The Test of a Lifetime

Screening for rare genetic disorders can change lives. BY AMY PATUREL, M.S., M.P.H.

When Trevor and Tyler were born in November 2008, Nicole and Steve Aldrian had no reason to suspect anything was wrong with either of their twin sons. Trevor was the first to hold up his head and mimic Mommy’s voice. Soon, though, he began having trouble with feedings. By the time he was four months old, he was vomiting, fussy, and stiff.

“He screamed every time he saw the bottle,” says Nicole. Doctors attributed his symptoms to colic, indigestion, and acid reflux. Finally, at six months old, Trevor was diagnosed with Krabbe disease, one of a group of rare genetic disorders called lysosomal storage diseases; others include Pompe disease, Hunter syndrome, and Gaucher’s disease. They are the result of an enzyme deficiency that causes the buildup of unwanted material in the cell’s recycling center, called the lysosome.

Babies with Krabbe disease lack the enzyme galactocerebrosidase, which is needed to protect nerve fibers. Without a stem cell transplant during the first weeks of life, the infantile-onset form of Krabbe disease is fatal. Most infants who have it don’t survive to their second birthday. But the trajectory of these young lives could be dramatically different with a $1 test performed at birth.

NEWBORN SCREENING

Krabbe disease is extremely rare. The incidence of the infantile-onset form is 1 in 100,000. However, its also one of only a few hundred rare diseases with known treatments—not to mention a screening test that can potentially identify affected patients at birth.

When a baby is born, doctors prick his or her heel, taking a small amount of blood and dabbing it on a card. This dried blood spot is then sent to that state’s newborn screening lab. But unless parents request supplemental screening, the number of diseases a newborn is screened for depends entirely on where the baby was born. Some states test for as few as seven diseases; others, such as New York, test for more than 40, one of which is Krabbe disease.

The push for more widespread screening of rare diseases is largely the result of impassioned campaigns led by parents of affected children. Among the most notable advocates is Hall of Famer and former Buffalo Bills quarterback Jim Kelly, whose son died of complications from Krabbe disease at age seven. In 2006, Kelly successfully lobbied the New York State Department for the inclusion of the disease in its mandatory newborn screening program.

One of the problems with testing for rare diseases is that when a baby has a positive screen, a lack of consensus may exist about treatment. “A disease like Krabbe is associated with more than 140 genetic mutations,” says Patricia Duffner, M.D., prior clinical director of the Hunter James Kelly Research Institute, pediatric neurologist, founder of the World-Wide Krabbe Registry, and member of the American Academy of Neurology.

Another problem is the lack of standardization for enzyme testing. “It’s not like getting a blood test for anemia, where all labs measure the same way,” explains Dr. Duffner.

Some of the other lysosomal storage diseases are easier to diagnose. In Pompe disease, which affects 1 in 40,000 infants, a genetic mutation prevents the body from making the enzyme acid alpha-glucosidase (GAA). A baby either has a GAA deficiency or he doesn’t.

Take seven-year-old Haley Hayes, who showed signs of weakness in her first months of life. At six months old, she finally...
received a blood test that revealed a GAA deficiency. Without that critical enzyme, Haley's heart and muscle cells are unable to convert a form of sugar called glycogen into energy. As a result, glycogen accumulates in lysosomes, ultimately weakening her heart and skeletal muscles.

**NAVIGATING THE DIAGNOSTIC ODYSSEY**

By the time Haley received an official diagnosis of Pompe disease, it was too late to reverse the damage. She's not alone: many children with lysosomal storage diseases initially have vague symptoms that can be attributed to common ailments such as colic, allergies, and acid reflux.

In the case of Pompe disease, patients typically receive enzyme replacement therapy, which replaces the deficient GAA and reduces the accumulated glycogen in the heart and skeletal muscle cells. Early diagnosis is critical. Without this life-saving treatment, the infantile-onset form of the disease leads to almost certain death during the first year of life.

“Two months before Haley was diagnosed, the only treatment for Pompe disease (brand name Myozyme; generic name alglucosidase alfa) had just been approved by the U.S. Food and Drug Administration (FDA). Our doctor had only seen one other patient with the disease,” says her mom Krystal. She transferred her daughter to Duke University, where the treatment was developed.

Now seven, Haley still can’t walk, skip, or jump. “Instead, she scoots across the room when she wants something,” says Krystal, a labor and delivery nurse in Richmond, VA.

“Even one extra day without a diagnosis can sometimes mean the difference between a child being able to walk versus one who is in a wheelchair, or one who can breathe on his own versus one who is dependent on a ventilator,” says Priya Kishnani, M.D., Sue Chen professor of pediatrics and division chief of Medical Genetics at Duke University.

Infants with Krabbe disease also present with symptoms that mimic other medical conditions, such as colic, acid reflux, and static encephalopathy, which is brain damage caused, for example, by fetal alcohol syndrome. “Kids are irritable, weak, and may have difficulty gaining weight, so their parents embark on a diagnostic odyssey, visiting specialists in every facet of medicine until someone finally comes back with a diagnosis,” Dr. Duffner says.

Some research suggests that a stem cell transplant shortly after birth may slow the progression of infantile-onset Krabbe disease. Currently, the best treatment seems to be umbilical cord blood stem cells from an unrelated donor, although bone marrow transplantation may benefit mild cases early in the course of the disease. (See box, “Cord Blood Transplant: What’s Involved.”) Unfortunately, treatment is only successful when performed before symptoms appear, a virtual impossibility without newborn screening or prenatal diagnosis. Trevor missed the window of opportunity for a transplant because he was born in California, not New York.

**POST-SCREEN PROTOCOL**

Faced with a diagnosis of a rare congenital disease, families often don’t know how to proceed. Doctors, too, may have more questions than answers.

