

August 11, 2015

Krabbe disease was reviewed by the SACHD just over 5 years ago. The evidence review was released on 12/21/2009 (Knapp, Kemper and Perrin). Following an extensive review of the evidence prior to Mid 2009, the subsequent data is based on this summative report and review of the literature. Over 1,000 abstracts meet search criteria and were reviewed by the chair of the metabolic subcommittee (see attachment).

Summary of findings of the 2010 SACHDN and subsequent publications by WI criteria:

Criterion 1: Causes serious health risks in childhood that are unlikely to be detected or prevented in the absence of NBS.

Childhood onset Krabbe disease is estimated to account for 90% of symptomatically identified individuals with Krabbe disease. Most will present with progressive neurological symptoms before the age of 6 months. Symptomatic presentation was estimated prior to newborn screening to occur in 1/100,000 infants, data from New York and Missouri have suggested that the real incidence is closer to 1:400,000 (Turgeon, Orsini et al J Inherit Metab Dis. 2015 Mar 12). Without intervention individuals who present clinically with infantile Krabbe disease will die before the age of 6. There is clear data that proposed therapeutic intervention (HSCT) is not effective at the time that children are significantly symptomatic.

Criterion 2 information about the incidence, morbidity and mortality and the natural history of the disorder.

The natural history is well described for clinically identified individuals with Krabbe disease (Hunters Hope registry data, cited in (Knapp, Kemper and Perrin and in Duffner et al. 2009)

The original evidence review in 2009 concluded that there is poor genotype-phenotype correlation (Tatsumi et al. 1995) other than homozygosity of the 30-kb deletion, which is strongly predictive of EIKD. Low levels of galactocerebrosidase activity (Duffner et al. 2009) do not entirely predict the age of symptom onset or severity of white matter changes. Subsequent conclusions from the registry suggests "The later onset Krabbe phenotypes differ from those with early infantile disease, but no specific predictor of phenotype was identified." (Duffner, Barczykowski et al *Pediatr Neurol*. 2012 May;46(5):298-306.). Further the authors of the New York state program concluded: Higher galactocerebrosidase activity was predictive of later symptom onset times ( $P = 0.0011$ ), but did not predict survival after symptom onset ( $P = 0.9064$ ) when controlling for the logarithm of age at onset. (Jalal K, Carter R, Yan L, Barczykowski A, Duffner PK (*Pediatr Neurol*. 2012 Nov; 47(5):324-9.)

This has been confirmed by further studies (e.g. Fiumara, Barone et al *Clinical Genetics*. 80(5):452-8, 2011 Nov) with the authors concluding "No correlation was found between enzymatic activity, onset age and disease progression". That "current knowledge about onset age, residual enzyme activity and molecular analysis still fail to allow the identification of patient candidates for treatment".

Criterion 3: Conditions identified by NBS should be linked to interventions that have been shown in well-designed studies to be safe and effective in preventing serious health consequences.

As is typical of orphan diseases, there are no randomized controlled trials of therapeutic intervention. Instead studies for FDA approval have typically be based on a comparison of historical or registry controls versus an intervention group. Escolar et al. reported that early HSCT offers advantages. In that paper, the outcomes of 11 asymptomatic newborns and 14 symptomatic infants with Krabbe disease who received HSCT were compared. The survival rate was 100% among the asymptomatic newborns and 43% among the symptomatic infants. Although cognitive function and language skills continued to develop appropriately in patients who underwent HSCT before symptom onset, gross motor impairment was noted even in some of these patients. (Escolar ML, Poe MD, Provenzale JM, Richards KC, Allison J, Wood S, et al. Transplantation of umbilical-cord blood in babies with infantile Krabbe's disease. *New Eng J Med.* 2005;352: 2069–81). Subsequently a single case report from Japan has demonstrated a similar good outcome. (Yagasaki H, Kato M, Ishige M, Shichino H, Chin M, Mugishima H. (*Int J Hematol.* 2011 Apr;93(4):566-8). The long term data from the New York program has not demonstrated prevention of neurological problems. Duffner et al (P.K. Duffner, V.S. Caviness Jr., R.W. Erbe, M.C. Patterson, K.R. Schultz, D.A. Wenger, et al. The long-term outcomes of presymptomatic infants transplanted for Krabbe disease: report of the workshop held on July 11 and 12, 2008, Holiday Valley, New York *Genet Med*, 11 (2009))note: Although transplanted children are far better neurologically than they would have been had they followed the typical fulminant course of early infantile Krabbe disease, anecdotal reports have surfaced suggesting that the majority of presymptomatic children transplanted for Krabbe disease have developed motor and language deterioration. The workshop concludes all infants with presymptomatic Krabbe disease transplanted at Duke University to date have developed neurologic and other deficits, many of these severe.

