Hugo Wolfgang Moser 1924-2007

• Son of a Viennese actress and Jewish German art collector
• Spent most of childhood as a refugee fleeing Nazis till arrival to US in 1940
• Served in WWII and Korean war
• Got Recommendation Letter from Albert Einstein to enter medical school
• Trained at Mass General Hospital (Harvard)
• President of KKI between 1976-88
• Through studying neurochemistry essentially established the field of leukodystrophies
• Survivor guilt was perhaps his thrive to help those with orphan diseases.
Neurodiagnostics and treatment

Bladder Management

Endocrine evaluation and treatment

Clinical Laboratory testing

Rehabilitation Medicine

Physical, Occupational Therapy

Social Counseling

Behavioral Psychology

Genetic Counseling

Family planning
Clinical Team

LBSL Clinical Research Study:
Amena Smith, MD, PHD
Miriam Kaufman
Connor Murray
Chris Joseph, DPT
Jennifer Keller, DPT
Amy Bastian, PhD, CSO

“Our patients have a neurological disease, but it also often involves other organ systems. We recognize that we need to address all aspects of their care.”

– Dr. S. Ali Fatemi, director of the Moser Center for Leukodystrophies
Laboratory Research Team

- Christina Nemeth Mertz, PHD
- Sophia Tomlinson
- Melissa Rose
- Oscar Larrazo
- Carol Tiffany, MSc
- Benjamin Theisen, MD student
- Bela Turk, MD
- Philippe Hubo, MD student
- Paul Watkins, PhD
- Richard Jones, PhD
- Ann Moser
Leukoencephalopathy with Brainstem and Spinal Cord Involvement and Lactate Elevation

Ali Fatemi
A New Leukoencephalopathy with Brainstem and Spinal Cord Involvement and High Lactate

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Johan S. H. Vles, MD, PhD,6 Peter Rieckmann, MD,9
and Petra J. W. Pouwels, PhD10

We identified eight patients with a distinct magnetic resonance imaging pattern of inhomogeneous cerebral white matter abnormalities and selective involvement of brainstem and spinal tracts. Proton magnetic resonance imaging showed increased lactate in the abnormal white matter. Clinically, the patients had slowly progressive pyramidal, cerebellar, and dorsal column dysfunction. The uniform, highly characteristic magnetic resonance imaging pattern and the similarities in clinical and magnetic resonance spectroscopy findings provide evidence for a new disease entity. Autosomal recessive inheritance is likely.


Mitochondrial aspartyl-tRNA synthetase deficiency causes leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation

Gert C Scheper1, Thom van der Klok1, Rob J van Andel1, Carola G M van Berkel1, Marie Sissler2, Joël Smet3, Tatjana I Muravina4, Sergey V Serkov5, Graziella Uzièle8, Marianna Bugiani8, Raphael Schiffmann7, Ingeborg Krægeloh-Mann9, Jan A M Smeitink9, Catherine Florentz2, Rudy Van Coster3, Jan C Pronk10 & Marjo S van der Knaap1
The Anatomy and MRI Signature of LBSL

1. Cerebral white matter

Diagram showing different parts of the brain and nervous system, including grey matter, white matter, ventricle, and various cellular components such as axons, myelin sheath, and Schwann cells.
The Anatomy and MRI Signature of LBSL

2. vibration/positional sense tract

3. Motor tract
The Anatomy and MRI Signature of LBSL

1. Cerebral white matter
2. Vibration/positional sense tract
3. Motor tract
Forms of LBSL

- Neonatal
- Infantile
- Childhood
- Adolescent
- Adult
Childhood Onset Form

• Normal initial development
• Often episodic decline in balance – falling often, getting wobbly, slower in speed
• Slowly progressive stiffness of the legs = spasticity
• Some individuals have clumsiness and hand tremors
• Gross cognitive function appears normal during childhood. Very limited knowledge about long-term outcome show difficulty in memory and processing speed.
Adolescent/Adult Onset Forms

- Normal development
- First symptoms in teen years
- All reported cases were first balance issues
- Slowly progressive stiffness in legs = spasticity
- At least one individual known with cognitive decline in her 30s.
- Peripheral neuropathy
Neonatal early infantile form

- Small head size at birth
- Low muscle tone at birth or early on
- Difficulty feeding and failure to thrive
- Motor and cognitive delays
- Often have severe epilepsy
Progression of gait symptoms

What is the basis of LBSL?

Cell

Chromosomes
Each chromosome is composed of one large continuous DNA molecule.

Gene
A gene is a segment of DNA that encodes a protein product.

Protein
A protein is a complex organic compound composed of hundreds or thousands of amino acids.

DNA

- Adenine
- Thymine
- Guanine
- Cytosine
Translation - the way proteins are made.

https://www.youtube.com/watch?v=gG7uCsJuORA
What are transfer RNA Synthetases?

