

2017 MCT8 Symposium
Summary for Parents
Wednesday, 1/4/17-Friday, 1/6/17

Los Angeles, California
Ritz Carlton, Marina Del Rey

Approximate Number of Attendees: 42, of that approximately 14 parents & grandparents.

Definitions to know as parent:

Analog: A compound that resembles another in structure, a substance that is similar function or action, but not identical, to the parent compound.

Blood brain barrier (BBB): prevents selectively materials from the blood from entering the brain tissue. It is formed by brain endothelial cells lining the cerebral microvasculature, and is an important mechanism for protecting the brain from fluctuations in plasma composition, and from circulating agents such as neurotransmitters and xenobiotics capable of disturbing neural function

Chaperone: is literally a compound that accompanies another substance to be transported in other parts of the cell or out or in the cell:

- stabilize the replacement therapeutic enzyme needed to treat this disorder;
- keep the enzyme properly folded;
- improve its uptake and activity in muscle tissue; and
- reduce the likelihood or magnitude of an immune response against it.

Gene Therapy: Gene therapy is when DNA is introduced into a patient to treat a genetic disease. The new DNA usually contains a functioning gene to correct the effects of a disease-causing mutation.

- Gene therapy uses sections of [DNA?](#) (usually [genes?](#)) to treat or prevent disease.
- The DNA is carefully selected to correct the effect of a mutated gene that is causing disease.

Certain viruses are often used as vectors because they can deliver the new gene by infecting the cell. The viruses are modified so they can't cause disease when used in people. Some types of virus, such as retroviruses, integrate their genetic material (including the new gene) into a chromosome in the human cell.

Nueral Dynamics:

Phenotype: Clinical and biochemical but not genetic manifestation of a condition. A genetic defect produces a characteristic phenotype.

Transporter is a protein that facilitates transport of another protein or smaller chemical. This transport can be across the cell membrane, either in or out. It can be located in the endothelial cell (blood brain barrier) and transports Thyroxine or some other substance across. MCT8 (monocarboxylate transporter 8) is a transporter mainly of T3.

Peripherals:

The discussions about MCT8 usually refer to effects within the brain and everywhere else. Peripheral refers to all the effects on the body outside the brain.

Patient Organization is usually a non-profit organization that aims to support patients by fundraising, and advocating for recognition and awareness of the particular disease.

Registry; “systematic collection of standardized data about a group of individuals”

Models used for Research: 2 human brains,Zebrafish & Mice

1. **Treatments:** Present and Potential

- a. Triac-an analog, Currently trialing via Edward Visser

- i. Trial involves 36 boys and 9 countries

- ii. Preliminary results:

- 1. Peripherals:

- a. T3= decreased
 - b. Creatine=increased
 - c. Bone Formation = increased
 - d. Heart Rate=decreased
 - e. Body Length=no affect
 - f. BMI= Increased

- 2. Nuerological Exam:

- a. No change in seizure activity
 - b. Gross Motor=increased-noted better head control
 - c. Cognitive=some changes at individual level, but do not know if it is treatment or natural progression.

- iii. Triac is most beneficial if started before 2 years of age, largest changes are seen in younger patients.

- iv. Finishing trial 1

- v. Next step is to launch the next trial

- 1. Focus will be 0-3 year old patients which will focus on nuerological and physical phenotype.

- 2. Trial will last a couple years to track changes.

- 3. Launching trial 2 will be difficult due to funding, trying to find a co-funder.

- vi. Unable to register drug at this time due to still in trial phases

- b. OATP1C1-it's important role for thyroid hormone transport in mouse brain-Theo Visser

- i. It is a specific T4 transporter

- ii. It facilitates entry of T4 in astrocytes where it is converted by D2 to T3

- iii. Like D2, OATP1c1 is under negative control of TH

- iv. Mutation of OTP1c1 is associated with autistic feature and early neurodegeneration (only one human case so far)

- c. Intranasal delivery of thyroid hormone-Maria del Carmen Grijota-Martinez

- Potential of baclofen pump delivery?

- d. Chaperone=Gene therapy=virus

- i. Dr. Refetoff presentation on AAV9 virus carrying the normal human MCT8. Increases T3 in the brain of Mct8 deficient mice.

- ii. Concern/issue: poor quality of virus batch? The second batch of AAV9 purchased commercially was defective.

