

*Universal Newborn Screening
for Krabbe Disease:
The NYS Experience*

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Leukodystrophies

- *Inherited disorders*
- *Result from defects in synthesis or catabolism of myelin*

*Krabbe Disease
(Globoid Cell Leukodystrophy)*

- *1st Described in 1916 (Knud Krabbe)*
- *Enzymatic defect identified 1970*
- *Gene cloned 1993 - 1994*

*INCIDENCE
(literature)*

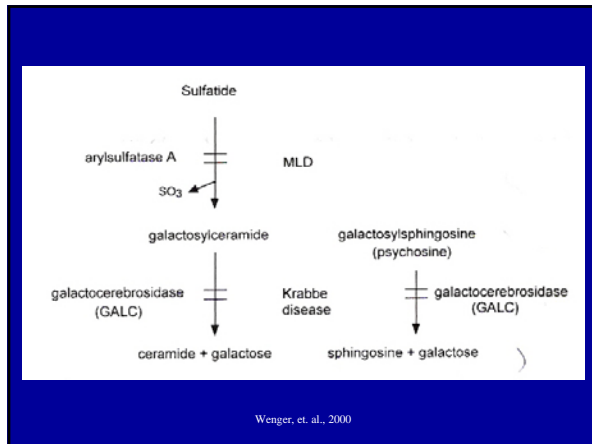
- *1/100,000*
- *90% infantile form*

Genetics: Autosomal Recessive

- *> 75 mutations (published)*
- *26 novel mutations (NYS)*
- *Linked to chromosome 14Q25-31*

Pathophysiology:

- *Deficiency Galactocerebrosidase (GALC)*
- *Loss of ability to degrade galactolipids (myelin) (Galactosylceramide)*
- *Loss of ability to degrade galactosylsphingosine (psychosine)*



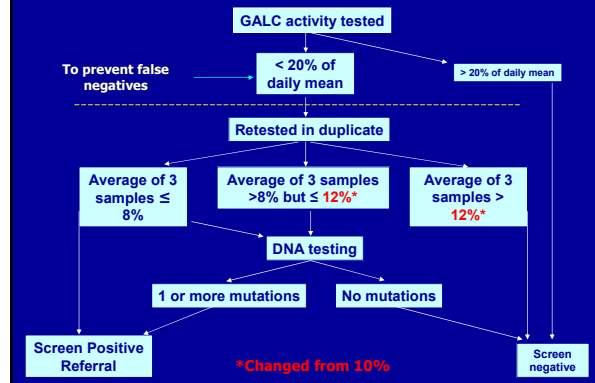
Diagnosis

- *Extremely low GALC activity WBC or Fibroblasts*
- *Mutation analysis*
 - *30 Kb homozygous deletion (early infantile KD)*
- *Prenatal diagnosis possible if prior affected sibling*

Timeline

- *August 2005 – NYS Legislature mandates NBS for Krabbe disease*
- *February 2006 – NYC meeting of the Directors of the Inherited Metabolic Disease Centers*
- *August 2006 - Universal Newborn Screening Krabbe Disease begins in New York State*

Krabbe Screening: Cutoffs and Testing Algorithm



KRABBE DISEASE

- *Early Infantile*
- *Later Onset Krabbe Disease*
- *Adolescent*
- *Adult*

ISSUES WITH NEWBORN SCREENING

- *Genotype does not predict phenotype (except 30 Kb homozygous deletion)*
- *Degree of GALC activity does not predict clinical course*

Treatment Issues

- *UCB transplantation: high morbidity & mortality*
- *Identify babies with infantile Krabbe disease before they become symptomatic*
- *Only refer affected children for transplant*

NYS KRABBE CONSORTIUM

- *Albany Medical Center*
- *SUNY at Buffalo*
- *SUNY at Stony Brook*
- *SUNY at Syracuse*
- *Strong Memorial Hospital*
- *Mount Sinai School of Medicine*
- *Montefiore Medical Center*
- *New York Medical College (Westchester Med. Ctr.)*
- *Wadsworth Laboratory (NYS DOH)*
- *New York University**
- *Mayo Clinic**
- *Cornell University**
- *Kennedy Krieger Institute (Hugo Moser, consultant)**

** Consultants*

To Develop a Uniform Approach (Based on Consensus) for Babies who Screen Positive for KD

- *Information on the initial clinical presentation for EIKD and LOKD*
- *Age at onset of EIKD and LOKD*
- *Reliability of various neurodiagnostic studies*

