LEUKODYSTROPHY
Care Network

2020 Winter Meeting
March 3, 2020

Alexander Disease

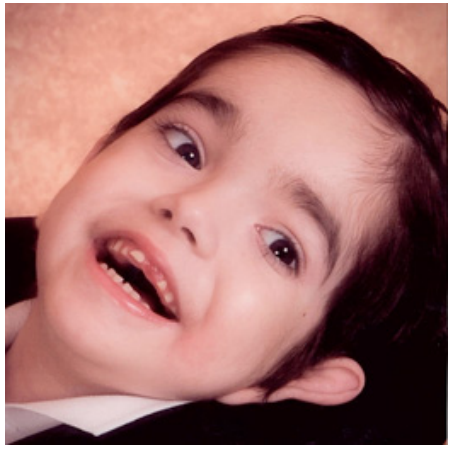
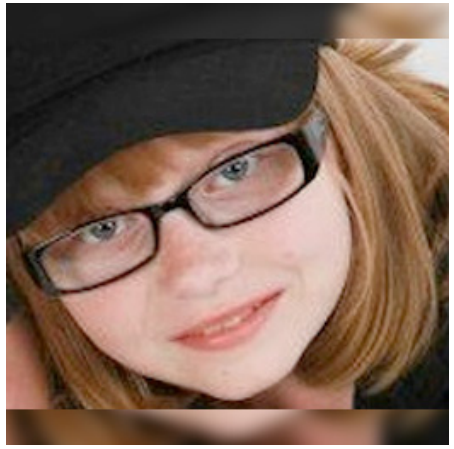
Speakers

- CHOP : Katy McDonald, MSN,CRNP
- Family Advocate : De Flohre

Alexander Disease Children

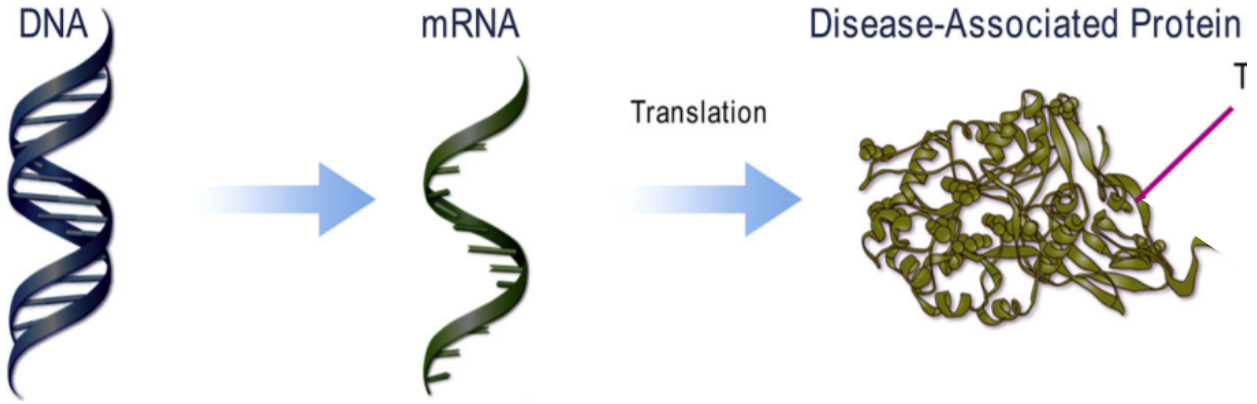




What is Alexander Disease?

