with Glut1 Deficiency:

- myoclonic seizures in infancy
- movement disorder in adulthood
- moderate intellectual disability
- neurobehavioral disturbances

This profile has characterized the majority of Glut1 Deficiency patients

The neurological domains affected in Glut1 Deficiency:

- *Cognitive phenotype* domain which is a lifelong disability
- *Epileptic phenotype* which includes migraines and disturbances in behavior
- *Dyskinetic phenotype* that emerges as the epileptic phenotype resolves and is characterized by a number of movement disorders such as spasticity, ataxia, and dystonia

The management of the patients has remained constant over the past 30 years.

- Early diagnosis and treatment improves outcome
- KDT remains as the standard of care
- It is recommended to measure ketone bodies in the blood as opposed to the urine
- A multidisciplinary approach is important (physicians, therapists, dieticians, etc.)

The cessation of symptoms with rise in glucose and insulin suggests that if able to maintain an elevated blood glucose, can improve these patient's symptoms.

The mouse model has revealed that restoring Glut1 early in life, pre-symptomatically, protects against Glut1 Deficiency. However, if restored later in symptomatic mice, it fails to rescue phenotype.

Newborn screening test is needed to be able to determine potential patients within therapeutic window.

Clinical Consensus Guidelines

Prof. Dr. Jörg Klepper

We first understood Glut1 Deficiency as an energy crisis in the brain. We thought that to diagnose you need to exhibit the classical symptoms, low CSF glucose, and a mutation in the Glut1 gene, and if you had all three of these diagnostic tools, you can obtain a Glut1 Deficiency diagnosis.

This energy disturbance in the brain causes:

- Epilepsy
- Movement disorder
- Cognitive/behavioral disturbances

KDT therapy works to refuel the brain through ketones rather than glucose.

As more and more patients were diagnosed, it was realized that this condition is more complicated than originally thought. This was the driving force for establishing an international consensus guidelines.

It was learned that there is a variability in symptoms presented by patients. It was through this that it was understood that the presentation of Glut1 Deficiency changes over time.

In infants and toddlers, epilepsy is predominant symptom whereas in adolescence and adulthood, movement disorder is the main problem, specifically the dystonia and ataxia.

This led experts in the field to come together and publish a consensus on how to diagnose and treat this condition, which is an open access paper.

What was agreed upon among this group of experts:

- For the diagnosis of Glut1, the presence of a low CSF glucose, the classical symptoms and the genetics, it is confirmed Glut1 Deficiency
- Various combinations of these criteria suggest probable or possible true Glut1 diagnosis
- Paroxysmal eye head movements tend to be the first, and a very characteristic sign of Glut1 Deficiency
- In addition to diagnosis, other topics discussed in the consensus paper include: clinical presentation, treatment, research and future direction

- As many know, KDT is a very effective treatment for Glut1 Deficiency but it does fail some patients who do not respond properly to the diet both for epilepsy and movement control, so the possibility of ketones, ketoesters, or anticonvulsants are discussed in the paper as well

Ketogenic Diet Treatment

- The ketosis gets higher the more you add fat but taste becomes limited the harder the ketosis is
- 4:1 – can be done in children, should not be used in infants
- 3:1 – the most recommended diet in children and infants up to 2 years. With Glut1 Deficiency, you should try to maintain as high a ketogenic diet as you possibly can
- Modified Atkins Diet is preferred by most parents because it's easier to apply but generates lower levels of ketosis. It is more commonly applied in adolescents and adults
- Low glycemic Index Diet is not recommended for Glut1 Deficiency

Gene therapy is the option of loading a virus with a non-mutated copy of the Glut1 gene, injecting that into an animal and the mouse can be cured by this gene therapy. They were also able to replicate this in a pig.

There is a lot of debate regarding alternative energy. The keto salts are too big in volume to be taken as an alternative to KDT, it can maybe be supportive for older patients. More information on the pros and cons can be found in the consensus paper.

Open questions among other experts are:

- What about the other GLUTs?
- What about other tissues?

The first consensus is only the beginning and the feedback from families and patients is highly important.