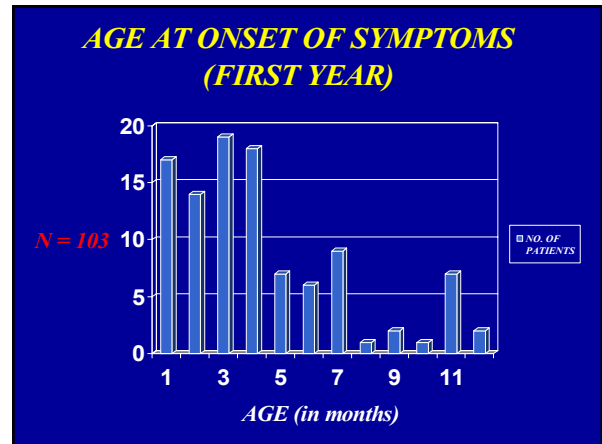
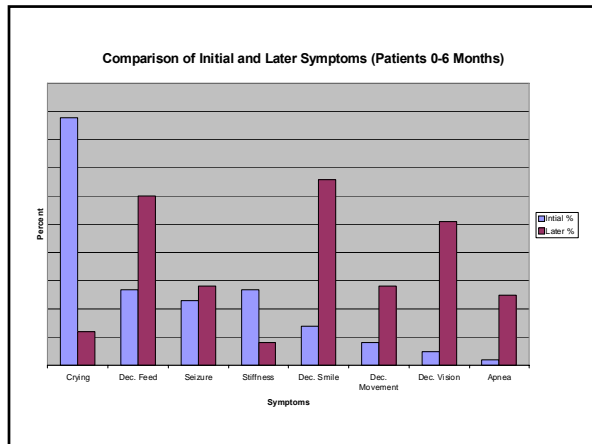
Hunter's Hope Family Registry

INITIAL SYMPTOMS 0-6 MONTHS (N = 78)

<i>SYMPTOM</i>	<i>PERCENT OF CASES</i>
<i>Crying/Irritability</i>	<i>88%</i>
<i>Stiffness</i>	<i>27%</i>
<i>Poor Feeding</i>	<i>27%</i>
<i>Poor Head Control</i>	<i>26%</i>
<i>Seizures</i>	<i>23%</i>
<i>Fisting</i>	<i>18%</i>
<i>Decreased Smiling</i>	<i>14%</i>

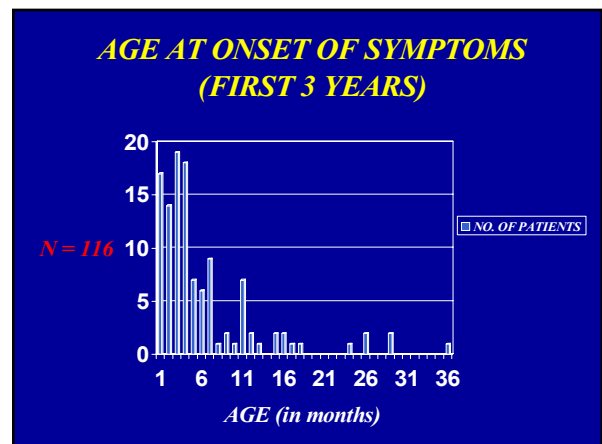
INITIAL SYMPTOMS #2 0-6 MONTHS (N = 78)

<i>SYMPTOM</i>	<i>NO. OF CASES</i>
<i>Vomiting</i>	<i>8%</i>
<i>Decreased Movement</i>	<i>8%</i>
<i>Arching</i>	<i>6%</i>
<i>Decreased Vision</i>	<i>5%</i>
<i>Decreased Hearing</i>	<i>2%</i>
<i>Apnea</i>	<i>2%</i>
<i>Motor Regression</i>	<i>1%</i>



- Initial Symptoms (LOKD)**
- *Stumbling*
 - *Change in gait, difficulty walking*
 - *Visual failure, initial manifestation in 25%*
 - *Spastic paraparesis*
 - *Hemiplegia, later becomes bilateral*
 - *Cerebellar ataxia*
 - *Irritability*
 - *Intelligence initially preserved, but deteriorates over time*
 - *Seizures, both febrile and /or intractable*
 - *Peripheral Neuropathy*