The data from New York noted: Two children were subsequently diagnosed with Krabbe disease and underwent stem-cell transplantation, of whom one died from complications. (Kemper AR, Knapp AA, Green NS, Comeau AM, Metterville DR, Perrin JM. *Genet Med.* 2010 Sep;12(9):539-43)

Orchard and Tolar from the other key center performing transplants, summarized in 2010 (*Semin Hematol.* 2010 Jan;47(1):70-8):

“Krivit reported the results of allogeneic transplantation for five patients with globoid cell leukodystrophy in 1998.<sup>37</sup> Four of the patients had later-onset disease, while one had typical infantile globoid cell leukodystrophy. For the older patients, transplant appeared to stabilize, or even improve, their condition. The patient with infantile disease was transplanted at 2 months of age, and had a much different course than did a prior sibling who died of globoid cell leukodystrophy. There is now sufficient experience with transplantation of symptomatic patients with infantile disease to state that transplantation is not effective. In addressing this question, Escolar reported a means of clinically assessing patients with globoid cell leukodystrophy in the pretransplant period, and correlated these assessments to outcomes. (M.L. Escolar, M.D. Poe, H.R. Martin, J. Kurtzber A staging system for infantile Krabbe disease to predict outcome after unrelated umbilical cord blood transplantation *Pediatrics*, 118 (2006)) There has recently been great interest in the outcomes of patients predicted to have infantile globoid cell leukodystrophy if transplantation is performed in the neonatal period. Very young, as yet

asymptomatic, patients predicted to have a severe phenotype clearly have had a less severe clinical course than what would have been anticipated without transplantation. (Escobar ML, Poe MD, Provenzale JM, Richards KC, Allison J, Wood S, et al. Transplantation of umbilical-cord blood in babies with infantile Krabbe's disease. *New Eng J Med*. 2005;352: 2069–81) Newborn screening has been proposed as a means of identifying patients prior to the onset of symptom. However, the long-term outcome of patients with severe genotypes who are transplanted in the first weeks remains uncertain. (P.K. Duffner, V.S. Caviness Jr., R.W. Erbe, M.C. Patterson, K.R. Schultz, D.A. Wenger, et al. The long-term outcomes of presymptomatic infants transplanted for Krabbe disease: report of the workshop held on July 11 and 12, 2008, Holiday Valley, New York *Genet Med*, 11 (2009), Their significant motor limitations are likely at least in part to be due to peripheral nerve demyelination, as is observed in the twitcher mice, a model for globoid cell leukodystrophy. (A. Kondo, P.M. Hoogerbrugge, K. Suzuki, B.J. Poorthuis, D.W. Van Bekkum, K. Suzuki Pathology of the peripheral nerve in the twitcher mouse following bone marrow transplantation *Brain Res*, 460 (1988)) There has not been universal agreement in favor of neonatal testing for globoid cell leukodystrophy, although screening is currently done in New York and is likely to be in place soon in several other states. Due to the severe time limitations in attempting to transplant asymptomatic neonates, a large proportion of these infants will require cord blood grafts."

As Steiner (*Genetics in Medicine* (2009) 11, 411–413) noted, "At best, treatment is effective in preventing severe cognitive deterioration but progression of some aspects of the disease continues nonetheless in some patients; at worst, transplant is unproven and experimental"

Criterion 4: the interventions should be reasonably available to affected newborns.

HCST is considered experimental or unproven by some experts in the field and may therefore not be covered by insurance.

Criterion 5 Appropriate follow up should be available for newborns that have a false positive newborn screen.

The estimates for New York State suggest that the chances of having Krabbe disease with an abnormal enzyme test was between 5 and 8%. Although most symptomatic patients with the early infantile phenotype manifested abnormal cerebrospinal fluid protein, magnetic resonance imaging, brainstem evoked responses, and nerve conduction velocities, studies of affected children may be normal. (Duffner, Barczykowski et al *Pediatr Neurol*. 2011 Sep;45(3):141-8.). It is therefore challenging to exclude a diagnosis with an abnormal screen. Indeed 2 children with high risk enzyme levels were reported to be normal at 8 and 16 months of age (Steiner 2009)

Criterion 6: The characteristics of mandated tests in the newborn population should be known including specificity, sensitivity and predictive value.