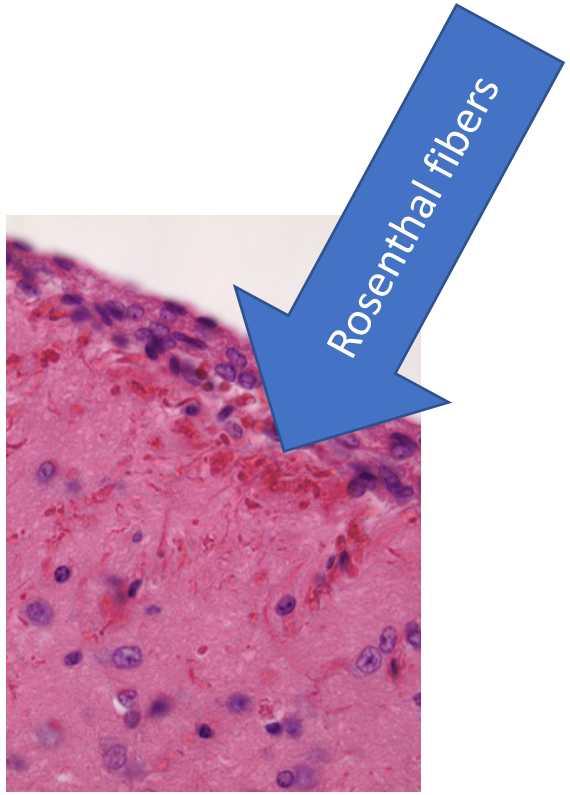
- Referred to as ALX, AxD, Demyelinogenic Leukodystrophy, Fibrinoid Leukodystrophy, White Matter Disease, and other names
- Alexander Disease is a fatal neurodegenerative disorder that destroys structure and functionality of neurons in the brain
- Demyelination caused by lack of Glial Fibrillary Acidic Protein (GFAP)
- Only leukodystrophy in which Rosenthal Fibers appear
  - Rosenthal Fibers are abnormal protein deposits that cause improper cell function



GFAP

Gain of function

Too much protein



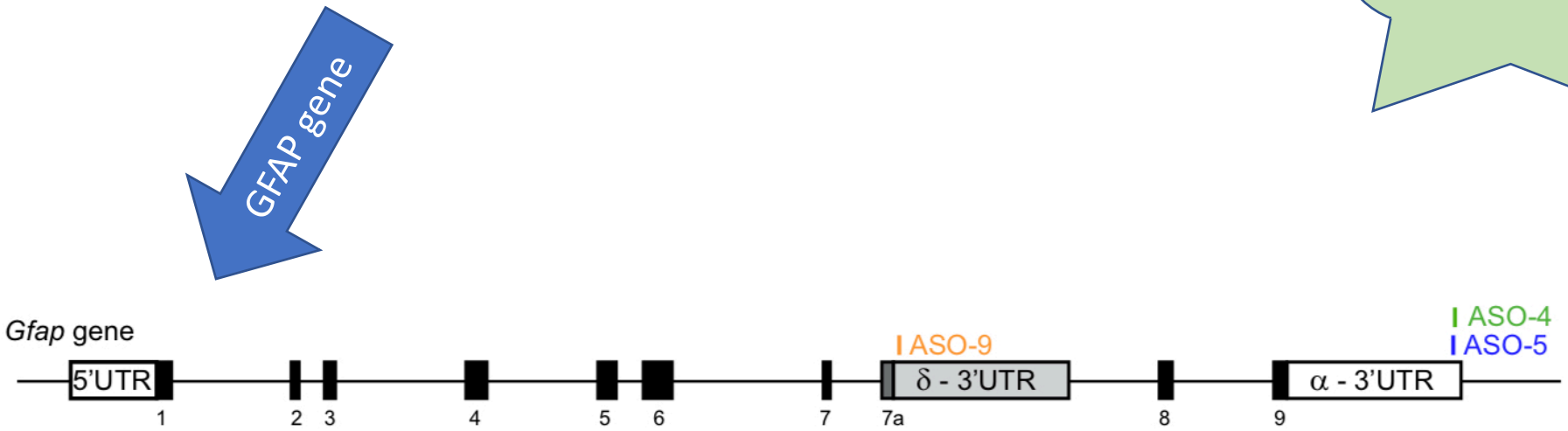
Mice (couresy of Albee Messing)

Morphologically and biochemically identical to human Rosenthal fibers

How do you get Alexander Disease?

- Typically Genetic
  - 95% of patients have a mutation in *GFAP*. No other genes have been associated with AxD.
  - Mosaic parents
- Later-onset is classically genetic
  - autosomal dominant form

In our cohort at CHOP, approximately 90% Type I (younger) patients have a de novo mutation on Chromosome 17 that expresses Glial Fibrillary Acidic Protein (GFAP)



How Does Alexander Disease Affect the Individual?

- Alexander Disease is a demyelinating disease and causes the loss of many functions such as walking, talking, and eating

- Alexander Disease is progressive and causes severe loss of previously attained milestones or failure to thrive in the infantile form

What are Initial Symptoms of Alexander Disease?