- Later Onset Krabbe Disease**
- *LOKD 15 months - 10 years (excludes adolescent and adults)*
 - *1/3 children < 3 years have the aggressive form (progression over 3 months)*
 - *Same symptoms as older children with LOKD but very aggressive*
 - *Variability in families with same genetic mutation.*
 - *No difference in GALC activity between early infantile and LOKD*
 - *Survival variable, spanning 2 years – 40+ years*



NEURODIAGNOSTIC EVALUATIONS: PRIOR EXPERIENCE (DUKE/MINNESOTA)

Neurologic Examination

4/11 Abn (Duke)

- **Hypotonia**
- **Hypertonia**
- **Poor Suck**
- **Poor Rooting**

Escobar NEJM, 2005

LUMBAR PUNCTURE

- **Increased CSF Protein**
 - **7/9 Asymptomatic**
 - **12/12 Symptomatic**

Escobar 2005

MRI FINDINGS

	<i>PYR. Tract</i>	<i>Cerebellar WM</i>	<i>Deep Gray Nuclei</i>	<i>Post CC</i>	<i>Par- Occipital WM</i>	<i>Atrophy</i>
<i>Early Onset (<2yrs) N=10</i>	90%	80%	70%	60%	50%	40%
<i>Late Onset (>2yrs) N=9</i>	100%	0%	0%	89%	100%	0%

Loes

MRI

- *Presymptomatic children may have minimal or NO changes on MRI.*
- *Diffusion – Tensor images 1st month: Relatively normal myelination and axonal integrity*

McGraw et al
Radiology 236:221-330, 2005

ABNORMAL MRI (Asymptomatic)

- **3/11: increased T2 posterior limb Int. Capsule**
- **4/11 Hyperintensity adjacent lateral ventricles**

Escobar NEJM, 2005

Abn. Neurophysiologic Assessments Pre-symptomatic (EIKD)

	Husain 2004	Escolar 2005	% ABN
VER	0/4	3/8	0% - 37.5%
BAER	2/4	4/8	50%
NCT	4/4	9/10	90%-100%
EEG	0/4	3/11	0% - 27%

Neurodiagnostic Studies (LOKD)

- MRI: Parieto-occipital, periventricular areas of demyelination
- In Lyon's study 7 of 50 had normal neuroimaging at onset
- CSF protein increased in about 30-50%
- NCV (sensorimotor demyelinating neuropathy) abnormal initially in 30-50%, sometimes not until later in their course

TITLE: A Consensus Protocol for the Clinical and Neurodiagnostic Evaluation of Infants with Positive Newborn Screens for Krabbe disease (Abstract # P24)

Authors :P Duffner, D Adams, M Andriola, G Arnold, A Aron, M Caggana, E Ciafaloni, M Cohen, C Crosley, G Diaz, A Djukic, R Erbe, L Helton, E Kolodny, B Kosofsky, D Kronn, J Kurtzberg, J Kwon, P Levy, J Mink, H Moser, T Naidich, J Orsini, P Parton, M Patterson, J Pelligrino, S Rothman, M Wasserstein, D Wenger

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NEURODIAGNOSTIC STUDIES

- MRI Brain (T2, FLAIR, DWI, DTI)
- Lumbar Puncture
 - Protein – abnormal if > 25 mg/dl above norm for age
- BAER
 - Abnormal if:
 - Prolongation interpeak latency I-V
 - Loss waves III-V
- VER (flash)
 - Abnormal if absent P100

NEURODIAGNOSTIC STUDIES #2

- Nerve Conduction Times (one sensory and one motor in one upper and one lower extremity)
 - Abnormal if:
 - Absent response
 - F waves unobtainable or with prolonged latency
 - Prolonged distal latency
 - Slow conduction velocity
 - Conduction block > 50% reduction of CMAP amplitude proximal vs. distal (partial)
 - Conduction block (complete) loss CMAP on proximal stimulation

WENGER LAB (GALC activity)

0.0 → 0.15 High Risk

0.16 → 0.29 Mod Risk

0.3 → 0.5 Low Risk

> 0.5 No Risk

EVALUATION SCHEDULE

	<u>Neurological Evaluation</u>	<u>Neurodiagnostic</u>
High Risk	Year 1 Q Month	Q 3 Months
	Year 2 Q 3 Months	Q 6 Months
Mod Risk	Year 1 Q 3 Months	Annual
	Year 2 Q 3 Months	Annual
Low Risk	Year 1 Q 6 Months	Annual*
	Year 2 Q 6 Months	Annual*

