Questions and Answers

Submitted on Slido

Question: There are a number of G1D mice. Do multiple models replicate disease symptoms or should everyone use the same mouse model?

Answer:
In my opinion, it is better to do a few models since genetic background can have a very large effect on the results *(Hudson Freeze, PhD - Sanford Burnham Prebys)*

Question: Is there a comparison group looking to see what ketones do to the reversibility of seizures in the Glut1 model that received two different amounts of glucose?

Answer:
Comparison studies to gain insight into the effect of ketone bodies on seizure reversibility in the brain slices of the Glut1 mouse model are planned and are hoped to take place in the fall. *(Elysandra Solis - The University of Texas at Dallas)*

Question:
Has cornstarch therapy ever been used for treatment of Glut 1 (used in glycogen storage disorders to maintain glucose levels)?

Answer:
Yes, this was one of the first treatments tried early in the disease history and some still use it. There was a paper published on the use of Glycosade in a small number of Glut1 Deficiency patients and an individual case report. *(Glenna Steele - Glut1 Deficiency Foundation)*

Question: The high throughput screening of molecules to improve outcomes in G1D patients excluded the blood brain barrier. Will the BBB interfere in human trials?

Answer:
The high throughput chemical screen that we ran with Drs. Pascual and Park did not address the BBB. Generally speaking, it's hard to model the BBB in primary high throughput screens. From a biology perspective, this is addressed later in hit optimization for advanced lead compounds using in vitro and in vivo pharmacology. From the chemistry side, there are some computational models that can predict whether a given compound can penetrate the BBB. Medicinal chemists have also empirically derived chemical properties that aid a small molecule in traversing the BBB. Both approaches can help prioritize hits from screens for further development. *(Bruce Posner, U.T. Southwestern Medical Center)*

Question: We heard about fucose experiments in Glut1DS mice. Are there plans to coordinate efforts in patients?

Answer:
Those experiments, as promising as they are, need to be repeated, especially since only male mice were used. Plans are underway to do this in this model and especially in a separate mouse model, if they pass preliminary tests. It will be very important for the community to be coordinated if a small clinical trial comes into view….we hope it won't be long, but unknown for now. *(Hudson Freeze, PhD, Sanford Burnham Prebys)*

Question: I've been assuming the "stroke-like episodes" were hemiplegic migraine. Is that not the case?

Answer:
There is indeed substantial overlap between the two phenomena. In the case of hemiplegic migraine, headache generally dominates the problem, in the case of "stroke-like episode" headache generally is only a minor problem or absent. The underlying mechanism explaining the hemiplegia might be rather similar (or even be the same ….) for the two. *(Prof. Dr. Michel Willemsen, Radboud)*

Question: Do the stroke-like episodes leave brain damage like a more commonly known stroke?

Answer:
No, they don't. *(Prof. Dr. Michel Willemsen - Radboud)*

Question: Dr. Gropmam said there were good therapies for executive dysfunction - what are they?

Answer:
Some therapies include occupational therapy, speech therapy, executive function coaching. Medication(s) depends on the underlying condition. Potential medication types include stimulants (especially for ADHD), antidepressants and antipsychotics.

Psychotherapy (mental health therapy). Cognitive behavioral therapy (CBT) is a very common form of mental health therapy for conditions that cause executive dysfunction. It's common for treatment to involve only therapy or in combination with medication treatment. *(Prof. Dr. Joerg Klepper - Aschaffenburg Children's Hospital)*

Question: Dystonia and ataxia increases in adults however the keto diet often loses efficacy in adults. What treatments are recommended for adults with increased symptoms?

Answer:
Ketogenic diet therapy can still be an effective treatment in adults. An adult team with expertise in ketogenic diet therapy can help make tweaks to improve the efficacy. Routine lab monitoring is essential. We have seen adults with GLUT1 deficiency present with carnitine deficiency because they had gone without care from a keto team for several years due to lack of local adult expertise. Uncorrected carnitine deficiency can impact the efficacy of ketogenic diet therapy. Some of our patients have had success with adding one carton of keto formula per day to treat movement issues or use it to prevent movement issues when they feel it coming on. MCT oil is another great tool. *(Kelly Faltersack MS, RDN, LD, CD – dietitian at the UW Health Adult Ketogenic Diet Therapy Clinic, Medical Advisory Board member for the Glut1D Foundation)*

Answer:
Acetazolamide is a drug that improves paroxysmal movement episodes in about 1 of 4 patients *(Prof. Dr. Joerg Klepper, personal experience)*. It may aggravate acidosis when on a ketogenic diet, so blood gas analyses are recommended when introduced.

Question: Are there any types of therapies or treatments that may help with slow processing (for adults out of the school environment).