The Different Types of Alexander' Disease Present Differently

- Macrocephaly
- Seizures
- Developmental Delays
- Vomiting, swallowing or feeding issues
- Ataxia
- Speech difficulties
- Failure to thrive
- Walking difficulties
- Spasticity

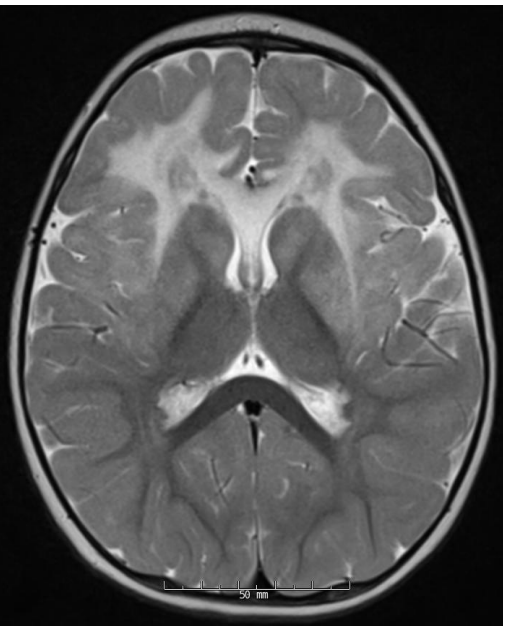
Patients with juvenile alexander's disease are sometimes misdiagnosed with anorexia due to the severity of their failure to thrive and feeding issues.

How is Alexander Disease Diagnosed?

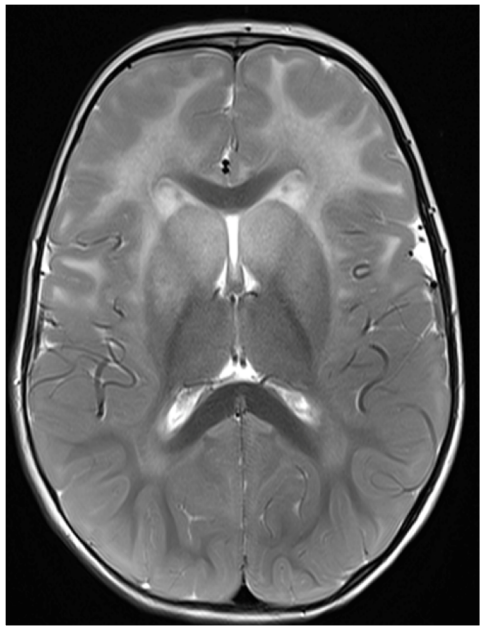
- Genetic testing to identify changes in GFAP gene
- Prior to identifying the GFAP gene, AxD was diagnosed based on MRI findings

MRI Criteria (Van Der Knapp)
extensive cerebral white matter abnormalities with a frontal preponderance, either in the extent of the white matter abnormalities, the degree of swelling, the degree of signal change, or the degree of tissue loss (white matter atrophy or cystic degeneration)
presence of a periventricular rim of decreased signal intensity on T2-weighted images and elevated signal intensity on T1-weighted images
abnormalities of the basal ganglia and thalami, either in the form of elevated signal intensity and some swelling or of atrophy and elevated or decreased signal intensity on T2-weighted images
brain stem abnormalities, in particular involving the midbrain and medulla;
contrast enhancement involving one or more of the following structures: ventricular lining, periventricular rim of tissue, white matter of the frontal lobes, optic chiasm, fornix, basal ganglia, thalamus, dentate nucleus, and brain stem structures.

