X-ALD: The story of a family and the drive to change the Newborn Screen

KELLY AVERILL M.D, PEDIATRIC NEUROLOGY
PEDIATRIC GRAND ROUNDS 9/29/2017
But before we begin:

**MITOCHONDRIAL MEDICINE 2017: REGIONAL SYMPOSIUM**

**November 3-4, 2017**
**San Antonio, TX**

**GRAND ROUNDS**
Friday, Nov 3, 2017
7:30am - 8:30am
UT Health Science Center - Medical Building

**CLINICAL SESSION (CME)**
Friday, Nov 3, 2017
9:00am - 5:00pm

**FAMILY & PATIENT SESSION**
Saturday, Nov 4, 2017
10:00am - 4:00pm

**GRAND ROUNDS**
Friday, November 3, 2017
Mitochondrial Disease Primer- Getting a Diagnosis & Beyond
Speaker: Mary Kay Koenig, MD

**CLINICAL SESSION TOPICS**
Friday, November 3, 2017
Potential Treatments and Therapies
Mitochondrial Medicine 2017 - Highlights and Hot Topics
Screening, Evaluation and Case Studies
Endocrine Considerations and Management in Mitochondrial Disease Patients
Sleep Disordered Breathing in Mitochondrial Patients/Advances in Noninvasive Pulmonary Support
Palliative Care - An Important Team for the Mitochondrial Patient

Speaker Reception immediately following the meeting.
Both Friday and Saturday registrants are welcome to join us!

**PATIENT & FAMILY SESSION TOPICS**
Saturday, November 4, 2017
Speakers

Local:
- Dr. Glenn Medellin and Dr. Wisdeen Wu from Palliative Care/Chronic Care Clinic
- Dr. Karen Hentschel-Franks from Sleep Medicine
- Dr. Kelly Averill and Dr. Sidney Atkinson from Pediatric Neurology

National:
- Dr. Mary Kay Koenig from UTHouston
- Dr. Russell Saneto from Seattle Children’s Hospital
- Dr. Shana McCormack from Children’s Hospital of Philadelphia
Learning Objectives

- Understand the 4 major present of X-linked Adrenoleukodystrophy
- Understand why there is a drive to add this disease to the newborn screen
- Understand some of the ethical implications and practical challenges of doing so
The Story of a Family
A boy named Parker was brought to the ED by his parents.

His family had noticed that he seemed to have trouble seeing things.

His teacher had noticed a decline in his handwriting skills.

An optometrist could find nothing wrong with his eyes.

Prior to this he was healthy; only some symptoms of hyperactivity.
Initial hospital stay

- His initial head CT done in the ED was abnormal
- Ophthalmology exam was done and showed:
  - Normal fundoscopic exam
  - Apparent left-sided hemianopsia
- MRI brain and LP then followed
  - LP showed elevated protein and Myelin Basic Protein
Parker’s MRI
Parker’s Maternal Uncle had a longstanding history of neurological abnormalities.

He had onset of trouble walking in his 20s following a back sprain.

This progressed to a spastic paraparesis.

Imaging and lab work failed to find a definitive cause.

By the time of Parker’s illness he could no longer ambulate.
Further Testing and Events

- Very Long Chain Fatty Acids were sent in the hospital and were elevated.
- Sequencing of the ABCD1 gene was sent and showed a known pathogenic mutation.
- The family traveled to Minnesota to be evaluated by Dr. Troy Lund for a possible BMT.
Following the diagnosis
The ensuing months
Parker was not a good candidate for BMT due to the severity of disease already present at the time of diagnosis.

His family made compassionate choices regarding his care.

He had an Nasogastric tube, but Gastrostomy and Tracheostomy were not pursued.