Answer:
Some therapies that may work are occupational therapy for sequencing/processing, and executive function coaching. Regular physical exercise has helped to improve movement abnormalities in some patients. *(Prof. Dr. Joerg Klepper - Aschaffenburg Children's Hospital)*

Question: Dr. Klepper mentioned Glut1 is vascular. I have a child with cold, purple feet. Is that something seen in others?

Answer:
We currently collect patient and caretaker reports - I know of one Glut1DS patient with cold, purple feet - it is yet unclear whether this is related to Glut1DS. *(Prof. Dr. Joerg Klepper - Aschaffenburg Children's Hospital)*

Question: How do we get Glut1 Deficiency added to newborn screen? What are barriers or delays to getting this in the newborn screening? Does it need to be added state by state?

Answers:
It is a state by state process in the US as states have the final say on what is included in their screenings, but some states use the Recommended Universal Screening Panel (RUSP) list, so that is the best first step. It takes a lot of advocacy and patient engagement (sharing stories, convincing the agencies of the cost value in early diagnosis, etc.), but there are some good models from other groups who have been successful in these efforts.

The remaining hurdle for Glut1 Deficiency is the simple, cheap, and reliable screening tool. There is no simple blood test currently to detect it and no straightforward biomarkers identified in the blood other than through genetic testing for variants. The METAGlut1 test might fill this role eventually, but it is not uniformly approved, the reliability may not reach the needed threshold at this time, and the current cost is prohibitive for newborn screening.

The cost for the complete newborn screening panel (including hearing tests and heart evaluations) in each state in the US ranges from $100 to $200 per person, so each individual disease test has to be inexpensive. The lumbar puncture is a reliable and relatively inexpensive way to diagnose Glut1 Deficiency through the cerebrospinal fluid (CSF), but it is not an appropriate newborn screening tool due to the invasive nature of the procedure.

There are some pilot projects underway to try to prove the value in using genetic testing as part of the newborn screening process, but so far there are no state programs that use it broadly and routinely, likely due to costs but also around some of the ethical concerns with routine genetic testing of the entire population, even healthy individuals, the fact that there are many variants that may be identified that in reality don't actually cause disease or it is uncertain if they do or will, and how the results of any individual's genetic testing may be used in the future. *(Glenna Steele - Glut1 Deficiency Foundation)*

Question: How do we educate doctors about G1D? They often have never met a patient or are not honest about their familiarity. It's dangerous and we suffer because of this.

Answer: The Glut1 Deficiency Foundation hosts exhibits annually at major medical meetings to reach

neurologists, geneticists, and others in a position to make a diagnosis or provide patient care. These efforts have been successful, but not all physicians attend meetings of this type. Many members of our Medical and Scientific Advisory Board do regular talks, do grand rounds trainings at medical centers, spread awareness and knowledge of Glut1 Deficiency among their professional organizations, and engage in a variety of other ways. As our patient population ages and more are identified in adulthood, these efforts are especially important among adult providers now, too.

With nearly 10,000 different rare diseases and with the nervous system disproportionately affected, there is no way a doctor can know about all of them, and many in the neurodevelopmental category share many common features and symptoms. The key we believe at the G1DF is to keep up the educational efforts but also for individual families to search out a doctor with a willingness to learn and become part of a team and start creating new experts. It is OK if they don't know everything they need to know about Glut1 (no one does - we are all still learning and there is much still to learn), but it does make a huge difference if they are willing to learn along with you, be part of the team approach to care with patients and families as critical and guiding members of the team, help search for answers, and help apply them to their very individualized patients.

Families can also share the consensus guidelines paper with their care team and take copies of the brochure as a way to share trusted, concise information, which busy doctors seem to appreciate.

Another important way to educate others is by participating in research and the Natural History Studies so we can learn about the full patient experience across the lifespan and have data to share to help tell the story. *(Glenna Steele - Glut1 Deficiency Foundation)*

Question: Is there a way to make Lumbar punctures more successful and less invasive for patients/ less failure rate - as it seems to be critical for dx?

Answer:
Lumbar punctures can best be performed under (short and "not very deep") general anesthesia. If performed under good conditions, it really is a simple procedure that doesn't hurt and is not dangerous. Unfortunately, optimal circumstances are not available everywhere, and there are many myths about lumbar punctures. *(Prof. Dr. Michel Willemsen - Radboud)*

Question: Is there any look into migraine (theory neuro vascular) and glut 1 links?

Answer:
There are only speculations. The precise mechanisms are poorly understood. *(Michel Willemsen - Radboud)*

Question: The experts mentioned continuing speech therapy which has been important for my adult son. Our phenomenal SLP wonders where to focus. Suggestions appreciated!

Answer:
There are no evidence-based speech therapies currently available for GLUT1, but some tested in other conditions may be helpful. Whatever is promoted by clinicians, for treatment to be effective it needs to be intensive, frequent, with strong models of feedback (from the listener, other models). Ideally focussed on enhancing self monitoring. *(Adam Vogel, PhD - University of Melbourne)*

Question: Acetazolamide tends to cause significant acidosis (greater than topiramate and zonisamide)- could the class of carbonic anhydrase inhibitors be helpful vs just acetazolamide?