• For each amino acid there is a
  • unique tRNA
  • Unique tRNA Synthetase
Mitochondria

- Energy factories
- Have their own DNA with 37 genes
- Have their own protein synthesis
What is DARS2?

- **DARS2** encodes mitochondrial **aspartyl-tRNA synthetase**, the enzyme that attaches aspartate to the correct mitochondrial transfer RNA
  - Aspartyl-tRNA is necessary in the translation of mitochondrial messenger RNA into protein
What are DARS2 mutations?

- Inheritance pattern is autosomal recessive \textsuperscript{van der Knaap 2010}
- 60+ mutations \textsuperscript{Brain 2014}
DON’T PANIC!
Is there mitochondrial dysfunction?

• Lactate in spinal fluid suggests impaired mitochondrial metabolism
• Complete absence of DARS2 in mouse tissues results in mitochondrial failure in those tissues.
• BUT patient skin and muscle cells seem to show normal mitochondrial function.

• Defect specific to brain cells?
• Is the DARS2 mutation in patients sufficient to cause stress to cells but not full mitochondrial dysfunction?
Integrated Stress Response (ISR)

New concept/pathway

Stressor to cells
→ ISR activation
→ Decrease in protein production
→ Cell protection

“Hyper protective state”?
Why do individuals with DARS2 mutations develop LBSL?

• Hypothesis 1:
Decreased DARS2 $\rightarrow$ decreased or impaired mitochondrial protein production $\rightarrow$ decrease mitochondrial function $\rightarrow$ oxidative stress and inflammation

• Hypothesis 2:
Abnormal DARS2 $\rightarrow$ dysregulation of integrated stress response $\rightarrow$ hyper suppression of protein production and delayed recovery

• Hypothesis 3 (my guess): Both of the above are contributors.
What happens to the MRI over time?

• Patients slowly get worse over decades often in episodic fashion
• Spontaneous recovery from acute episodes reported.
• MRI tends to get “better” on initial view
  • Decrease in inflammation?
  • Decrease in swelling of myelin?
  • Detailed look shows progression
    In brainstem and spinal cord
What do we not know?

• Does the gene change predict severity and time of onset?
• What is the rate of progression of symptoms?
• Which symptoms get worse most?
• How does MRI change over time in larger group?
• What markers can be used to predict response to therapy?
• Is height and weight and bone growth affected?
• What are the triggers or risk factors for disease progression?
• What kind of cells are most affected?
• Which hypothesis is true in terms of mechanism of disease?
How to fix a Genetic Disease...

• Fix the gene/protein defect and prevent disease onset
• Arrest disease progression by small molecules that correct abnormal cell function
• Restore whatever has been damaged
• Overcome pathophysiology
**GENE DELIVERY**

**In Vivo Gene therapy**

A) Viral vector - Systemic administration (intra-venous)

B) Viral vector - Intra-parenchymal administration (brain, liver...)

**Ex Vivo Gene therapy**

1) Patient’s cells are collected and hematopoietic stem cells are isolated

2) The therapeutic gene is inserted in an inactivated virus

3) Viruses are mixed with patient’s stem cells, restoring the healthy genotype

4) Transduced stem cells are reintroduced in the patient
Challenges

• How to deliver the virus to its target
• Systemic injection may result in
  • Expression of the gene in wrong places (eg. neuronal gene being expressed in heart)
  • Formation or presence of antibodies against the virus and protein product
Ongoing pediatric CNS AAV9 gene therapy Trial

• Phase I - Intrathecal Administration of scAAV9/JeT-GAN for the Treatment of Giant Axonal Neuropathy

• ClinicalTrials.gov #NCT02362438

• Patients with GAN > 5 years of age

• Primary outcome: safety after 8 weeks

• Intrathecal injection of scAAV9 virus in 10-12 patients

• Preliminary Results presented suggest it is safe
• Antisense RNA prevent protein translation of certain mRNA strands by binding to them.
• Antisense DNA can be used to target a specific complementary RNA.
Limitations of ASO

- Antisense agents have to be protected against nucleolytic attack.
- Large doses are required for therapeutic response.
- The difficulty in directing to a particular cells.
- The half-life in plasma is short.
Neural Stem Cell Transplantation in Patients with Pelizaeus-Merzbacher Disease

• Phase I study in 4 patients
Despite successful study, meaning intervention was safe company went bankrupt.

Challenges:
- Source of cells (if fetal) very limited
- Concern for malignancy
- Concern for graft versus host disease
- Immunosuppression

Small Molecules that may slow disease progression

• Molecules that improve Mitochondrial function/metabolism in the brain?
• Molecules that improve inflammation in the brain?
• Molecules that normalize the Integrated Stress Response?
Ebert & Svendsen, Nature Reviews Drug Discovery 2010

Disease Discovery and Biology

Therapeutic Target Discovery

Disease Model Systems

Outcome Measures

Biomarkers

Clinical Proof of Concept

Natural History

Clinical Trials

CROSSING THE VALLEY OF DEATH
THANK YOU!

A Cure for Ellie.org