Scientific Meeting Summary

Sandra Ojeda, PhD

Earlier this year, the foundation held its first inaugural scientific meeting. The goals of this meeting were to:

- Share key areas of current research in Glut1 Deficiency and identify critical gaps
- Establish connections and identify overlaps and synergies among related research areas
- Identify potential researchers for participation in a collaborative research network
- Identify potential projects for strategic research plan to drive progress

Overview of Glut1 Deficiency natural history:

- Glut1 Deficiency was first described in 1991 by Dr. De Vivo where he published a paper on the symptoms for this condition with the ketogenic diet as treatment.
- In 1998 the Glut1 gene was discovered and in 2008, movement disorders were described as also being part of the symptoms for this condition.
- In 2012 certain types of epilepsies were also described as part of this condition.
- In 2020, the first Glut1 Deficiency State of Art consensus guideline was published - which was a collaborative effort among many experts
- Earlier this year (June 2021) we had our inaugural scientific meeting

What has been learned about Glut1 Deficiency:

- Epilepsies tend to decrease in frequency and severity beginning in late childhood
- Movement disorders tend to worsen in adolescence
- Intellectual disability and behavioral problems if present, are stable throughout life

- Evidence from mice shows that there is a decrease in brain microvasculature
- Studies indicate that Glut1 DS patients have heads smaller than the general population but microcephaly is not as common as initially thought

Biomarkers in Glut1 Deficiency:

- DNA
- EEG
- CSF glucose and lactate
- Red blood cell glucose uptake
- Glut1 transport kinetics
- PET

All of these markers have benefits and drawbacks

Glut1 Deficiency Current Research:

Studies using mice deficient in Glut1 in brain endothelial cells have concluded that:

- Glut1 is important in brain endothelial cells
- Reduction of Glut1 expression is enough to trigger Glut1 DS symptoms
- Glut1 Deficiency in brain endothelial cells can trigger neuroinflammation and neuronal loss
- Targeting Glut1 in brain endothelial cells is imperative for gene therapy
- Glut 1 gene therapy needs to be done early in life to make a difference in the outcome of the condition

Other therapies being developed:

- SINEUPS- non-coding RNA that upregulates the production of target proteins. This would be used to increase the amount of Glut1 protein
- In vitro studies to identify proteins that interact with Glut1 protein and are involved in the translocation of this protein to the cell membrane
- Studies in the non-coding genome could lead to answers about why people with no mutations in the SLC2A1 gene develop Glut1 DS
- High throughput screening of chemical libraries to search for chemical activators of Glut1 DS
- Metabolic therapies for treatment such as C7 oil
- Blood replacement of Glut1 DS patients with donor blood

Glut1 in other diseases:

- Stroke: there is an upregulation of Glut1 followed by stroke in a mouse model of stroke
- Cancer: cancer cells upregulate the expression of Glut1 and Glut3 transporters in certain cancer types. Glut1 expression in tumors is an indicator of poor prognosis in lung cancer
- Alzheimer's Disease: Glut1 is downregulated Glut1 Deficiency accelerates BBB breakdown and amyloid beta pathology. Glut1 deficiency together with amyloid beta pathology accelerates neuronal dysfunction and microcephaly

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Newly Diagnosed – Advice for the Journey

Darry De Vivo, MD and Maria Rebbechi, RN

There is no doubt that as a parent, it incredibly overwhelming to have a child with a condition not many around them know much about and it's important to know that there is an opportunity to reach out to individuals who will be helpful in guiding you through this condition.

It is important to work with a physician who is committed to understanding the problem and doing whatever is possible to facilitate the growth and development of the child.

Keep yourself informed – sometimes some of the things you may read may seem very scary but remember that what happens to some patients isn't what happens to all patients, but it is good to be aware of the things that could potentially happen down the line.

You will become the expert in Glut1 Deficiency and you will become your child's best advocate. Asking questions to the community is a great way to learn. It's so valuable to hear about others experiences. It can be very isolating taking care of your child because you are so overwhelmed and reaching out to someone who understands the condition is very therapeutic.

How can you meet people?

- Neurology or keto programs
- Glut1 Foundation Family Network
- Quarterly Zoom meetings
- Facebook groups
- conferences

If you are new to keto, getting settled can take some time- its marathon not a sprint.
Don't overwhelm yourself, you will get there. There are peaks and valleys so don't lose hope. Supportive therapies need to continue through all of this (speech, physical, occupational therapy).

There is a balance and you can be doing too many things. Talking to other parents really helps you get an idea what is normal and what your child is entitled to in a school setting.

Worrying about the future is normal. Fostering independence from an earlier age is hard but it's definitely good to practice. Focusing on life skills in early education. Mindfulness- you need to take time for you and your family.