Answer:
Topiramate and zonisamide are antiepileptic drugs, their effect on movement abnormalities in Glut1DS has not been tested. There are reports that zonisamide interferes with ketogenic diet and increases the risk of kidney stones. *(Prof. Dr. Joerg Klepper - Aschaffenburg Children's Hospital)*

Question: Dr Pearson, movement disorder of GLUT1, is this just episodes of not walking or brief intense jerks? Or is it the overall gait and tone problems?

Answer:
Several different symptoms can affect muscle tone in the legs and gait. One common one is **spasticity**, which refers to increased muscle tone and resistance to stretching the muscle when it is at rest - this may cause toe-walking and a 'scissoring' pattern of walking (feet crossing over each other). Spasticity tends to be present as a regular symptom, i.e. not episodic. Another movement symptom that affects gait is **ataxia**, or unsteady balance: in Glut1 DS, ataxia may fluctuate up and down in severity, being worse in some situations (e.g during illness, or when fasting, such as first thing in the morning) and being barely noticeable at other times.

Episodic involuntary movements that typically last minutes to 1 hour, (**paroxysmal dyskinesia**) can be varied, and if the legs are involved, can temporarily interfere with a person's ability to walk. Some people experience leg stiffening and unusual posturing, such as turning in of the ankles (**dystonia**). Jerky or wriggly types of movements may also occur (**chorea, athetosis**).

The experience of individuals with Glut1 is quite variable: some people experience all of the symptoms I described above, others may have none or one. The movements may also change over time. (*Toni Pearson, MD - pediatric neurologist at Nationwide Children's Hospital, Medical Advisory Board member for the Glut1D Foundation*)

Question: Movement episodes increased at the onset of puberty after being well-controlled by the diet. Is there any evidence of them decreasing upon reaching adulthood?

Answer:
According to data from the Collective Voices Project, 55% of people with GLUT1 deficiency reported changes in symptoms during puberty. Worsening of movement issues, seizures, energy, and anxiety were noted. About half needed to make adjustments to the diet. There may be strategies that can be implemented to make the diet more effective. (See my answer to question 18 above.) For female patients, the menstrual cycle can play a role, and sometimes targeted nutritional strategies can help address movement issues that seem to occur in a catamenial pattern. *(Kelly Faltersack MS, RDN, LD, CD – dietitian at the UW Health Adult Ketogenic Diet Therapy Clinic, Medical Advisory Board member for the Glut1D Foundation)*

Question: My daughter was diagnosed based on CSF glucose and clinical presentation. She does not have the SLC2A1 gene. What do you now understand about this?

Answer:
We know that circa 5-10 % of patients with the clinical features of G1D and the CSF profile of G1D remain without an SLC2A1 mutation. We don't know if the mutation is still there but simply can't be identified (for technical reasons), or alternatively, that these patients have a mutation in another gene. Note: it is important to know CSF glucose, CSF lactate and blood glucose, and to decide about the diagnosis G1D based on all three parameters. *(Prof. Dr. Michel Willemsen - Radboud)*

Question: What do we know about individuals that have been diagnosed with a mosaic of Glut1?

Answer:
Generally they are diagnosed because they have signs / symptoms of G1D. These patients have problems which are similar to patients who have no mosaicism. Sometimes mosaicism is found in otherwise healthy parents, without any medical problem. In such cases we assume that the mutation is in the blood cells (the cells used for DNA analysis) but not in the brain cells and blood brain barrier, and thus (logically) leave the brain without problems. *(Prof. Dr. Michel Willemsen - Radboud)*

Question: What is the difference between a case report vs an anecdote?

Answer:
Good question! A case report refers to a published description of an individual patient's experience in a medical journal. Doctors tend to use the term 'anecdote' to describe individual patient experiences - these may be published case reports, but they may also be unpublished observations from a doctor's

clinical experience. So I guess we could say that all case reports are anecdotes, but not all anecdotes are necessarily published case reports.

We often distinguish both anecdotes and case reports from larger studies of groups of people (e.g. clinical trials) when talking about the effect of treatments, recognizing that the experience of one person does not tell us how likely a given treatment might be to work in other people. Larger studies try to answer such questions by comparing treatment vs. no treatment (using either a separate group of untreated people, or by carefully recording participants' symptoms with and without treatment), and by having consistent and systematic ways of measuring outcomes. (*Toni Pearson, MD*)

Question: What do ketones/metabolic shifts in the keto diet do to other body cells, such as red blood cells, kidney cells, lung cells, bone cells?

Answer:
Chronic acidosis may cause failure to thrive - we know this from chronic kidney disease. This is an overall and unspecific adverse effect of an acidotic environment in the body. *(Prof. Dr. Joerg Klepper, Aschaffenburg Children's Hospital)*