2020 Winter Meeting
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Krabbe
Globoid Cell Leukodystrophy
Speakers

- Tara West, LCN Care Coordinator, Duke
- Jullie Rhee, LCN Care Coordinator, Children’s National Hospital
- Family Advocates: Jacque Waggoner and Amy May
Krabbe Children
What is Krabbe Disease?

- Krabbe (crab-ay) Disease, also known as Globoid Cell Leukodystrophy, is a genetic disorder that affects the central and peripheral nervous systems.

- Krabbe disease is caused by mutations in the GALC gene which reduces the activity of the Galactosylceramidase (GALC) enzyme. This enzyme breaks down certain fats called galactolipids and an excess of these fats can cause damage to cells that help form myelin (protective covering of the nerve cells).

- Psychosine (is a cytotoxic lipid)- also accumulates due to the deficiency of the GALC enzyme and causes oligodendrocyte destruction and subsequent demyelination.

- It is classified as both a Leukodystrophy and Lysosomal Storage Disorder (LSD).

- Lack of GALC enzyme causes deterioration of the myelin sheath and interference with the central (white matter) and peripheral nervous systems.
How do you get Krabbe?

• Krabbe Disease is a genetic, or inherited, disorder and is also classified as an autosomal recessive disorder.

• The gene for Krabbe is found on Chromosome 14 and abnormalities with gene expression causes a lack of GALC to be produced.
What are the Different Forms of Krabbe?

• Early Infantile Krabbe Disease (EIKD)
  – Symptoms appear within the first few months of life and is the most severe form
  – Characterized by extreme irritability, feeding difficulty (may be present from birth), stiffness, loss of or unmet developmental milestones, seizures, and muscle spasms.

• Late Onset Infantile Krabbe Disease
  – Symptom onset between 6 months and 3 years
  – Similar symptoms to EIKD

• Adolescent and Adult Onset Krabbe Disease
  – Symptoms begin with loss of motor skills at 3 years and later vision problems
  – Slower progression than infantile onset, with symptoms appearing over the course of several years
How Does Krabbe Affect the Individual?

• Krabbe Disease affects both the central and peripheral nervous systems, which are responsible for all of the body’s voluntary and involuntary functions.

• Destruction of the myelin sheath interferes with brain and nervous/peripheral systems’ communication
  • Interferes with all neurological functions such as walking, talking, swallowing, breathing, vision, and hearing
What are Initial Symptoms of Krabbe?

- Symptom onset is variable depending early versus later onset of Krabbe Disease.
- Most common symptoms include:
  - Delay in developmental milestones or loss of milestones
  - Irritability or difficult to console
  - Change in muscle tone (Low truncal tone with higher appendicular tone)
  - Hearing and vision loss - usually come later especially hearing
  - Seizures
  - Feeding difficulties - may be first sign especially in Early Infantile
  - Peripheral neuropathy
How is Krabbe Diagnosed?

• Krabbe Disease is a genetic, or inherited, disorder and is also classified as an autosomal recessive disorder.
• Newborn screening
• GALC enzyme levels through blood testing
• Psychosine- biomarker for 2nd tier NBS testing
• Gene sequencing analysis of \textit{GALC} gene for molecular confirmation
• Nerve conduction studies are abnormal, but are non diagnostic
• Neuroimaging to help guide diagnosis:
  • MRI: abnormalities in periventricular white matter, basal ganglia, cerebellum
  • CT: hyperdensity in cerebellum, brainstem, thalami, caudate nuclei
Is there NBS for Krabbe?

- Not currently on Recommended Uniform Screening Panel (RUSP)
- New York; Missouri; Kentucky; Ohio; Tennessee; Illinois; and New Jersey currently screen for Krabbe in routine NBS panels
- PA, NM, LA, SC, and IN have passed similar laws with implementation dates varying by states
- Can be tested in other states by ordering screening through Perkin Elmer Genetics, Hunter’s Hope, or EGL Genetics
NBS Follow-up Protocols for Krabbe

- Determining GALC levels through blood sample
- Cerebrospinal fluid (CSF) total protein test
- Brain MRI
- Nerve conduction velocity test
- Psychosine may be followed at intervals example every 3-6 months if child is asymptomatic but is also followed in transplanted children
Is There a Treatment for Krabbe?

- No cure but there are treatments
- Core Blood Transplant (CBT)
  - Can come from umbilical cord or core blood banks
- Bone Marrow Transplant (BMT)
  - Matches with family members or other donors
- Both treatments add in healthy levels of GALC to the body but cannot reverse demyelination or damage that has already occurred
Medical Issues

*Management of symptoms:*

Respiratory: excessive drooling, poor airway clearance, respiratory insufficiency
Gastrointestinal: GERD, swallow/feeding, Constipation
Musculoskeletal: Management of tone, routine surveillance for hip and spine, Monitoring for contractures, ongoing PT/OT
Neurology: seizures, irritability
Infectious: fever management, prevention of illness, monitoring for UTIs
Eyes: routine evaluation with Ophthalmology
Hearing: routine evaluation with Audiology
Other: ST

*Prevention*

The key is to be proactive with their care!
Research and Clinical Trials

• Research
  – Hunter James Kelly Research Institute (University at Buffalo)
    • Studies demyelination process and consequences of myelin damage
  – Passage Bio

• Clinical Trials
  – Newly Diagnosed Krabbe Patients at Duke
    • Testing DUOC-01 cell, grown from umbilical cord blood, which then travels to the brain within months of transplant.
    • “The DUOC cell can be given into the child’s spinal fluid through a spinal tap 4 weeks after a cord blood transplant reaching the brain within a few days after injection. The hope is that this will be safe and will be a way to help the brain months earlier than the transplant does. This should slow or stop disease progression earlier and preserve more function in the child with Krabbe disease after transplant.” (Hunter’s Hope)
LCN & Other Centers with Expertise in Krabbe

- Ann & Robert H. Lurie Children’s Hospital of Chicago
- Children’s Healthcare of Atlanta
- Duke Children’s Hospital
- Golisano Children’s Hospital at University of Rochester
- Kennedy Krieger Institute
- Massachusetts General Hospital
- Monroe Carell Jr. Children’s Hospital at Vanderbilt
- Primary Children’s Hospital, Utah
Family Advocate Organizations for Krabbe

- Hunter's Hope
- Leukodystrophy Care Network
- National Organization for Rare Diseases
LCN Care Coordinator Shared Files for Krabbe

• Review: Clinical Management of Krabbe Disease paper in Journal of Neuroscience Research- 2016
• Medical Care Letter template
Resources for Medical Professionals

- Leukodystrophy Care Network
- American College of Medical Genetics Krabbe Disease ACT SHEET for Medical Professionals
- Mayo Clinic: Krabbe Disease
- National Institutes of Health: Krabbe Disease
- NIH Gene Reviews: Krabbe Disease
- US National Library of Medicine: Krabbe Disease
- New York State Department of Health: Newborn Screening for Krabbe Disease
Resources for Families

- Leukodystrophy Care Network
- Hunter’s Hope Foundation – Family Care
- Hunter James Kelly Research Institute
- Duke Children’s Hospital: Bone Marrow and Stem Cell Transplantation
Thank you!

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