Preparing for Puberty and Adulthood

Kelly Faltersack, MS, RD, LD, CD and Elizabeth Felton, MD, PhD

Pediatric to adult transition:

- Transition refers to patients moving from a pediatric neurology clinic to an adult neurology clinic
- Typically takes place at age 18

KDT clinics:

- Pediatric KDT clinics are very accepted and exist in academic medical centers
- For transition clinics, they are almost non-existent for young adults on KDT
- There are very few dedicated adult clinics with an adult neurologist and ketogenic dietician focused on adults
- In general, there is a higher acceptance of ketogenic therapy in pediatric population vs adult

The transition plan:
Ages 10-13:

- Ongoing care for treatment of epilepsy
- Assess need for additional workup
- Start discussion of transition plan
- Start discussion of realistic plans for adult life
- Start fostering responsibility and independence

Ages 14-15:

- Continue work started in earlier years
- Keep talking about the transition to adulthood
- Encourage independence, allowing teen to give history, ask questions, etc. during visit

Ages 16-17:

- Review transition plan
- Discuss plans for future living and care
- Employment/job programs/ college plans after high school
- Guardianship, if needed

Age 18:

- Implement adult model of care
- Review transition plan and update
- Create/continue transition summary/notes
- Consider advance meeting of patient with neurologist

Recommendations:

- Discuss how long you anticipate being on KDT with your epilepsy provider and dietician
- Ask about the availability of adult epilepsy providers and nutritionist familiar with KDT
- If appropriate, help adolescent take more ownership of KDT

Clinical Trials 101

Adrian Avila

What is a clinical trial? A clinical trial study involves research using human volunteers to add medical knowledge.

Goals: construct the most efficient research study that will address safety, efficacy, and/or the mechanism of action on the new treatment/drug/device that is being developed for the target population.

Types of Clinical trials:
Observational: collecting information, no treatment given
Interventional: new treatments, drugs, combinations of drugs, surgical procedures, new ways to use existing treatments

IRB: Institutional Review Board – ensure studies are ethical and participant rights are protected. All clinical trials are required to have an IRB in the United States, ensuring medically important questions are being asked and answered in a scientifically responsible way.

It can take 5 to 15 years to conduct a clinical trial.
Typical Example: 20,000 drugs screened, 250 of those are selected for preclinical research, only one drug makes it to approval.

Phases of Clinical Trials:
preclinical – studying the treatment in cells, animal models. Is it safe, does it work?
phase I – small studies, 20-80 people, what are the safe dosing ranges, side effects
Phase II - larger group, does it get the same results?

Phase III - much larger group of people, monitoring side effects, comparing to commonly used treatments. Can this treatment be given safely, does it work?
Phase IV – additional data collected after approval of drug and once it is being used with patients

Why are clinical trials important?
There is a pressing need for new effective therapies for people, especially rare disease patients.
Each new drug or treatment must be extensively tested before making it to patients.
Without clinical trials, we'd have no new treatments.
Clinical trials help us learn what works or doesn't in patients.

What are the risks involved in participating in clinical trials?

- may work for some but may not for you
- new things aren't always better than standard of care
- may have side effects
- health insurance and providers don't always cover
- learn about risks and benefits before participating

clincaltrials.gov – website listing clinical trials available

- search for disease name
- filter further by what is open and recruiting, what is not open yet
- explains more about the studies, where they are happening, what are the goals

Important questions to ask before enrolling:

- ask for a copy of informed consent form
- what is the purpose or goal?
- who is allowed to participate?
- how long will study last?
- how will this study affect my daily life?
- what are the risks/benefits of participating in the trial?
- will I have to pay for the study procedures/treatments?
- will I be paid for participating and reimbursed for my expenses?
- does it include a placebo?
- how will I receive the treatment?
- how will my privacy be protected?
- what happens if I leave the trial early?
- who is in charge of the study?
- what kinds of tests are involved?
- will hospitalization be required?
- how will I know if the treatment is working?
- can I continue taking the study treatment once it ends?
- will results of trial be provided to me?

Outcome Measures and Biomarkers

Terry Jo Bichell, PhD, MPH

What are they why are they important?
When someone does a clinical trial, what are we trying to find out? Trying to find out if the treatment actually helps, does it make your life better?

How do we measure that?