- iii. SMA-case trial presented-Brian Kaspar- with positive effects, determine if possible to do for MCT8

- 1. 2-3 years to develop

- e. Basal Ganglia: A new possible therapeutic target-Ana Guadano-Ferraz

- i. Need to further characterize the nervous system physiopathology of MCT8 mutations by analyzing the structure of affected brains using several histological technique's.
- ii. Hypothesis: The severe impairment in the motor control of MCT8 deficient patients, as well as the learning problems could be the result of the Basal Ganglia dysfunction.
- f. iPSCs from MCT8 patients indicates prominent role in the BBB-
- g. Other: Main issues:
 - i. Finding a solution that get T3 to pass through the BBB
 - ii. Important to not forget about T4 absorption to brain as well

2. MCT8 Structure & Function

3. Ask the Doctor's! Open Discussion:

- a. Doctors thoughts:
 - i. Be as normal a family as possible.
 - 1. 50%-80% of kids do better, have improvement with what the parent does for them
 - ii. Dystonic posturing causes reflux issues
 - 1. When there are stomach issues it is more common to have seizures
- b. This disorder is not a leukodystrophy and should not be classified as one
- c. Treatments for symptoms:
 - i. Spasticity= Botox
 - ii. Movement Disorders = no good treatment at this time
 - iii. Drooling/Secretions=Glycopyrrolate(Cuposa), Botox, Artane, something not mentioned is tying off/salivary glands
 - iv. CBD Oil=they have seen in more patients with epilepsy, doctors feel there are other drugs that are more effective.
- d. Sleep Issues-they feel can be from variety of issues:
 - i. Medications
 - ii. Epilepsy
 - iii. Movement Disorders
 - iv. Reflux
 - v. Parent recommended a weighted blanket to help alleviate issues. Baclofen pump has helped for Jaeden.
- e. Why do the boys not talk?
 - i. The doctors feel it is due to a variety of issues-hypothesis:
 - 1. Cerebellum problem
 - 2. In MRI's, the frontal part of the cortex and the temporal do not communicate
 - 3. Dystonia
 - 4. Volume of brain mass decreased
- f. Movements Versus Seizures
 - i. Only EEG can confirm seizures. As a parent you need to be the advocate for your child and push for what you feel he needs. It also may require multiple tests and times due to EEG testing not always being able to catch when your son has them. 48 EEG video monitoring is recommended.
 - ii. LESS than 20% of boys have seizures
- g. Parental forms for donating brain
 - i. That is done by parent and child's doctor, can be done prior to anything happening.

4. Establishing a Registry-Edward Visser

- a. Goals:
 - i. Natural history

- ii. Defining phenotype & awareness (early treatment)
 - iii. Improve/standardize clinical care
- b. Counseling
- c. Create an infrastructure for future trials (therapy development)
- d. Creates a centralized data base
- e. Development:
 - i. Ethical & legal issues, Security & Confidentiality
 - ii. Web-based platform
 - iii. Cross-referencing other rare disease registries
- f. Neurocognitive:
 - i. Deterioration of motor function
 - ii. Spasticity
 - iii. Wakes up agitated/stressed
 - iv. Swallowing difficulties
 - v. Seizures
 - vi. Primitive reflexes
 - vii. Dystonia
 - viii. Elevated tendon reflexes
- g. Neuropsychological:
 - i. Cognitive
 - ii. Receptive language
 - iii. Language expression
 - iv. Fine motor skills
 - v. Gross motor skills
- h. Further develop registry
- i. Recruit parents and doctors to participate in registry

5. *Nueral Dynamics*

- a. Gisel Matheus-Brain MRI Imaging-Pilot Study
- b. Goal: Analyze with dedicated brain MRI images morphological details of the gray matter centers and white matter tracts as well as quantify their interactions.
 - i. Understand the imaging findings for the pediatric population
 - ii. Look for potential imaging biomarker
 - iii. Quantify gray and white matter abnormalities
 - iv. Assess MCT8 brain connectivity findings
 - v. Look for iron deposit pattern in the brain
- c. Conclusion: The acquired imaging data may help us to understand the brain parenchyma and its connections in patients with MCT8 and may also give us biomarkers for future treatments.

6. *Scientists Goals for 2018 Symposium*

- a. Anna: experiment to see in mice if delivering analog directly to CSF
- b. Theo & Heike: OATP1C1, compare human and mouse, analyze potential of promoter binding sites to enhance its expression
- c. Clive (treat double KO mice with the virus and test behavior) and Brian Kasper (produce virus) and Refetoff (analyze brain thyroid hormone and gene expression)
- d. Urlich: Look into new Chaperones

7. *Facebook Group History*

8. *Where do we want to go as group, what are our next steps?*

- a. Ideally we would like to be a part of establishing and maintaining the registry
- b. Create a patient organization-creates a legal identity for group
 - i. Ways to do this:

1. Create a NGO
 - a. One in US and one in Europe
2. Create a Corporation-recommended by Dr. Refetoff
 - a. Need a lawyer, tax exempt and can accept donation
- c. Who from group wants to be involved?
 - i. How do we want to communicate/meet?
 - ii. Issue we need to figure out is how to do this securely?