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Invited Commentary

Newborn Screening for Krabbe Disease: the New York State Model

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In this issue, Duffner et al. [1] introduce a clinical protocol developed in response to the implementation of Krabbe disease newborn screening in the state of New York in 2006. The authors are to be commended for creating a comprehensive and, in part, evidence-based newborn screening follow-up protocol. The article describes a standardized clinical evaluation protocol for newborns screening positive for Krabbe disease, criteria for transplantation for the early infantile phenotype, the creation of a clinical research database and registry, and a short-term research study of developmental and functional outcomes. The article serves as an up-to-date review of clinical and diagnostic features of a poorly understood condition for which a great deal of recent interest has been generated.

The protocol for newborn screening follow-up for Krabbe disease will prove useful to those entrusted with caring for the children identified. No attempt will be made here to debate the merits of the specific recommendations for evaluation, because the protocol was developed by a multidisciplinary group of experts and there is essentially no evidence base available to justify changes. Fortunately, the protocol will undergo review and revision, as it will be used and re-evaluated regularly and undoubtedly modified as more is learned about Krabbe disease. The authors have responded admirably to the problem presented to them, namely mandated newborn screening for a potentially fatal disorder with a controversial treatment, extreme variability in disease expression with no foolproof way to predict phenotype, and a need for great haste in follow-up. Unfortunately, the article falls short in virtually ignoring the considerable challenges that have arisen with the Krabbe disease newborn screening program.

A great deal has been learned about Krabbe disease recently, no doubt in part as a result of successful efforts to focus attention on the disorder by a very effective high-profile patient advocacy group. The Hunter's Hope Foundation was established by Pro Football Hall of Fame member Jim Kelly and his wife, after their infant son was diagnosed with Krabbe disease. Krabbe disease is a lysosomal storage disorder caused by deficiency of galactocerebrosidase. It is a neurodegenerative condition, a leukodystrophy, with clinical manifestations ranging from an early infantile form with death typically by 4 years of age, to an adult form with few or no manifestations in childhood. Intermediate and even possibly asymptomatic forms exist as well.

Until recently, there was nothing to offer in the way of definitive treatment. Now, however, hematopoietic stem cell transplantation (HSCT) has been investigated as a potential therapy. This work, pioneered first at the University of Minnesota and more recently at Duke University, continues; however, this treatment brings forth a dilemma, in that HSCT is most effective if performed prior to symptom onset. Disease progression may be so rapid after symptom onset that the therapeutic window within which HSCT is effective closes rapidly. Development of tandem mass spectrometry for newborn screening made significant expansion of newborn screening programs possible, and laboratory techniques for lysosomal storage disorder screening including Krabbe disease were developed, allowing presymptomatic diagnosis.

Advocates for Krabbe disease newborn screening convinced the governor of the state of New York and others to implement newborn screening for Krabbe disease in 2006, making New York the first state to mandate screening for this disorder. The stated purpose for newborn screening for Krabbe disease was to allow early diagnosis of early infantile Krabbe disease to be followed by HSCT to prevent or ameliorate symptoms of this devastating condition.

Newborn screening for Krabbe disease is in its third year in New York, and the protocol described by Duffner et al. [1] adequately addresses some, but not all, of the challenges that have arisen with screening. One major challenge is in prediction of phenotype. Krabbe disease can be a devastating condition, but milder forms exist and it can be difficult

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even with state-of-the-art testing and imaging to differentiate later-onset forms from the early infantile form in screen-positive newborns. Neither enzyme activity nor knowledge of the precise mutation reliably predicts phenotype. Compounding these difficulties, there is a striking lack of evidence base, other than expert opinion, for some important decision points in the protocol related to phenotype prediction. Galactocerebrosidase activity of ≤0.15 nmol/h/mg protein in white blood cells was chosen as the cutoff for identification of infants as high risk—apparently based on a single laboratory's experience. As is true in general for lysosomal storage disorders, and as discussed by Wenger et al. [2], measurement of galactocerebrosidase activity in peripheral cells in vitro does not correlate well with phenotype; only 8% of screen-positive infants with confirmatory testing revealing enzyme activity of <0.5 nmol/h/mg protein (the cutoff for referral) have manifested the early infantile phenotype. This implies that the vast majority of infants with positive screens and confirmatory testing do not have the condition for which the newborn screening program was designed.

Another challenge overlooked in the article concerns treatment efficacy. A complex treatment protocol exists for Krabbe disease, namely umbilical cord blood stem cell transplantation for the early infantile form, but long-term efficacy has not been demonstrated. It is has become apparent that even successfully transplanted infants often show progressive deterioration in some areas. The original report of transplantation results that led some advocates for screening to conclude that treatment for Krabbe disease was available included 11 asymptomatic infants, with median follow-up of 3 years [3]. Unfortunately, there is not yet a follow-up to that 2005 article reporting more recent and long-term results, but the Krabbe disease review in the Web-based reference GeneReviews alludes to ongoing deterioration after transplant: ''Hematopoietic stem cell transplantation (HSCT) in presymptomatic infants . . . provides a benefit over symptomatic treatment only. Treated individuals show improved and preserved cognitive function; however, many show progressive deterioration of peripheral nervous system findings'' [4].