Ask the person how they are feeling? Are they feeling better? How are they feeling better? This is an outcome measure.

A biomarker is a way to measure something physical in the body: a blood test, a PET scan, spinal fluid, EEG, etc.

Going back several years, clinical trials were based on lab findings. If the treatment helped mice, then they were tested in people. The mistakes they made in the past were to measure what was important to the mouse rather than the person.

Now we know it is a lot more imporant to measure what matters to the person rather than the mouse. It is important to find out what your life is like, how it is impacted by Glut1, how is the family life impacted? If you get a treatment, can we find out exactly how it improves your life and what matters to you?

Priorities identified in patient voice survey:

- improved cognition
- better speech and communication
- few seizures and movement issues
- better and easier treatments than the ketogenic diet

How do we know what your life is like, and what is important to families? Patient voice initiatives, registries and natural history studies.

What treatments work, how do they work, when do they work? Do they impact life, ease burdens? Outcome measures must be meaningful to patients. Patient reported outcome measures are outcomes that matter to patients. These may be surveys, questionnaires, interviews, etc.

Biomarkers:
These are measured at the same time as outcome measures. Biomarkers show whether there are physical changes in response to treatment.

Outcome measures and biomarkers are ways to prove whether the treatment is working, must show effectiveness and safety before FDA approves drug or treatment.

The clinical trial process takes a very long time. The better we design clinical trials, the faster and easier it will go. We learn even from failed clinical trials. We learn more about living with the disease, and we learn about outcome measures and biomarkers.

Day 2:

100 Years of Medical Ketogenic Diets

Eric Kossoff, MD

The ketogenic diet reaches its 100-year anniversary this year.
From 1921-1940 the ketogenic diet was of high interest (mainly Johns Hopkins, Mayo Clinic, Harvard) and that dwindled down in the 1940's. It was found that the experts moved on to other fields and they weren't collaborating. There was a lack of mentorship for the next phase of the ketogenic diet.

The Charlie Foundation led to a re-birth of the ketogenic diet. A few years later they initiated a study on the efficacy of the diet, this was a very powerful influential paper showing that this diet actually works and had a protocol on how to follow the diet.

There is a multicenter collaborative review on what was out there in the literature and how best to do the diet, which was recently updated in 2018. Today, the KDT is a mainstream nonpharmacological treatment. It is one of the major therapies beyond medications and surgery.
There are robust interest groups at conferences. There are biannual international meetings. Nearly every pediatric epilepsy center in the USA and most other countries offer a version of KDT.

Hot topics today:

- The extremes – infancy and adults; what is the best way to treat these groups
- Status epilepticus: when seizures fail to stop and you have to be hospitalized
- Non-epilepsy uses (still mostly neurologic) i.e. autism,
- First line use: use it before medications and Glut1 Deficiency is the perfect example

There has been a lot of interest in the diet because of Glut1 Deficiency. The consensus paper talks about the diet and how the KDT is the treatment of choice and should be started as early as possible.

- Classic KDT is preferred under age of 2
- Low glycemic index diet is not recommended
- Monitor blood ketones (goal 2-5mmol/L or as high as tolerated)
- The need for carnitine with KDT was controversial
- No recommendations regarding oral ketones or ketone esters
- Adult KDT is controversial given the side effects
- MAD is considered a reasonable alternative for adolescents and adults
- Diet discontinuation after 2 years is not appropriate for someone with Glut1 Deficiency- there is no clear end date

The 7th global symposium will be held in person and virtually October 19-22 in Brighton, UK. There is an international neurological ketogenic diet society forming which will help run these biannual meetings and help with guidance for patient support groups. There will also be the launching of the 7th addition of the ketogenic diet therapies book which is meant for parents and caregivers.

Ketogenic Dietary Therapy Best Practices for Glut1 Deficiency

Beth Zupec-Kania, RDN, CD

Glut1 Deficiency: consensus recommendations bring to light guidelines for KDT for those with Glut1 Deficiency.