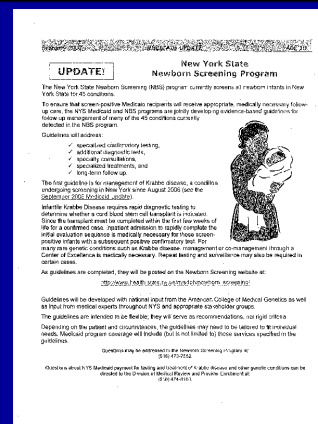
HANDOUTS FOR PARENTS

- **Symptom List**
 - **Early Infantile (1st visit)**
 - **Later Onset (12 month visit)**
- **Questions & Answers**

CRITERIA FOR UCB TRANSPLANTATION

Consider Transplantation for scores ≥ 4 Points

	<u>Points</u>
• Abnormal Neurologic Exam	2
• Abnormal MRI	2
• Abnormal LP (Increased Protein)	2
• Abnormal NCV	1
• Abnormal BAER	1
• Abnormal VER	1
• 30 KB Homozygous Deletion	4



THE CLINICAL DATABASE/REGISTRY FOR THE STUDY OF KRABBE DISEASE (STUDY PROTOCOL)

SPECIFIC AIMS

1. To develop a clinical database/registry for children identified with Krabbe disease on New York State's program of universal newborn screening.
2. To determine which neurodiagnostic tests, including results of mass spectrometry, molecular genetics, and levels of galactocerebrosidase activity predict outcome.
3. To modify mandated neurodiagnostic tests, where necessary, based on biannual review of testing results and correlation with clinical status.
4. To collect outcome data on children identified with Krabbe disease on newborn screening.

DEVELOPMENTAL/FUNCTIONAL OUTCOME STUDY

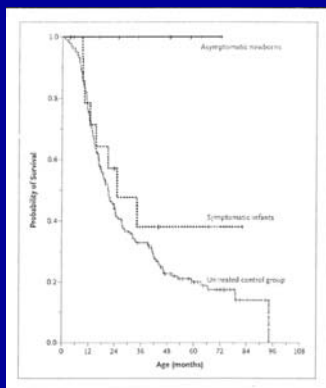
- **Phone Call Interviews: 4, 8, 12, 18, 24 mos**
 - **Ages and Stages Questionnaire**
 - **Wee FIM 0-3**
 - **Warner IDEA FS**
- **Early Intervention Referral PRN**
- **Comparison with annual Bayley III**

TREATMENT

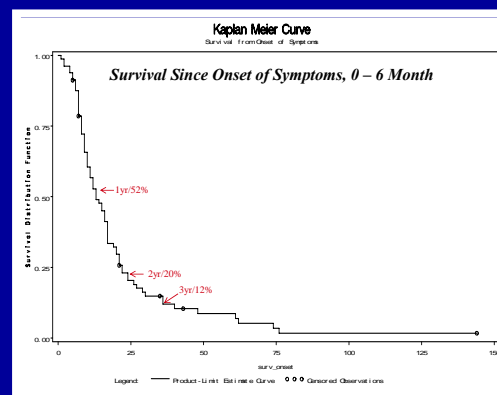
- Hematopoietic Cell Transplantation (HCT)

LONG TERM OUTCOMES

- Survival
- Neurologic Status



Escobar, NEJM, 2005

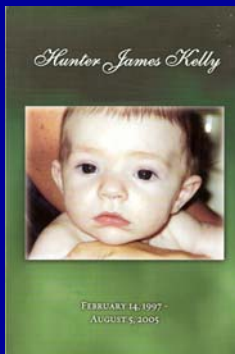


Duffner et al., Pediatric Neurology 2009;40:13-18.

Without transplantation all children with infantile Krabbe disease have severe neurologic dysfunction.

Majority of presymptomatic children following UCB transplant have significant motor and language deficits.