Umbilical cord blood stem cell transplantation is not a trivial procedure; the authors cite 10% mortality and significant morbidity. In actual practice, as of June 30, 2008, there have been 550,000 babies screened for Krabbe disease. Of 21 identified as moderate or low risk, none have developed symptoms. Of the four identified as high risk, one was transplanted and died, and another was transplanted and has no symptoms of early infantile Krabbe disease but is developmentally delayed; the other two remain normal (without transplant) at 8 and 16 months of age, ages at which they would be expected to have shown signs of Krabbe disease if they had the early infantile form.

These and other difficult issues that have arisen with implementation of the New York State Krabbe disease newborn screening program are only hinted at by Duffner et al. [1]. Newborns with biochemically proven Krabbe disease can indeed have the early infantile form, which is likely to be lethal if untreated in early infancy—but they can also go on to be asymptomatic for many years. Currently, it is impossible to differentiate one group from the other. The inability to predict the phenotype of screen-positive newborns, combined with the fact that the only treatment offered is very expensive and associated with high morbidity and mortality and in the face of unclear long-term efficacy, calls into question the wisdom of screening for this disorder.

Sadly, answers are not available for the most serious conundrums created by the Krabbe disease newborn screening program, only questions. How does the clinician tell which patients should be referred for consideration for transplant? 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.

Initially, the New York State program referred patients for transplantation to Duke University. Families had to travel to North Carolina and in some cases likely relocate there, at least temporarily. What is the burden to a family, already dealing with the recent discovery that their child has a devastating condition, to be uprooted and have to travel across the country for treatment that is unproven? The psychological burden notwithstanding, what are the financial burdens? Insurers are unlikely to pay for the full cost of transplant; insurers in the state of New York will not even pay for testing older siblings of those identified in the screening program to see if they are affected.

What is the burden to families who learn that their infant tests in the affected range, but who do not go to transplant immediately? Some of those newborns are destined to have later onset disease and develop symptoms at any time, including adulthood, whereas in rare cases others are probably destined to be asymptomatic. Currently, close monitoring is what is offered to families of infants who screen positive but do not clearly have the early infantile form of the disease. This involves frequent clinical examinations and testing; some of the tests are invasive, require anesthesia, are subject to difficulty in interpretation (especially given the young age group), and carry attendant risks for complications. Finally there is the problem of trying to synthesize the test results to allow some meaningful prediction of prognosis. Admittedly some of those newborns may go on to develop late-onset disease, which might be amenable to HSCT, so there is at least some chance that these newborns will benefit from screening. Still, it is unclear that the identification of these infants by screening is an improvement over clinical diagnosis.

With implementation of newborn screening for Krabbe disease, it seems as if the cart came before the horse. Screening was begun before there was sufficient knowledge about the diagnosis and natural history of the disease and its treatment. It is easy to understand how this happened, and everyone, especially those of us who have cared for affected infants, is sympathetic to the effort to develop newborn

screening. Krabbe disease is a devastating disorder, and there was hope that umbilical cord blood stem cell transplantation would be effective. Unless one has had a child die from a neurodegenerative disorder, it is difficult to fully comprehend the perspective of parents who have endured such a tragedy and want to prevent it from happening to others; newborn screening for Krabbe disease seems to offer that possibility. Nonetheless, clearly there are considerable risks with the current approach, ranging from the risk of harm to the family whose newborn screens positive but does not develop symptoms, to the risk of harm to the family whose newborn screens positive and who goes to transplant with an adverse outcome. Those risks should be weighed along with the potential benefits from such programs, in deciding whether to implement screening.

There are lessons to be learned from implementation of newborn screening for Krabbe disease. Newborn screening programs can be greatly enhanced by collaboration of multidisciplinary groups working toward a common goal, as was the case in the state of New York, where the authors came together to form the Krabbe Consortium. At the same time, it may be best to mandate newborn screening for disorders only after careful study and deliberation, to ensure the lowest risk and greatest potential for a favorable outcome.

The slow, deliberate, thoughtful approach to adding disorders to newborn screening panels may be distasteful to advocacy groups who see children continuing to suffer from these disorders during the process, but nevertheless, the end product of a carefully designed screening program with low risk for harm and high likelihood of success may justify the process. A multidisciplinary approach for developing newborn screening follow-up should also be used in evaluating whether conditions such as Krabbe disease should be added to newborn screening panels in the first place. The interested constituents who might come together to make these decisions would include disease advocacy groups, screening experts, scientists, and clinicians. Indeed, there is a process in place in the United States to allow nomination and review of disorders for addition to newborn screening programs [5]. Such a process cannot possibly preempt all of the challenges faced with a complex screening program such as the Krabbe disease program, but at least major issues such as treatment efficacy and phenotype prediction could be discussed in a public forum prior to implementation. In addition, pilot screening programs, research programs offering participation in screening only with informed consent, and the option to opt out of testing are alternative methods for introducing newborn screening on a limited basis to try to work out some of the difficulties prior to mandating screening for all newborns. There is much to be learned from close examination of the broader experience of implementation of Krabbe disease newborn screening with all the concomitant challenges.

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