- For Glut1 KDT is considered first line treatment.
- Initiation should be at the time of diagnosis, as early as possible, and should last as long as possible.
- Ketosis should be as high as tolerated.
- Ketosis that is caused by a well-planned diet with fat as the main source of calories, protein to meet individual needs, and with minimal carbs, achieves nutritional ketosis
- Fat is the main fuel no matter what time of variation of the diet you use
- Your body will then produce ketones

Carbohydrate guidelines:

- In USA: 130g / day
  Many people eat far more carbs than what is recommended
- In KDT there is a very large reduction in carbs

- Carbohydrates defined:
- Simple sugars, complex carbs, and fiber
    In KDT, you want to remove simple sugars

Glycemic index is the rise in your glucose after eating

- Simple sugars are what cause a rise in your blood glucose to rise
- Fat lowers the rising glucose and extends out the digestion
- With fat as the primary source, glucose remains stable

Fat is providing the energy to make ketones and when you enter ketosis, your body is not only getting less glucose, but it's using up its glycogen stores. Once that gets used up, ketones are produced causing beta hydroxybutarate levels to go up. Betahydroxybutyrate should be measured in blood.

The classic KDT is the oldest diet we have and still used today, it is very effective and very controlled.

Ketodietcalculator.org helps calculate meals

The ketogenic ratio is simply the ratio of fat to non-fat (carb and protein)

- Determines the amount of food for a person to consume to achieve ketosis
- The ratio affects ketosis

CharlieFoundation.org has a ketogenic diet booklet that is updated every 2 years and is available in English and Spanish. There is also a modified keto 2:1 and 1:1 intended for adolescents and adults. Diet therapy for Glut1 Deficiency should really be personalized.

The diet changes as you get older, the diet needs to have supplementation which is very individualized, it's important to be hydrated because with high fat, water is not retained and it needs to be monitored (glucose and beta hydroxybutyrate).

Carnitine helps change fat into ketones and on the KDT you use up more carnitine.
Carnitine should be monitored and potentially supplemented. The best sources of carnitine are from beef, pork, poultry, avocados.

Ketogenic whole (natural) food:

- olive oil
- coconut oil
- heavy cream
- vegetables (fruit is primarily carbs but more concentrated and less fiber) Hass avocado, bananas in the green are high in nondigestable fiber
- berries are the lowest carb fruit
- whole sources of protein, fish, eggs, meat

Heart disease is still the number 1 cause of death but the thinking that high fat diets are associated with heart disease is a myth.

The fats that are best are omega balanced:

- olive oil, especially EVOO
- flaxseed oil
- grass fed butter
- ghee

Extra virgin olive oil is high in omega 3, vitamin E vitamin K1 ubiquinol, 30 polyphenols which is very good for your gut and organs. They are mono unsaturated which is what you want.

MCTs come from coconut and palm kernel oil which has been fractioned to save the medium chain fats. MCT oil may be used in all ketogenic diets.

Transitioning to nutritional ketosis has physiological and emotional changes and guidance is needed to make sure the transition is done safely and as enjoyable as possible.

Nurturing Keto Independence

Leslie Holleman and Dana Pottschmidt, MSW, LSW, RBC

What does independence look like?
What are the abilities?
Focus on strengths - The CAN instead of the CANNOT
Goal oriented - Short term personal goals for patient
Empowerment - Always give choices, motivate, and encourage

Goals for Independence:

- Independent living skills
- Employment
- Diet management
- Self-care
- Emotional
- Physical
- Safety

Challenges with Independence:

- Motivation
- Adjustment to adulthood
- Depression
- Isolation
- Health factors- puberty
- Executive functioning
- Processing time
- Attention span
- Prompt dependent
- Ability

Backing off on the support forces them to step up and be more independent.
i.e. using alarms to know it's time to wake up, shower etc.

Structure is important:

- Develop a routine:
    - Meal/feeding time
    - Sleep time
- Daily Schedule
    - Visual schedule
    - Checklist

Expect independence where able
- Daily living skills
- Choices (choice boards)

Same routine every day/week will encourage:
- Decrease in prompting, increasing independence
- Better sleep
- Helps with executive functioning challenges, reduces non-compliance
- Helps build skills for employment

A visual routine can be helpful with checkmarks can be useful for some

Involvement:
Meal planning
Communicate!
- Explain purpose
- Provide choices
- Self-reporting

Ownership of Glut1/Diet
- Apps
- Training

Involvement in Meal Planning:
- Assist parent in cooking
- Plan meals for the week together
- Grocery shop together
- Allow for child to make choices throughout involvement
- Make visuals for simple recipes child can follow

Involvement: Self-Reporting
Visuals for reporting energy levels

Peer Support:
Connect child with peers with like situations

Future Planning Now – Disability and Medicaid Waivers

Glenna Steele

Why does this Matter?
Disabilities and chronic disease can make life hard and some of these programs can help ease some of these burdens

