September 5, 2014
9:00am
Holiday Inn Express, Delafield, WI

SSADH Family Meeting with Dr. Gibson, Report on Current Research

In attendance:
Mike Gibson (SSADH Research, WSU)
Jeff Speckman (SSADH Parent)
Kimberly Speckman (SSADH Parent)
Zach Speckman (SSADH Patient)
Melissa Gould (Zach's Aunt)
Aaron Reekie (SSADH Parent)
Heather Reekie (SSADH Parent)
Carolyn Hoffman (SSADH Parent)
Lisa Terzinski (Hoffman Family Friend)
Anne Kearney (SSADH Parent)
Alice McConnell (SSADH Parent)

Call in:
Alice Tebo (SSADH Parent)

******Dr. Gibson does not recommend anyone changing their child's course of treatment based on the discussions at this meeting. You should consult your child's personal physician before altering your child's course of treatment, and perhaps also contact Dr. Pearl at Boston Children's Hospital******

Dr. Phil Pearl has moved to Boston Children's Hospital & Harvard Medical School as the Director of Epilepsy and Clinical Neurophysiologyand Dr. John Schreiberhas taken Dr. Pearl's position as Pediatric Neurophysiologist at Children's National Medical Center in DC. Dr. Schreiber has both admitting privileges at the NIH and Children's National. Dr. Pearl will still be involved with SSADH-deficient patients and plans to run future trials out of Boston in collaboration with Dr. Gibson.

The future goal will be to have trials at several locations across the US, thus eliminating the need for families to travel so far to be part of future SSADH trials. These are commonly referred to as multi-center trials.

The need to update the patient registry was discussed. It was mentioned that it might be a good idea to post on the Metabolic/Geneticists listserv to find additional cases of SSADH deficiency.

Jeff Speckman mentioned that it might be a good idea to hold another symposium to bring SSADH families and researchers together. There are R13 grants from the NIH available for this purpose. Dr. Gibson and Dr. Pearl have begun initial discussions on this point. There should be some support from Boston Children's Hospital, and the thinking was that it would be advantageous to hold such a family meeting at that location, as that would be a primary location for future trials. Logistics are being discussed.

Early intervention for children with SSADH was discussed and how the case could be made for inclusion on the newborn screen uniform panel based on this. The challenge with SSADH deficiency is that the biomarker measured, GHB, is an organic acid and not an amino acid. Currently, most newborn screening programs look only at amino acids and carnitine esters of fatty acids.

Dr. Gibson was able to collect enough blood samples for the current IRB-approved autophagy study. Samples came from the US, Europe, and Australia. The Metabolic/Geneticists listserv was used to request the samples and a very positive response was received, especially many eager responses from Europe.

There has been no real relationship found between the genotype and phenotype in SSADH patients. Dr. Gibson told of a patient that had no measurable enzyme activity, but was only mildly affected. SSADH is a monogenic disorder (meaning one gene is directly impaired), but there must be other factors at play (socio-economic situation, environment, life style, diet/nutrition, in addition to numerous other genetic modifiers and epigenetic issues) that determine a patient's outcome.

Dr. Pearl is about to publish a paper regarding a 62 year old man who was newly diagnosed with SSADH living in Canada. This finding further highlights how it is likely that SSADH deficiency is underdiagnosed in the adult population.

The ketogenic Diet was discussed. The ketogenic diet is a high-fat, adequate-protein, low-carbohydrate diet that is used primarily to treat difficult-to-control (refractory) epileptic seizures. The diet forces the body to burn fats rather than carbohydrates. Normally, the carbohydrates contained in food are converted into glucose, which is then transported around the body and is particularly important in fuelling brain function and oxidative processes. However, if there is very little carbohydrate in the diet, the liver converts fat into fatty acids and ketone bodies. The ketone bodies pass into the brain and replace glucose as an energy source. An elevated level of ketone bodies in the blood, a state known as ketosis, can often associate with a decreased frequency of epileptic seizures in selected patients. The exact mechanism by which the ketogenic diet acts remains obscure.

It was hypothesized that the ketones could block the peripheral GHB from crossing the blood brain barrier, and could potentially lead to neurological improvements. Dr. Gibson is currently about to submit a grant application on this topic to NIH.

Again, it was stressed that SSADH patients should NOT be put on this diet without physician discussion. It is a challenging diet to implement and maintain.

Alice will add Aaron and Heather Reekie, and Melissa Gould to the SSADH facebook page.

Clinical Trials:

Taurine:
The taurine trial at the NIH is winding down. The taurine trial began based on results of improvement in a boy with SSADH under the care of Dr. Gargus and improvements in the phenotype of the SSADH-deficient mouse.
(http://trnres.com/ebook/uploads/elidrissicontent/T_134494374115%20El%20Idrissi%2015.pdf).

In the current study conducted at the NIH no neuropsychological improvement has been found, although there were some alterations in GABA B receptors seen on transcranial magnetic stimulation analyses at NIH. The Taurine trial began because the rights to SGS-742 compound were held by several commercial companies (Saegis (2005), Novartis, Lundbeck, (2010)) and it was difficult to obtain access to the drug until the proprietary rights were obtained by NIH.

SGS-742:
SGS-742 is a GABA B antagonist. It was first synthesized by Dr. Wolfgang Froestl in Basel Switzerland. Examination of the GABA(B) receptor antagonist SGS-742 in a phase II trial in SSADH-deficient patients is underway at NIH. This trial derives from preclinical efficacy data using SGS-742 and the GABA(B) receptor CGP-35348 in SSADH-deficient mice, where the SGS-742 drug revealed significant mitigation of seizures.