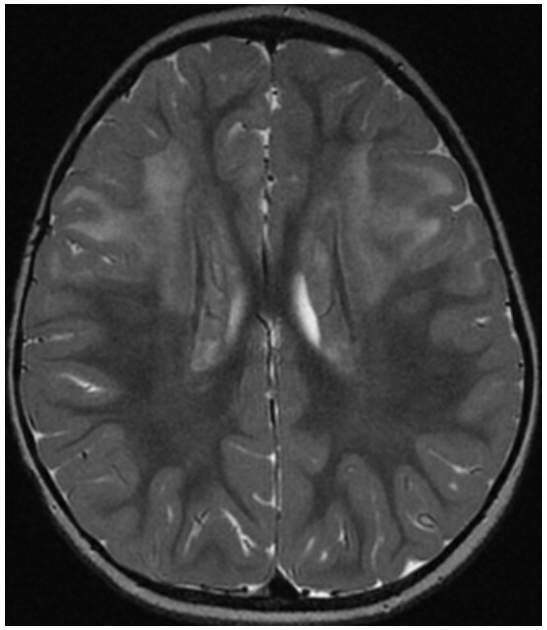
Imaging in Alexander's Disease



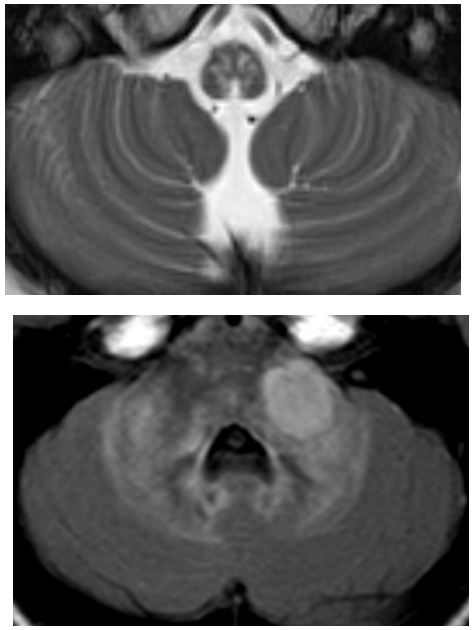
Extensive frontal white matter T2 hyperintensity



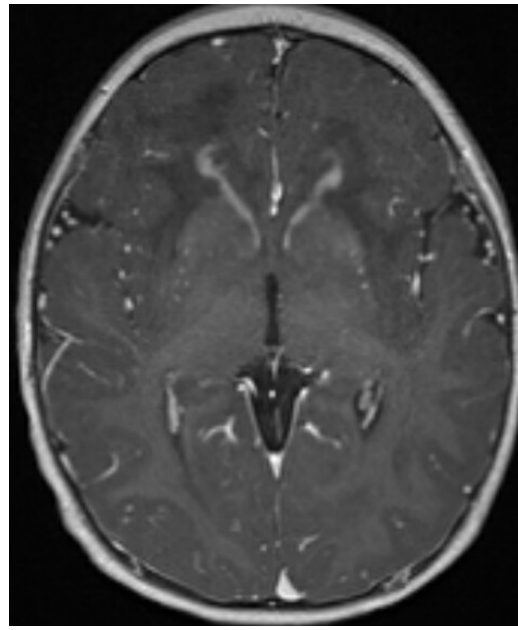
Basal ganglia or deep gray swelling or atrophy



Periventricular rim



Brainstem involvement



Contrast enhancement

van der Knaap M, et al.
AJNR 2001;22:541-552

What are the Different Forms of Alexander Disease?

- Neonatal:
  - Appears before birth
  - extremely rare
- Infantile Onset
  - Appears between birth and 4 years of age
  - Constitutes 80% of Alexander Disease diagnoses
  - characterized by seizures, enlarged brain and head, stiff legs, and delayed development
- Juvenile Onset
  - Appears between age 4 and early teenage years
  - Slower progression than infantile onset
  - characterized by difficulty swallowing, scoliosis, speech issues, and poor coordination
- Adult Onset
  - Similar symptoms to juvenile onset but slower progression

Types of Alexander’ s Disease

Neonatal (1%)

- Seizures
- Macrocephaly
- Severe motor and intellectual disability

Infantile (42%)

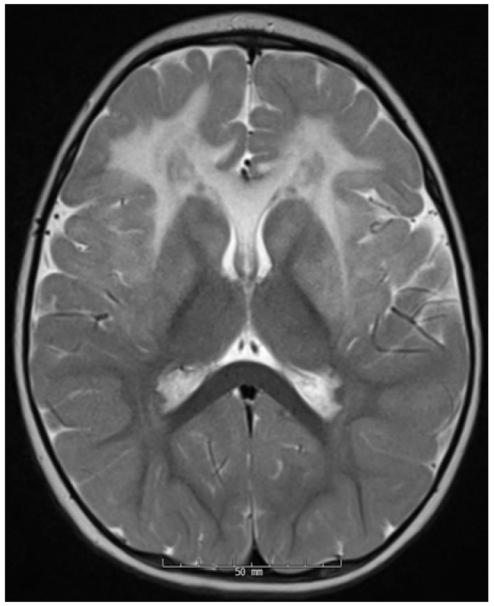
- Developmental delay
- Seizures
- Macrocephaly
- Progressive psychomotor retardation with loss of milestones