The Long Term Outcomes of Presymptomatic Infants Transplanted for Krabbe Disease



July 11 and 12, 2008
Ellicottville, New York

Sponsored by NINDS, ORD, and the Hunter's Hope Foundation

Special thanks to Dr. Danilo Tagle (NIH/NINDS), Dr. Rodney Howell (Child Health and Human Development/NIH), and Dr. James Evans (Genetics in Medicine)

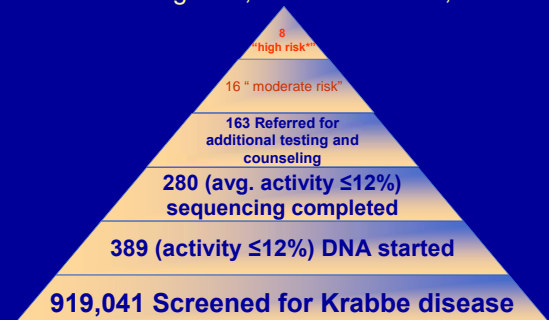


- HCT may improve survivals however numbers are small.
- HCT attenuates the course of EIKD, making it resemble the later onset phenotypes.
- Long term outcomes following HCT
 - Motor deficits secondary to ↑ spasticity (+/- progressive)
 - Somatic growth failure
 - Poor brain growth
- HCT is a treatment for Krabbe disease, not a cure.

POSSIBLE CAUSES OF NEUROLOGICAL DEFICITS

- ? Damage to oligodendroglia & myelin prior to engraftment
- ? Due to chemo neurotoxicity (busulfan)
- ? Due to disease progression

New York State Newborn Screening for Krabbe disease August 7, 2006 to Dec. 28, 2009



• Three newborns confirmed with infantile Krabbe, 2 transplants has been performed.
• High risk all with very low activity and 2 mutations detected in molecular workup

NYS EXPERIENCE (12/28/09)

- High Risk (8)
 - 2 transplanted
 - 1 death
 - 1 (30 Kb homo. del.)
 - Refused HCT
- Moderate Risk (16)
- Low Risk (54)

EXPECTED INCIDENCE
vs.
THE NYS "REALITY"

Published: 1/100,000 (9/900,000)
Reality: 78/919,041 (high, mod, low)
24/919,041 (high, mod)

Published: 90% EIKD
Reality: 3% EIKD (high, mod, low)
12.5% EIKD (high, mod)

AFTER 3 YEARS . . .

- *How can we better predict clinical course?*
- *Do low risk children have disease?*
- *Will all high and moderate risk children develop disease?*
- *Should we be testing older siblings?*
- *How can we improve outcomes of transplanted children?*

HCT in Neurometabolic Diseases

*Sponsored by HRSA (Maternal and Child Health Bureau)
and the Hunter's Hope Foundation*

*August 11 and 12, 2009
Beaver Hollow Conference Center
Java Center, New York*

*Session 1: Tuesday, August 11, 2009
HCT in Neurometabolic Diseases: How Do Results
Compare With Those of Krabbe Disease?*

*Session 2: Tuesday, August 11, 2009
HCT in Neurometabolic Diseases: Late Effects*

*Session 3: Wednesday, August 12, 2009
The Need for a Standardized Protocol for the Evaluation and
Long-term Follow-up of Children Transplanted for EIKD*

THE NYS MODEL

1. *Develop a multidisciplinary consortium of geneticists, child neurologists, neuroradiologists, newborn screeners, and biostatistician.*
2. *Establish a consensus protocol for the clinical and neurodiagnostic evaluation of infants with positive newborn screens for Krabbe disease*
3. *Hold biannual meetings of the consortium to review all test results and modify evaluations as deemed necessary by the group.*

THE NYS MODEL (continued)

4. *Develop criteria for transplantation*
5. *Develop and maintain a clinical database and registry with long-term follow-up (HJKRI).*
6. *Develop and conduct phone-based outcome study.*

Hunter James Kelly



FEBRUARY 14, 1997 -
AUGUST 5, 2005

*The Hunter James
Kelly Research Institute
is supported by the
University at Buffalo
School of Medicine, a
grant from HRSA
(Maternal and Child
Health Bureau), and
Hunter's Hope
Foundation*

Ethical Issues that have been raised by our group

- *Should mothers have the right to consent for newborn screening ?*
- *Should evaluation guidelines based on consensus of the consortium require an IRB submission and consent? (Is the evaluation process really research?)*
- *In view of the high morbidity, mortality, cost and relatively poor outcomes to date, is BMT ethical?*
- *Since treatment with BMT is ineffective once symptoms are present, should all children with very low GALC activity be transplanted?*
- *Is it ethical to screen for a disease like KD when we don't know for certain the significance of the "confirmatory" test's values, especially in the low risk group?*
- *Since transplantation for Later Onset KD can be helpful, do we refer all symptomatic children for immediate consideration of UBCT recognizing that some may have an indolent course over many years?*