He passed away at home on 10/16/16.
X-linked Adrenoleukodystrophy
The Pathophysiology
The Gene: ABCD1

- Located on the X chromosome
- Makes ALDP: Adrenoleukodystrophy Protein
- ADLP protein is found on the membranes of peroxisomes
- ALDP function: imports Very Long Chain Fatty Acids into Peroxisomes
Peroxisomes and their function

- Bud off of the Endoplasmic Reticulum
- Replicate by fission
- Numerous metabolic functions including Beta Oxidation of Very Long Chain Fatty Acids
Beta oxidation of VLCFA

- VLCFA = fatty acids with >22 Carbons
- They are transported into the peroxisome via ALDP
- They are oxidized until they are converted into Octanoyl CoA
- They are then transported to the Mitochondria for the rest of the oxidation process
What happens when ALDP can’t be made?

- VLCFA cannot be broken down
- VLCFA accumulate preferentially in the following cells:
  - Adrenocortical cells
  - Nervous system cells: Oligodendrocytes, Astrocytes, and Neurons
  - Leydig cells of the testes
Cellular pathophysiology

- VLCFA are hydrophobic and distort the cellular membrane
- Integrity of the cell membranes are disrupted
- Mitochondrial membranes are depolarized
  - ability to make energy is disrupted
- Electrolyte homeostasis is disrupted
- Cellular oxidative damage is increased
In cerebral ALD, a robust but unhelpful inflammatory response is triggered in the brain.

- This results in severe demyelination.
- Also leads to some of the imaging characteristics seen in ALD.
The Disease
There are multiple different phenotypes of the disease.

There is no genotype: phenotype correlation.

Within the same family, there can be:

- Different presentations
- Different age of onset
- Different lifespans
4 General Presentations

- Isolated Addison’s Disease
- Childhood-onset Cerebral Adrenoleukodystrophy (cALD)
- Later-onset Adrenomyeloneuropathy (AMN)
- Female Carriers
Why the Different Presentations?

- It is thought that there is at least one autosomal modifier gene
- That gene may regulate the body’s inflammatory response to the presence of the abnormal VLCFA
- The inflammatory response in the brains of those with cALD is not seen in the spines of those with AMN
Addison’s Disease
Addison’s Only ALD is uncommon: ~10%
Percent of males with Addison’s disease who will later be diagnosed with ALD: ~35%?
Percent who will be diagnosed with ALD is higher in those with negative adrenocortical autoantibodies
Adrenocortical Insufficiency

- May be the presenting sign of ALD
- Males in the first year of life may present in Addisonian crisis:
  - earliest case was a 5 month old
- May precede neurological symptoms by years or decades
- Glucocorticoid function affected first
  - Mineralocorticoid function becomes involved in 50%
Symptoms of Adrenocortical insufficiency

- Fatigue, anorexia, weight loss
- Abdominal pain
- Hyperpigmentation
Addisonian crisis

- Nausea, vomiting, abdominal pain
- Dehydration
- Hypoglycemia
- Hypotension
- Altered mental status
- Signs of sepsis or other stressor
Cerebral ALD
Cerebral ALD

- Present in Childhood.
  - Youngest age of onset: 2.5 years
- Most rapidly progressive, shortest lifespan
- Insidious onset initially
- Most common 1st sign: ADHD-type symptoms, decline in school performance
Progression of symptoms: Vision

- Visual symptoms usually follow ADHD symptoms
  - Not true vision loss initially
  - Visuospatial and visuomotor skills
  - Inability to process visual information
  - Decline in reading and writing skills
  - Eye exam is normal
Other sensory impairments

- “Word deafness”: cannot process words despite hearing being intact
- Visual acuity does begin to decline
- Hallucinations may ensue
- Astereognosis: inability to process information by touch alone
Stage of rapid deterioration

- Spastic paraparesis and seizures develop
- Ataxia also develops
- Once these symptoms have begun, a rapid deterioration takes place
  - Loss of ambulation
  - Loss of ability to communicate
  - Agitation and dementia symptoms predominate
Most boys enter a permanent vegetative state.

Death usually occurs between 2 and 4 years after the onset of symptoms.