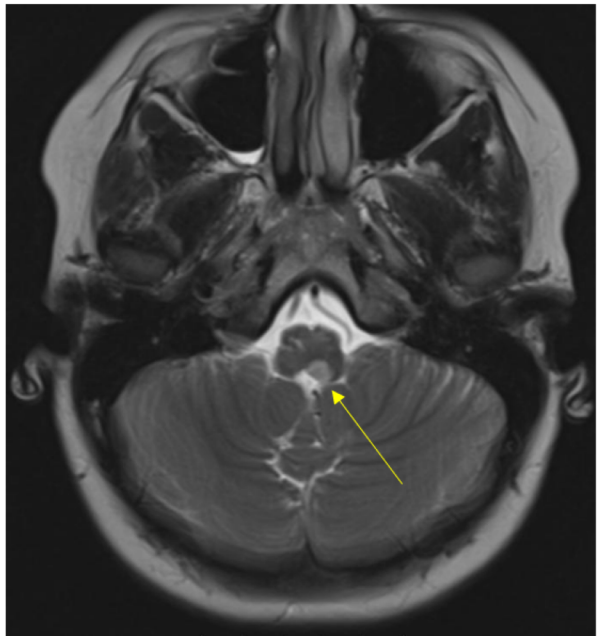
Juvenile (22%)

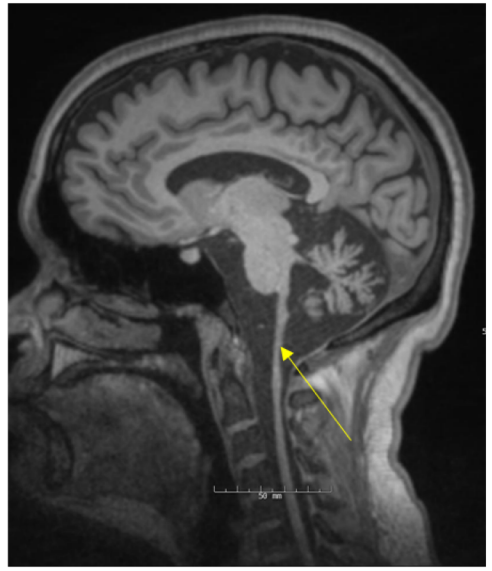
- Vomiting/failure to thrive
- Bulbar/pseudobulbar signs (dysphagia, dysphonia, dysarthria)
- Ataxia
- Gradual loss of intellectual function
- Respiratory insufficiency

Adult (33%)

- Bulbar/pseudobulbar signs (palatal myoclonus)
- Spasticity/abnormal gait
- Ataxia
- Sleep apnea
- Cerebellar signs
- Autonomic dysfunction