Disability:
Application process:
- Available online at SSA.gov
- Any age is eligible to apply
  - About the Child
  - Education and Work History (if applicable)
  - Medical History
- You do not have to provide copies of medical records yourself

Determination Process:

- Although it is a federal program, decisions are made at the state level
- Local offices verify that information
- Disability determination services makes final decisions
- Can take several months
- Approvals are retro-active to application date
- Appeal process for denials
- Disability determination is the key that unlocks services and benefits – this is an essential first step

Disability Benefits:
- Monthly SSI payments
- Eligible for additional programs and services
- Eligible for Medicaid in most states

Medicaid:
There are eligibility guidelines around financial resources

Medicaid Waivers:
- Allow the federal government to waive rules that usually apply to the medical program
- Intention is to allow individual states to accomplish certain goals such as reducing costs, expanding coverage, or improving care for certain target groups such as the elderly or women who are pregnant
- States can provide services to their residents that wouldn't usually be covered by Medicaid

SSI (disability) and Medicaid work together
- In most states, a child who gets SSI benefits can get Medicaid to help pay for medical bills
- At the states option, children under 18 who need institutional-level care and live at home may keep Medicaid eligibility while getting home care, if that care is less costly to the government

Institutional Level of Care:
- Intermediate care for individuals with intellectual disabilities (i.e. group care setting)
- Nursing facility
- Hospital setting

Types of Waivers:
- Provide opportunities to receive services in their own home or community rather than institutions or other isolated settings
- Often target special populations or conditions including intellectual disability, autism
- Important to note that:

Often long waiting lists
- You can get on more than one waiting list
- Can transition from one waiver to another

There are many benefits to waivers such as:
- provide support for continued learning
- social engagement opportunities
- takes some pressure off of family caregiving
- paid support
- support for employment and volunteer opportunities

Special Considerations:
- Periodic eligibility review

- Waivers differ by state- moving to a new state
- Must notify of income changes for SSI payments
- Estate recovery rule – "payback" for benefits
- Asset protection/estate planning

Take-Aways:

- Apply for SSI disability when you have enough "evidence"
  Even if you think you won't need it or won't qualify
- Collect and save supporting documentation
- Disability determination is key
  Appeal if necessary, hire outside help if necessary
- If you don't qualify for monthly SSI payments, you may get other help
- Find out about Medicaid Waivers in your state and how to apply
  Plan for the future…now
- Resources: Kidswaivers.org Medicaidwaiver.org

The Arc

Leann and Garon Mosby

Mission of the Arc:
Promoting and protecting the human rights of people with intellectual and developmental disabilities and actively supporting their full inclusion and participation in the community throughout their lifetimes.

Prior to the 1950's little was known about developmental and intellectual disabilities. There were few programs or supports available to families. Parents were encouraged to put children in an institution. A group of advocates came together to form the Arc to empower people with intellectual disabilities to give them a better life.

The Arc is the largest national community-based organization that advocates for people with developmental and intellectual disabilities and their families.

Their 3 Principles:

- Respect
- Collaboration
- Empowerment

Offer support through the life span and can stay in the programs through all stages of life:

- prenatal
- infancy
- early childhood
- school age
- adult

They work to connect families to resources.

Capable Kids and Family – monthly visit from Arc to get updates and find out needs and interests, connect to resources – advocate to get special assistance if needed in special programs.

- speech, occupational, physical therapies offered through Arc or connect you to therapy programs, including home-based therapies.

- respite care
- financial assistance
- safety equipment and tools

Parent Café – different topic every month (estate planning, disability, etc.)
The Arc is a tremendous resource – find the Arc in your area!

https://thearc.org

Supporting Siblings Successfully

Holly Senn, BS, CCLS

Communication:

- Help your child to understand their sibling's medical condition at an age-appropriate level and at their own pace or preference
- Sometimes withholding information can create mistrust
- Be prepared for tough questions
- Oftentimes what frightens children most is fear of the unknown
- Common thoughts/points to discuss regarding the diagnosis:
    - Name of the illness
    - When did it start?
    - Will it go away or get better/worse with time
    - Why/How did this happen
    - Is it contagious?
    - Did someone do something wrong
    - Physical changes
    - Cognitive and emotional changes

Psychosocial support:

- All siblings are different with different needs. What is good for one may not be good for another
- Things that appear "trivial" to adults can be huge stressors for children and teens
- Support can be found at medical facilities, in the community or online

Role Definition:

- Siblings need to know what role they can play in their ill sibling's care. This can change over time and should be discussed as the siblings age or as the child's needs change
- Try to limit the amount that the sibling is involved in caring for the ill child so they do not blur identity lines
- Siblings can experience feelings of accomplishment and empowerment when allowed to help their ill sibling

Routines, Normalcy, & Attention

- As hard as it may be, some sense of routine should be established
- Siblings should always be recognized for their own accomplishments and contributions for the family other than caregiving responsibilities
- Spend time individually with well sibling doing something they like to do
- Genuinely inquire about their interests
- Provide opportunities to be with friends and engage in activities they enjoy to help establish their own identity

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Day 3:

Hope on the Horizon

Juan Pascual, MD, PhD

A conference held earlier this year discussed metabolism-based therapies for epilepsy and is available online.

Sources of information in Glut1 Deficiency:
Clinical observations:
Value: Very important source of information, informs how a human being may be doing
Limitations: variable manifestations, no clear natural history of the disorder, differences among terminology used among experts, difficult to assess things that happen intermittently- must rely on what families say, all clinical studies are set out to treat something you already have in mind- it's hard to keep an open mind.

Mutation type:
Value: diagnostic (if conclusively pathogenic)
Limitations: great deal of variability in the DNA of a person
DNA is an important answer if DNA technology is accurate and reliable and its not yet
Not convinced that you can correlate mutation type with disease severity, although this is a controversial point. Not a lot of predications can be made based on DNA.

Cognitive and caregiver assessments:
Value: crucial
Limitations: it's difficult to obtain a cognitive profile on young people

EEG:
Indirect measure of brain network activity
Highly variable, not necessarily correlated with treatment success
Not useful in non-epileptic subjects

Clinical brain MRI:
Minimal value in Glut1
Abnormal in only 25% of subjects

CSF glucose:
Usually diagnostic but can be normal in some people with Glut1 Deficiency. Doesn't come solely from brain cells so may not be very indicative of brain function.

CSF lactate:
Diagnostic but not sure what cell type they come from

RBC glucose uptake:
Great deal of variability in doing this technique, insensitive to some Glut1 Deficiency mutations

Treatments:
Antiepileptic's are very unpredictable; they don't do much for movement spells or intellect

KDT:
Doesn't work in 1/3 people with Glut1
Limited or no effect on cognition
Detrimental or intolerable for some people
Decrease in glucose and pyruvate because you are limiting carbohydrates

MAD: commonly used as well but similar limitations to classical KDT

Acetazolamide:
transient efficacy
Diazoxide: run risk of induction of diabetes

Triheptanoin:
Gastrointestinal intolerance
Individual metabolic variability

Gene therapy:
Transitory, difficult to appropriately dose Glut1 so you have the possibility of it being toxic
Difficult to target one particular cell type
Potential for off target organ effects

Errors in concepts:

- The KDT does not fully substitute for glucose and there is a lack of universal efficacy- ketones are not equivalent to glucose
- Energy failure depends on how 'energy' is defined
- The idea that DNA will predict how a person does is not necessarily the case. There is a great deal of variability across subjects with shared mutations
- The idea that the less glucose activity you have, the more severe your symptoms are is not necessarily the case. This depends on how glut1 activity is defined. The clinical severity of shared mutations varies and several phenotypes arise from shared mutations
- Natural history is not linear or predictable
- The idea that treatment must start early has not necessarily been proven. What process is closing the window that would make intervention no longer accessible?

New research:

- What is the movement disorder?
  Movement disorder has been a very significant issue and is not an easy thing to treat and is often exacerbated by puberty. A mobile app is being developed to characterize movement disorders.
- Can the long term be predicated?
  Carefully assessing whether or not mutations determine severity. So far, there is no correlation
- What does the brain look like?
  There is a brain bank to obtain human brains
- How does the brain work in Glut1 Deficiency?

Advocacy and Teamwork at School

Heather E. Parrish, M.Ed., IDA/CERI C-SLDI and Deepika S. Gaur

Individuals with Disabilities Education Act (IDEA)

- Child with a Disability
- Children have to be evaluated and they have to qualify and fall under 1 of 14 disability categories

Other health impairment (OHI) means having limited strength vitality or alertness due to a chronic or acute health problem. Glut1 kids will fall under this category as well.