Variability in time to death after symptoms depends on care options chose by family:
- NG tube vs Gastrostomy
- Tracheostomy placement
- Hospice is an option
MRI features: early cALD

- 80% start with a demyelinating lesion in the corpus callosum
- This then progresses to involve the parieto-occipital areas
- Less common: starts in the genu of the corpus callosum and spreads to the frontal areas
- Usually bilateral and symmetric
MRI in advanced cases

- T2 shows abnormal signal in the white matter
- T1 enhancement is seen later and indicates a severe breakdown of the blood-brain barrier
- “Inflammatory demyelination”
- Leading edge of contrast enhancement occurs; reflects active spread
Adrenomyeloneuropathy (AMN)
Onset is much later than cALD
- It is more slowly progressive
- Lifespan can be normal
- Many affected males have children prior to receiving a diagnosis
Symptoms can develop between adolescence and adulthood (30s to 40s)

- 70% also have Addison’s disease
- The spinal cord and peripheral nerves are initially involved
- Gradually progressive spastic paraparesis
- Sensory ataxia
- Sphincter control: urinary retention
- Impotence
AMN is a noninflammatory axonopathy: long tracts of the spinal cord and (to a lesser extent) peripheral nerves

EMG/NCS shows an axonopathy usually

Peripheral neuropathy may be the first sign: mixed axonal and demyelinating on EMG/NCS
Neuroimaging in AMN

- Spinal imaging:
  - If long-standing: nonspecific atrophy can be seen
  - To see abnormalities in the spine, need DTI or magnetization transfer sequences (not readily available)

- Brain imaging:
  - Usually normal, but may show subtle changes
  - “Wallerian degeneration”
  - 20% of AMN males watched over 10 years developed some amount of cerebral demyelination
  - Once contrast enhancement begins in the brain, prognosis becomes poor
Females
Initial assumption was that females are not affected.

At national conferences, neurologists began examining female “carriers” and found that 50% have an abnormal neurological exam.
Symptoms

- Onset is between 4th and 5th decade
- By age 60, 65% will have some symptoms
- Sometimes symptoms are profound enough to lead to a referral to the neurologist
- Females can be the first identified in the family
Symptoms

- Spinal symptoms also predominate
- Sensory ataxia
- Incontinence
- Pain in the legs
- cALD and Addison’s is very uncommon: (2% and 1%)
The Treatment
Sources of VLCFA

- VLCFA synthesized in the body >> VLCFA in diet
- Restriction of dietary sources alone does not lower plasma levels of VLCFA
- A cookbook has been developed by the Kennedy Krieger Institute with recipes that are low in VLCFA
- Restriction should be done with advice of a nutritionist and doctor familiar with the therapy
Lorenzo’s Oil

- Addition of Glyceryl Trioleate Oil (GTO) oil + restriction of VLCFA can lower levels in blood
- Does not change outcome of already symptomatic patients
- ? benefit in delaying onset of symptoms/slowing progression in cALD
- Likely no effect on slowing AMN
- Lorenzo’s oil: 4:1 mix of Glyceryl trioleate and Glyceryl Trieructate
Allogeneic BMT

- Currently the only known intervention to arrest cALD.
- The best chance for efficacy is to perform it when:
  - Radiographic disease burden is low.
  - Symptoms are not present or minimal.
- Not effective for AMN.
Challenges:

- Allogeneic BMT is a serious procedure with significant morbidity and mortality risks.
- We would not do it on someone with no evidence of cALD because they may never develop cALD.
- When a boy is diagnosed with cALD because he has symptoms, he may be a poor candidate for BMT:
  - BMT in these patients may accelerate progression of cerebral disease.
  - It may stabilize disease, but in someone profoundly devastated, that may not be an acceptable ethical decision.
In summary regarding BMT

- It works best on someone with no symptoms but some minimal evidence of cerebral disease.
- So... we have to know a boy is at risk to develop the disease in order to intervene in time.