SGS-742 has already been shown to be safe and well-tolerated in clinical trials in adults with mild cognitive impairment (MCI). The trial for SSADH-deficient patients is a double blind trial, so neither the researchers nor participants know if they are in the control or experimental group. The trial is six months on medication/placebo, two months wash out, and then six months on medication/placebo. Only the NIH pharmacy knows who is getting drug and who is getting placebo at any given time.

The trial is open to patients, age 8 years and older, with a confirmed SSADH diagnosis. The invasive procedure (Lumbar Puncture) is not mandatory to participate in the trial. Currently there are 6 of the 22 needed patients enrolled in the trial. The goal is to have 16 patients complete the trial. Recruiting for the trial will go through mid 2015 with the grant funding lasting till 2017. The data from the trial should be finalized by late 2016.

Kimberly Speckman spoke about her and her son Zach's experience with the SGS trial and visits to the NIH. The NIH coordinates all of the patient's travel and accommodations. You stay right across the street from the trial location and all US domestic travel and accommodation costs are covered as part of the trial.

Anne Kearney spoke about her concerns in traveling to the NIH due to one of her son's mobility and health issues, and that more information about the exact protocol and procedures of the trial need to be disseminated.

The group spoke about ways of helping families whose children are more severely affected participate in the trials. It was suggested that families that have already participated post on the facebook group about their experiences and share pictures. Also those families could directly reach out to families that have concerns about participating in the trial. These issues might be partially alleviated with another family meeting as is being planned at Boston Children's.

The contacts for the trial at the NIH are:

Tamika N. Mason Patient Care and Recruitment Specialist 301-496-1923 Tamika.mason@nih.gov	Irene H. Dustin, C.R.N.P. Nurse Practitioner for SGS Trial at NIH (301) 451-9284 dustini@ninds.nih.gov

Both Ms. Mason and Ms. Dustin are available for discussion about the trial, either by phone or e mail.

Current Research in the Animal Model:

- Characterization of autophagy-inducing drugs in SSADH-null mice. Published studies have shown that high levels of GABA block autophagy, leading to accumulation of mitochondria in the mutant mouse brain and liver, and associated enhanced oxidative damage. The goal is to provide pilot data for the concept that autophagy-inducing drugs (sirolimus, temsirolimus, torin) will reverse these processes, with treatment ramifications for our patients.

- Examination of autophagy processes in human blood samples derived from patients with SSADH deficiency.

- Characterization of the content of GHB-glucuronide in the urine, blood and csf of patients with SSADH deficiency. Enhancing glucuronidation of peripheral GHB could have therapeutic benefit for SSADH-deficient patients through enhanced detoxification of GHB and excretion in the urine.

Planned Studies in SSADH Deficient Patients and Null Mice:

- With collaborators in Denmark, Petrine Wellendorph, PhD Medicinal Chemistry Research(http://forskning.ku.dk/search/?pure=da/persons/319020), Dr. Gibson has submitted a proposal to the NIH to examine the pharmacokinetics and metabolism of the GHB receptor ligands, NCS-382 and HOCPCA (see Bay et al 2014 for further details; PMID 24269284). The hypothesis is that optimal treatment of SSADH deficiency will require multiple therapeutics, targeting both GABAergic and GHBergic affects. In pilot studies of null mice, NCS-382 (GHB receptor antagonist) was most effective at extending the lifespan of null mice (premature lethality by 30 days of age). It is proposed that antagonism of the GHB receptor in patients will be beneficial, similar to our rationale for use of GABAB receptor blockade with SGS-742. The

challenge is that no toxicology or safety data is available for either NCS-382 or the novel GHB receptor ligand HOCPCA. One or both of these compounds could have therapeutic relevance for SSADH-deficient patients, but pilot feasibility must be done in knockout mice and safety/toxicology data needs to be accrued. Without that, an application for use of these compounds to the FDA (IND) would not be possible. In order to jump-start this work, the SSADH Association has provided $100,000 over two years to Dr. Gibson's laboratory to begin baseline studies. This will also provide time to re-apply to the NIH should they not look favorably on the first iteration of the grant application (review 10/19/14).

- A pilot trial of the NSAID diclofenac, with Dr. Wellendorph, in SSADH null mice is planned. Diclofenac has the capacity to bind to GHB receptors (with an affinity comparable to that of GHB), and pilot data on efficacy in the murine model could pave the way for a potential clinical intervention. This type of drug application is faster in that it is what the NIH terms drug "repurposing" (e.g., using a drug approved for one application in another disease setting). An IND application for the use of diclofenac, if there is efficacy data from the mouse model, would be fairly straightforward.

- The Gibson laboratory is embarking on pilot studies to assess the potential of monocarboxylic acid transporters (MCTs) as a treatment mechanism in SSADH deficiency with Dr. Marilyn Morris, Professor of Pharmaceutical Sciences (http://pharmsci.buffalo.edu/CEPKPD/faculty/MORR.HTML). The rationale for this type of study is highlighted below.

- We previously demonstrated that mammalian liver harbors ~70% of the amount of SSADH activity measured in brain. This suggests that drugs targeting receptor mechanisms in the brain are going to be challenged by chronic re-supply of GHB to the brain from the periphery (GHB which freely crosses the blood brain barrier on MCTs). If we can block GHB transport into the brain, or enhance peripheral excretion (as glucuronide or other derivative), this could be therapeutically relevant.

- A SSADH-null zebra fish model is also being developed by Dr. Kara Vogel, PhD, a Post-doctoral fellow in the Gibson laboratory at WSU. Zebrafish are excellent vertebrate models for many genetic disorders that can be much more facile in high-throughput drug screening.