You have to show a need that it's affecting the child's educational performance
OHI is:

- A wide range of health conditions with symptoms ranging from mild to severe
- A continuum of options and services
- A focus on presenting problems or needs
- An individualized eligibility decision that specifically describes strengths and needs

Special Education Eligibility under OHI:
- Defined as strength vitality or alertness
- A medical diagnosis is not a necessary or a sufficient criterion (when used by itself) for establishing OHI eligibility
- If the school district requires a medical assessment or diagnosis for a student, the school district is responsible for the cost of the assessment or diagnosis
- Remember that you will be the Glut1 expert and will have to advocate for your child. Having a good, positive relationship with your team is important so work with them to help them help your child

Keto Diet at School:
- Anything you deal with on an everyday basis, the school will have to deal with as well
- Educate school staff
- The school counselor can assign your child to a class where no one has nut-allergies
- Teaching that everyone's food can be different
- One-on-One Aid for eating
- Too many lunch items are overwhelming
- Back up frozen meal at school
- Back up fat-source
- Just right carbs
- Extra snacks: keep the brain fueled with ketones

Legal rights:
In the US, schools are legally required to provide ketogenic meals at no extra charge

Lunch Prep:
- Keep entrees ready in the freezer. Portion cream/oil/butter the night before
- Every weekend, make one big batch

It Takes a Village!
- Maintaining good relationships with staff at school especially front desk, class teacher, nurse and counselor
- Volunteer occasionally.
- Write thank you cards during teacher appreciation week
- Be genuine and nice to your child's doctors, nurse, therapists, and dietician. They will be more involved.

Advocacy and Teamwork in Medical Care

Rachel Finn and Kathy Davis, MD

Every provider has their goal and every family has their own goals
Dream big, set goals, and take actions!

Engage with families and providers:
- Talk about other topics of interest
- Engage entire team during diet initiation or follow up visits
- Make it fun

- Understanding that this is a lifelong journey

Advocating for your family:
- Share what you are most proud of
- Share what you hope for
- Share what you are afraid of
- Share what you need

Communication and trust are very important in the relationship between patient, family, and caregiver.

- It helps to be prepared for your scheduled visits including medication names and doses
- Make a list of questions you may have; it's easy to get overwhelmed during visits
- Feedback from teachers, therapists, nutritionist is helpful to talk about during the visit
- It's helpful to know beforehand if you'll need refills to medications or paperwork; the more time you give your provider the better
- Take notes during visits to be able to reference the information later on

A 'sick letter' is a letter your doctor writes that can be shared with another doctor which can be helpful for Glut1 Deficiency patients. This can be especially helpful in cases such as an emergency room visit and can state important information about your child's health

Ask your doctor what the expectation is for communication (i.e. will you always communicate through nurse or can you request to speak directly to doctor).
It's very helpful to have a good trustworthy relationship with your child's provider. It can take time to build a trusting relationship but if you feel you don't trust your doctor, find someone who does make you feel comfortable. Make sure you reach out to your provider about reliable resources.

Glut1 Genetics

Kris Engelstad MS, CGC and Ran Naot

We know from the Glut1 Deficiency Collaborative Voices Project:
92% of Glut1 patients have had a genetic test, in 82% a variant was found, 50% did not know the mutation

SLC2A1 is the gene that codes for Glut1. Every individual should have 2 copies of this gene, and a mutation in just one is sufficient to cause Glut1 Deficiency.

Changes in the DNA sequence can be:
Pathogenic, likely pathogenic, uncertain, likely benign, or benign

Why do we have gene mutations?
- Random changes in DNA, sometimes they're inherited and sometimes they're just toxins in the environment
- The majority of the Glut1 cases are autosomal dominant meaning they get passed down to offspring

In point mutations: to identify what the problem is here is an example:
c.972G>T in this mutation, at location 972, what should be a G is actually a T

Another type of mutation is a nonsense mutation. This calls for a stop codon where a change in nucleotide (G to T) causes the cells are trying to make the protein but there's an instruction to stop making protein.

The insertion of an extra nucleotide or deletion of a nucleotide will mess up the reading frames to make the correct protein.

Some people have splice site mutations although less common.

There are new treatments being developed that target the mutation or variant type instead of the specific gene. It is important to understand your genetic results.