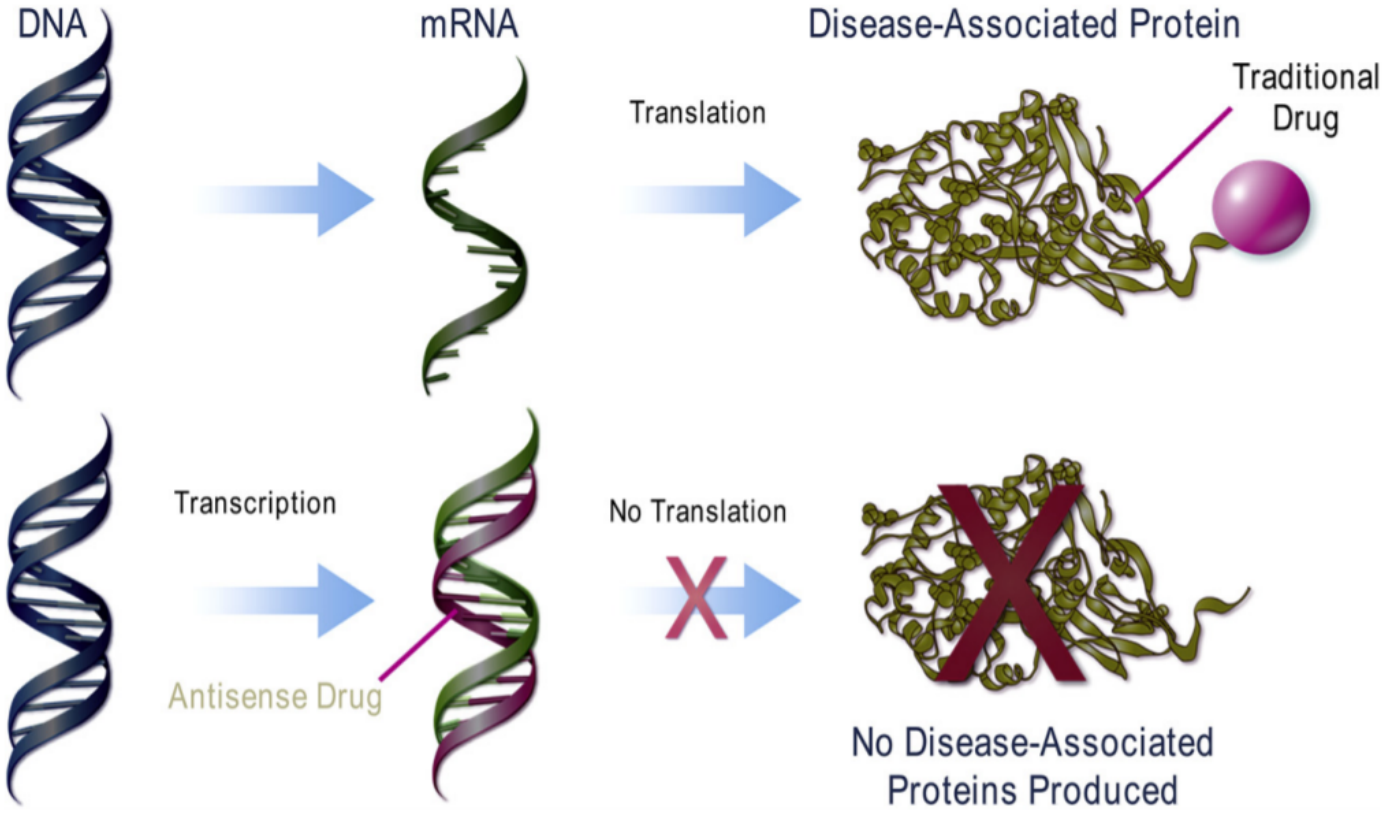






Is There a Treatment for Alexander Disease?

- No currently approved treatments but symptoms can be managed
- Antisense drug in development



Medical Issues

Manage

- Seizures
  - Preferred medications for AxD: Keppra, valproic acid
- Vomiting
  - reflux meds and valproic acid
- Pain
  - Often times headaches, which we can treat with Diamox.
- Eating Issues
  - failure to thrive, dysphagia, sometimes early G-tubes
- Tone
  - Spasticity which often comes later in the disease
  - Hypotonia, particularly axial is present early in the disease

Using an independent local pharmacy may be easier than a "big box" pharmacy for prescriptions, especially if compounded medications are needed.

Medical Issues

We recommend maximizing therapies such as PT, OT, ST . If available hippotherapy and aquatic therapy can be great!

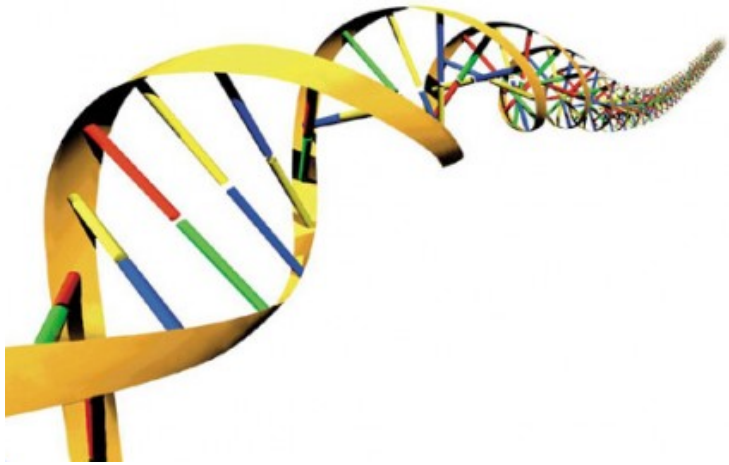
Adaptive sports are great as well!