And that is why there has been a drive to include XALD on the Newborn State Screen in multiple states.
The Drive to Update the Newborn State Screen
Several states have updated their screening programs:

- 1st state to add ALD was New York
- A young boy named Aidan Seeger passed away at the age of 7 in 2012
- Mrs. Seeger began a campaign to add ALD to the newborn screen
Federal efforts: What is RUSP

- **RUSP** = Recommended Uniform Screening Panel
- A list of disorders that the Department of Health and Human Services recommends states screen for
- Ultimately, states decide what to screen for
- To be considered a candidate disorder, there should be:
  - A net benefit to knowing someone is positive
  - An ability to screen for it (i.e.: have a biomarker)
  - An effective treatment for it
Federal Efforts continued

- ALD was approved for addition to the RUSP in 2016 by the HHS

---

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

FEB 16 2016

Joseph A. Bocchini, Jr., M.D.
Committee Chairperson
Advisory Committee on Heritable Disorders in Newborns and Children
3600 Fshers Lane
Room 18W68
Rockville, MD 20857

Dear Dr. Bocchini:

Thank you for your letter on behalf of the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) regarding the ACHDNC’s recommendations to add X-linked Adrenoleukodystrophy (X-ALD) to the Recommended Uniform Screening Panel (RUSP) and to provide federal funding to state newborn screening programs to implement the screening of X-ALD.

I would like to commend the ACHDNC on your evidence review that included an analysis of the benefits and harms of newborn screening for X-ALD as well as the capability of state newborn screening programs to offer comprehensive testing and follow-up services for infants identified with X-ALD. After reviewing the ACHDNC’s report, Newborn Screening for X-Linked Adrenoleukodystrophy (X-ALD): A Systematic Review of Evidence, and taking into consideration the utility of current screening technologies, treatment for X-ALD, and the impact on public health systems, I accept the ACHDNC’s recommendation to expand the RUSP to include the addition of X-ALD. As you may know the Affordable Care Act requires that most health plans cover without cost-sharing certain children’s preventive services. Because the RUSP is a component of preventive services guidelines supported by the Health Resources and Services
Texas Efforts

Now that ALD has been added to the RUSP, the next step is to add it to the Texas Newborn State Screen

This past August, multiple physicians, nurses, and other practitioners from several specialties met in Austin at the State Department of Health to begin planning for implementation
Screening Protocol

- VLCFA can be tested in the dried blood spots already in use
- Positive tests will be rereferred on for sequencing of the ABCD1 gene
- PCPs and ordering providers will be notified of positive results and referrals to various centers will be initiated
How many babies will this affect?

- New York’s experience suggests about 1:14,000 will have elevated VLCFA and require further testing.
- Prior incidence rates: 1:17,000 to 1:20,000 male births.
- # of male babies per year in Texas in 2014: 204,000.
- # of female babies per year in Texas in 2014: 1:194,000.
- Likely number of “referrals” per year in Texas could be: ~30.
The Challenges

- VLCFA are elevated in other disorders:
  - Most of these have no treatment and even more grave prognoses
- 80-85% of female carriers will be diagnosed
  - First issue for most females will involve reproductive decisions
- Among males: Test will not identify who will develop cALD vs who will develop AMN or Addison’s only
  - We will have a treatment for only about 30-40% of males and we have no way to know which ones will benefit initially
What will happen when males are identified?

- A positive results will initiate a series of screening and visits to many doctors
  - Genetic counseling for family
  - Endocrinology for adrenal insufficiency
  - Neurology for serial exams and MRIs every year
  - Bone marrow transplantation when needed
The Robertson's efforts:
Aiden's Law (Test all babies for ALD)

Test All Babies for ALD - Vote Yes on Aiden's Law

Aidan Jack Seeger Foundation

Aidan Jack Seeger was a happy, healthy, spirited NY boy who, at age 6, suddenly developed vision and concentration problems. His parents thought he just needed glasses. He was misdiagnosed several times. His sight went entirely, then his ability to walk and talk. Eventually, doctors figured out that

Sign this petition
- Your info will stay private.
- 184,083 supporters
- 15,417 needed to reach 200,000

First name
Last name
Email

Share with Facebook friends

Keep me updated on this campaign and others from Aidan Jack Seeger Foundation

By signing, you accept Change.org’s Terms of Service and Privacy Policy, and agree to receive occasional emails about campaigns on Change.org. You can unsubscribe at any time.
Parker’s Legacy
My Thanks To

Parker’s family
&
the physicians who participated in his care with me