In 2006, New York State began screening all newborns for Krabbe disease, and by 2008 roughly 550,000 newborns had been screened. Four newborns were placed in the high-risk category based on GALC activity below 0.15 nmol/h/mg; two of these newborns received a positive diagnosis based on subsequent mutation analysis and abnormal neurodiagnostic studies. The other two had negative neurodiagnostic studies and remained asymptomatic at follow-up at 8 and 16 mo of age. Six were placed in the moderate-risk category (GALC between 0.16–0.29 nmol/h/mg protein) and 15 were placed

in the low-risk category (0.3–0.5 nmol/h/mg protein). All moderate- and low-risk children were asymptomatic at follow-up. (Duffner PK, Caggana M, Orsini JJ, *Pediatr Neurol*. 2009;40:245–52) Presently, only subsequent follow-up will be able to determine whether these asymptomatic at-risk children will develop symptoms at a later date, whether they are carriers of the disease or whether they simply harbor non-pathogenic GALC-lowering polymorphisms. (Jalal K, Carter R, Yan L, Barczykowski A, Duffner PK (*Pediatr Neurol*. 2012 Nov; 47(5):324-9.)

All states currently screening or piloting screening use an enzymatic method as the initial step followed by molecular (DNA testing). As noted above the enzymatic testing has a very poor positive predictive value with 20 infants identified as positive for every one confirmed Krabbe case (detailed in SACHDN Evidence Review). More recent data has suggested a disease incidence of 1:400,000 with 1:6000 individuals having an abnormal screen and variants of uncertain significance in the gene (Turgeon, Orsini et al *J Inherit Metab Dis*. 2015 Mar 12). It is estimated that 10% of cases with abnormal screens will undergo extensive studies including brain MRI scans, lumbar puncture to obtain cerebrospinal fluid, painful nerve conduction velocities as well as brain stem auditory evoked potentials and visual evoked potentials (Turgeon 2015)

There have been several important papers demonstrating that there is no correlation between enzymatic activity and age of onset of disease and aside from the common deletion there is no concrete correlation between genotype and phenotype (Steiner 2009, Wenger 2011, Wenger, Luzi, Rafi *Mol Genet Metab*. 2014 Mar;111(3):307-8).

There are currently no plans to use DNA testing for the common deletion as a primary screen but this would have a significant false negative rate.

Evaluation of psychosine levels on dried blood spots is currently being considered. However, it is not feasible as a primary screen as it has a 17 minute run time (Turgeon, Orsini et al *J Inherit Metab Dis*. 2015 Mar 12). The sensitivity or specificity in the context of newborn screening has not been determined

The sensitivity and specificity of DNA sequencing in the context of newborn screening for Krabbe has not been published

Criterion 7: If a new sample collection system is needed to add a disorder, reliability and timeliness of sample collection must be demonstrated

N/A

Criterion 8: Before a test is added to the panel, the details of reporting, follow up, and management must be completely delineated, including development of standard instructions, identification of consultants, and identification of appropriate referral centers throughout the state/region

Parental brochures have been developed by Illinois and Missouri that will be modified if a decision is made to proceed. Consultants will be drawn from the metabolic consultants. Children will need to be referred to a center equipped with appropriate neurological services able to perform nerve conduction

velocities, to provide pretest counselling and preauthorization for molecular testing if not provided as part of the program and to be able to provide or refer for HCST.

Criterion 9: Recommendations and decisions should be include consideration of the costs of the screening test, confirmatory testing, accompanying treatment, counselling and the consequences of false positives. The mechanism of funding those costs should be identified. Expertise in economic factors should be available to those responsible for recommendations and decisions.

Screening test: The addition of Krabbe screening would require the addition of extra equipment and personnel to the state laboratory. The exact costs will depend on whether the state adopted the tandem mass spectrometry method used in Illinois and New York or the microfluidic solution. New York has published costs for first 3 years for the enzymatic testing of their program including approximately 750,000 infants at approximately \$3million. Scaling to Wisconsin with 70,000 births per year this would scale to a cost of \$300,000 per year or ~\$4 per screening card.

Confirmatory testing: Families will pay approximately \$3,000 for confirmatory molecular and enzymatic testing. One of the important discussions in Illinois has been the challenge of getting such testing covered as many insurance plans exclude DNA testing as a covered benefit (David Dimmock personal communication).

In addition approximately 10% of positive screens (about 10 per year in Wisconsin) will undergo serial nerve conduction studies, MRI scans, lumbar punctures and neurological examinations. These examinations will likely total over \$10,000 per series. This is likely to be covered by insurance

Treatment: The cost of a stem cell transplant and immunosuppression is estimated to be approximately \$1m. This may be covered by the patients insurance