Prevention

- Aspiration pneumonia
  - control vomiting with medications
  - Monitor for dysphagia with swallow evals or swallow studies
- Constipation
  - Managed with Miralax
- Hip Dislocation
  - Monitoring with hip x-rays
- Scoliosis
  - Many patients will develop scoliosis, more data is needed on benefits and risks of surgery. Surgery and management should be made on individual basis and referral to orthopedics could be considered.
- Bone Health
  - Assessments with dietician to maximize nutrition, Vitamin D supplements can be considered and referral to bone health clinic for further management.

Research and Clinical Trials

- Research
  - Waisman Center, University of Wisconsin
    - Examining GFAP mutations in the body
- Clinical Trials
  - Natural History Study of Alexander Disease Patients at Children's Hospital of Philadelphia
    - Physical and cognitive examinations



Is there NBS for Alexander Disease?

- Not currently on Recommended Uniform Screening Panel (RUSP)
- Challenges to a newborn screen
  - De novo mutations in children so diagnosis through family members won't help (argues for NBS)

ASO is in clinical trial development (may change the future of NBS like it did for SMA)

NBS Follow-up Protocols for Alexander Disease

- No newborn screening so no newborn screening protocols because there is currently no treatment

LCN & Other Centers with Expertise in Alexander Disease

- Children's Hospital of Philadelphia
- Kennedy Krieger Institute
- Massachusetts General Hospital

Family Advocate Organizations for Alexander Disease

- Hunter's Hope
- Leukodystrophy Care Network
- National Organization for Rare Diseases
- Leukodystrophy Family Forum

Find additional support and respite from your local community.

LCN Care Coordinator Shared Files for Alexander Disease

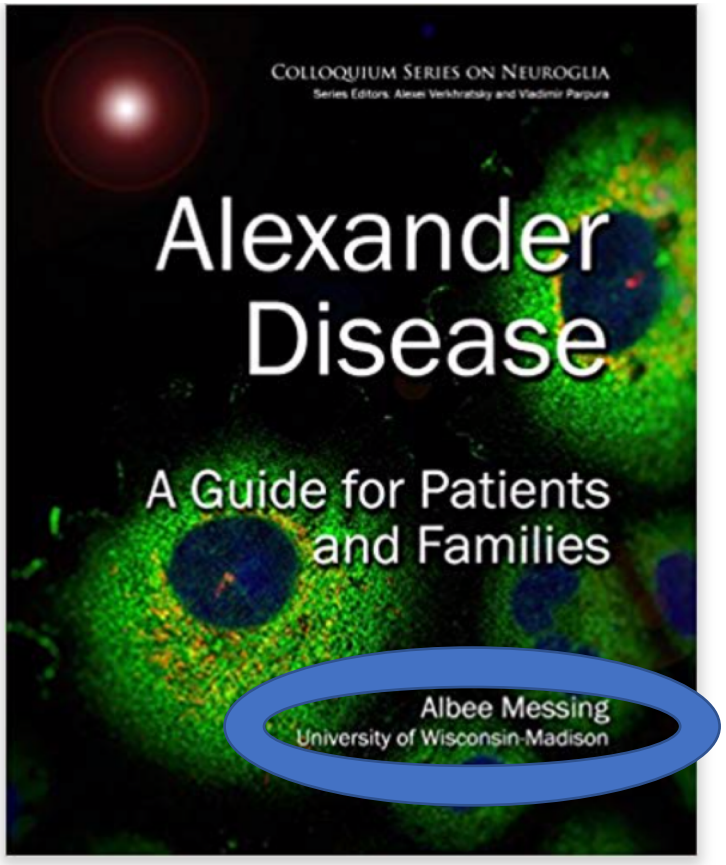
Resources for Medical Professionals

- Alexander Disease Research – University of Wisconsin – Waisman Center
- Alexander Disease Research – Children's Hospital of Philadelphia
- National Institutes of Health: Alexander Disease
- US National Library of Medicine: Alexander Disease

Resources for Families

- Leukodystrophy Care Network
- Hunter's Hope Foundation – Family Care
- Alexander Disease Research – University of Wisconsin – Waisman Center
- Alexander Disease Research – Children's Hospital of Philadelphia

Available on amazon!



Thank you!

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