Stem cell transplantation in Krabbe disease

New truths discovered and opinions change

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> …Institutions must go hand in hand with the progress of the human mind. As that becomes more developed, more enlightened, as new discoveries are made, new truths discovered and manners and opinions change, with the change of circumstances, institutions must advance also to keep pace with the times.
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> —Thomas Jefferson, July 12, 1816

Innovation and advancements in medical technology can lead to new treatments for human disorders and diseases. Evaluation of such therapies, especially the most expensive treatments for rare diseases, deserves ongoing research analysis for efficacy, safety, tolerability, permissibility, and cost-effectiveness in relation to long-term outcomes. Even after the standardization of treatments, economic and ethical dilemmas evolve with the acquisition of new data—and these dilemmas are particularly germane to many pediatric neurologic diseases.

A good example is Krabbe disease, or globoid cell leukodystrophy, a rare autosomal recessive disease caused by galactosylceramidase (*GALC*) gene mutation, galactocerebrosidase (GALC) enzyme deficiency, noxious galactosylsphingosine accumulation, and demyelination.[1] Clinical signs of severe progressive Krabbe disease begin in early infancy but milder phenotypes often develop later in childhood and adulthood due to milder *GALC* mutations, allelic heterogeneity, and variable penetrance—even among siblings.[2] Success in diminishing the mortality and morbidity of early-onset Krabbe disease depends on accurate presymptomatic diagnosis, attained through family history or carrier screening with prenatal diagnosis, or through newborn screening (NBS).[3,4] Currently, hematopoietic stem cell transplantation (HSCT) is the only available effective treatment for this leukodystrophy.

In this issue of *Neurology*®, Wright et al.[5] analyze long-term outcome in a group of 18 infants who received HSCT for early-onset Krabbe disease. Sixteen of these 18 infants received one type of HSCT, umbilical cord blood transplantation from unrelated donors after myeloablative chemotherapy; and 2 had bone marrow transplantation. These infants had neonatal diagnosis and deficient blood leukocyte GALC activities as well as baseline neuroimaging and neurologic examinations when they received HSCT before 7 weeks of age. Of the 15 children (83%) who survived the HSCT procedure, 1 had average cognitive abilities with mild motor impairment, 2 died of Krabbe disease or its secondary complications, 1 had profound disabilities, and the remaining 11 children had major motor impairments along with a range of sensory, language, and learning disabilities. Although the study analyzed various growth measures, neurologic biomarkers, and neurodevelopmental abilities, it did not evaluate parental perspectives or other qualitative dimensions of health-related quality of life.

The good news is that the results of this study confirm the improved survival and neurologic function in HSCT-treated infants with early-onset Krabbe disease. Escolar et al.[6] previously compared 11 of the 18 patients in this study to a group of HSCT-treated symptomatic infants up to 9 months of age and to a larger group of nontransplanted infants with Krabbe disease. GALC activities normalized in those patients whose posttransplant enzyme activity was measured. The collective evidence suggests that some presymptomatic HSCT-treated infants will live better lives into their teenage years—and the earlier the transplant is performed, the better the outcome will be.

The unwelcome news is that early HSCT for infancy-onset Krabbe disease often only delays disease progression and is not an effective cure. Most early HSCT-treated patients have substantial motor impairments with spasticity because of corticospinal tract pathology that may in fact begin prenatally.[4] In addition, many HSCT survivors have variable degrees of feeding, vision, hearing, language, and cognitive impairment.

Fifteen of the 18 patients in this study were identified prenatally because of family history, and only 3 infants were identified by state-mandated NBS. Since New York became the first state to initiate NBS for Krabbe disease in August 2006, only 5 out of approximately 2.4 million screened newborns have had infancy-onset high-risk Krabbe disease. Compared to the prenatally diagnosed Krabbe disease newborns, infants identified by NBS generally have longer delays until the HSCT procedure due to the additional time

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needed for confirmatory testing, parental counseling, and other factors such as insurance approval. This extended interval between NBS diagnosis and HSCT contributed to the negative correlation between older age at transplantation and better outcomes noted by Wright et al. These circumstantial delays pose challenges for the overall efficacy of NBS for Krabbe disease.

The developmental outcome findings in this study should help future parents, and state institutions, make difficult treatment decisions for their infants with Krabbe disease. For many parents, the hope that HSCT could help attain a better outcome will sway their natural inclinations to treat. Other parents may decide against HSCT following comprehensive and unbiased counseling, and after weighing its potential benefits with its risks and limitations. Similarly, many states may decide against NBS for Krabbe disease because of its expense and low benefit–risk ratio.[7]

Future improvements in the care of all patients with Krabbe disease are expected, including better diagnostic biomarkers, reduced-intensity chemotherapy in preparation for HSCT, substrate reduction therapies, antioxidant therapies such as N-acetylcysteine, the prospects of virus-mediated and neural stem cell gene therapies, and multimodality therapies.[8] New discoveries will be made, and with the change of circumstances, opinions may change with the times.

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