“Within five minutes of finding out I had breast cancer earlier this year, I had people calling me with referrals, advice, and support,” says Nicole. “When we found out Trevor had Krabbe disease, the doctor said, ‘I’m sorry to tell you that most children with this disease die before their second birthday.’ Then, it was silence.”

In New York, they’re just beginning to develop a way to clearly identify the infantile-onset form of Krabbe disease. The key: a point system that researchers use to determine whether children with a positive screen should consider a stem cell transplant.

“If a baby has at least four points, the parents are counseled for transplant,” explains Dr. Duffner. “A positive magnetic reso-
NORMAL START  Trevor and Tyler at 10-days old; Trevor doing well at two months; the brothers today; mother Nicole taking care of Trevor.

Despite the potential drawbacks, parents seem to want more information. One of the key findings from pilot screening projects in Taiwan and Italy is that, when given the option, more than 98 percent of parents elect to move forward with testing. Studies like these have helped nudge Pompe disease into the realm of universal newborn screening. On May 17, 2013, the Secretary’s Discretionary Committee on Heritable Diseases in Newborns and Children approved a recommendation to the Health and Human Services Secretary to add it to the Recommended Uniform Screening Panel.

NO PERFECT TREATMENT

In the event of a positive screen for Krabbe disease, parents have to decide within 24 hours whether they are going to move forward with a stem cell transplant. Without long-term data on the outcomes for these kids, that decision can be very difficult, although the procedure has become safer.

“Ten years ago, three out of 10 kids would die from the procedure,” says Maria Escolar, M.D., director of the Program for the Study of Neurodevelopment in Rare Disorders and associate professor of pediatrics at the University of Pittsburgh School of Medicine. “Over the past two decades, the risk of dying from the procedure has decreased dramatically when performed by an experienced team of professionals.”

With a successful transplant, some children with Krabbe disease may go on to lead full lives, but the window of opportunity for a patient to get a transplant is so small that most patients can’t take advantage of the treatment.

With private insurance and Medi-Cal (California’s Medicaid health care program), the Aldrians have been able to secure around-the-clock care for Trevor, who at four and a half years old isn’t able to walk, talk, sit up, or eat on his own.

Even with Pompe disease, which has a standardized treatment protocol of enzyme replacement therapy, questions remain about the long-term effects and viability of treatment.

On the one hand, in a study that included the largest group of patients with infantile-onset Pompe disease treated with enzyme replacement therapy, alglucosidase alfa extended the amount of time patients could breathe on their own—and how long they survived—compared to an untreated control population. By the age of 18 months, 98 percent of babies in the untreated control group had died. In contrast, all patients treated with alglucosidase alfa were alive at 18 months.

Based on the results from several states with newborn screening for Pompe disease, early initiation of enzyme replacement therapy has dramatically improved the outcome of the disease. Many of these children reach normal motor developmental milestones.

On the other hand, the treatment isn’t problem-free. “Since these babies are born without the GAA enzyme, when they get exposed to it through enzyme replacement therapy, their bodies recognize it as a foreign substance and begin producing antibodies, which neutralize the effect of the enzyme,” explains Dr. Escolar. “So they have to be on the therapy for their entire life, and lifelong enzyme therapy comes with significant physical, emotional, and financial costs.”

At just seven years old, Haley already sacrifices one day of school every week for the six-hour infusion. “Our day at Duke is usually from 8 a.m. to 5 p.m. because Haley (like most children being treated for Pompe disease) also receives physical, occupational, and speech therapy,” says Krystal.

Dr. Kishnani’s oldest surviving patient who has been treated with enzyme replacement therapy for infantile-onset Pompe dis-
“Even **one extra day** without a diagnosis can sometimes mean the difference between a child being able to walk versus one who is in a wheelchair, or one who can breathe on his own versus one who is ventilator-dependent.”

—PRIYA KISHNANI, M.D.

The Status of Newborn Screening

The availability of effective treatments for certain rare diseases has prompted scientists to develop reliable newborn screening methods. Several small pilot projects are in the works, but whole-population newborn screening for lysosomal storage diseases is still in its infancy.

**T**

he availability of effective treatments for certain rare diseases has prompted scientists to develop reliable newborn screening methods. Several small pilot projects are in the works, but whole-population newborn screening for lysosomal storage diseases is still in its infancy.

Due to recent technological advances, Michael Gelb, Ph.D., of the University of Washington, has been able to develop a newborn screening assay that detects six lysosomal storage diseases—Gaucher’s, Krabbe, Pompe, Niemann-Pick, Fabry’s, and Hurler’s—all with a single blood spot.

“We had to create a screening protocol that would work on hundreds of samples every day in the hands of non-experts,” says Dr. Gelb. “It can’t just work well once in a while on a good day.”

Not only have Dr. Gelb and his team been able to develop that reliable test, but the cost of screening is also shockingly low—about $1 to $2 per disease. Since 2009, Dr. Gelb’s supplemental newborn screening assay for Krabbe disease has been available through New York State’s Newborn Screening Lab, and his assay for Krabbe, Pompe, Gaucher’s, Fabry’s, and Hurler’s has been available through PerkinElmer Genetics Lysosomal Storage Diseases Supplemental Newborn Screening Packet.

With the simplicity of testing, Dr. Gelb believes having newborns screened is a no-brainer. “I believe in science, and the science shows that the earlier you catch these diseases, the more treatable they are,” says Dr. Gelb. “If I were a parent to a newborn, I would have the screening done, no question.”

To learn what your state’s routine newborn screening covers, visit savebabies.org or call 888-454-3383. If your state screens for less than 50 disorders, supplemental newborn screening is an option. Visit perkinelmergenetics.com.

For more information on newborn screening, see Resource Central on page 35.