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Perils of Newborn Screening

Doctors may be testing infants for too many diseases

The first symptoms often appear a month or two after birth. The babies' muscles stiffen. They lose their hearing and vision, stop sleeping and scream in pain. Some develop seizures. By the time many parents learn that their children have Krabbe disease—a rare genetic disorder that degrades nerve cells—it is too late for the only viable treatment, a transfusion of umbilical cord blood stem cells from healthy donors. Children with full-blown Krabbe who do not receive medical treatment, as well as many who do get treated, usually die by age two.

In some cases, doctors can prevent this grim outcome by screening infants at birth for genetic harbingers of disease. Right now such tests are mandatory in only a few states—something that many parents want to change. “If we don’t screen for this disease at birth, those children will never have a chance at life,” says Jacque Waggoner, CEO of Hunter’s Hope Foundation, one of several advocacy groups lobbying state politicians to add mandatory tests for Krabbe and other rare diseases. The politicians are starting to listen. In the past year four states have passed legislation that requires hospitals to check newborns for abnormal enzyme levels linked to as many as seven new diseases.

Within the medical community, however, doctors are debating the rapid expansion of screening programs. As a whole, the programs have saved many lives. But some experts worry that states may be aggressively demanding tests for diseases that do not always develop in those who show signs of risk or cannot be safely or effectively treated even when they are caught. Doctors who have recently started screening for Krabbe and similar rare diseases are swiftly realizing that, in many cases, the results of such mandatory tests unnecessarily frighten parents and fail to help the children the tests were designed to save.

THE BIRTH OF NEWBORN SCREENING

THE CURRENT DEBATE has origins in the earliest forms of newborn screening. By the early 1960s microbiologist Robert Guthrie had perfected a test for phenylketonuria (PKU) that simply required a drop of blood from a baby’s heel. Children with PKU suffer brain damage and seizures because they cannot break down the amino acid phenylalanine, which is found in high-protein foods.

Although most states adopted the procedure, a few doctors worried that some babies who did not have PKU would test positive and suffer malnourishment as a consequence of a low-protein diet. Ultimately the doctors’ fears proved unfounded. (In a 2006 review of the medical literature on PKU, Jeffrey Brosco and his colleagues at the University of Miami found “no published cases of children who suffered permanent harm after an erroneous [newborn screening] test and treatment for a condition they



HARD TO HEAL: Screening infants’ blood for signs of disease may not make sense if effective treatment does not exist.

did not have.”) States soon began using similar tests to screen for the likelihood of developing other easily treatable diseases, including congenital hypothyroidism and sickle cell disease.

Today all states require newborn screening for between 28 and 57 medical disorders. Overall, these mandatory programs mark “one of the most significant advances ever in public health,” says Stuart Shapira, a medical geneticist at the Centers for Disease Control and Prevention. Of the four million babies born in the U.S. every year, newborn screening identifies 12,500 with medical disorders. Catching and treating many of these disorders early, Shapira says, can prevent intellectual and developmental disabilities, organ damage and death.

Recently, however, doctors have raised new concerns, this time about the repercussions of widespread newborn screening. By the 1990s a tool known as tandem mass spectrometry had drastically expanded the number of disorders laboratory technicians could detect with a single drop of blood—from one to as

many as 20. A mass spectrometer sorts and counts variously sized molecules in the blood, somewhat like a change machine sorts coins. Unusually high levels of certain molecules indicate the enzymes that normally break down these molecules are missing or deficient, which in turn suggests a genetic disorder.

Before 1995 no U.S. state had screened babies for more than eight disorders. A decade later some states were screening for anywhere from seven to 52. States lacked clear consensus on which disorders warranted mandatory screening, says Michael Watson, executive director of the American College of Medical Genetics and Genomics. To remedy the situation, the Health Resources and Services Administration commissioned Watson to review the scientific literature on 84 disorders and to determine which of the screens clearly benefited newborns.

In a report made in 2005 Watson recommended that all states screen for 29 disorders that doctors could clearly predict and treat. He further advised against screening for Krabbe and other diseases because there was not enough evidence that early intervention did more good than harm. Most states currently screen for all 29 recommended disorders, but some, like New York, also test for Krabbe or other conditions outside the uniform panel—including Pompe (a muscle-weakening disease) and Fabry (a metabolic disease causing severe pain). The outcomes of New York's decision to screen for Krabbe underscore why some doctors believe that enthusiasm for screening has gone too far.

PREMATURE ENTHUSIASM

SINCE ITS INCEPTION in 2006 New York's program has tested one million babies and identified more than 200 infants with unusually low levels of some enzymes, indicating risk for Krabbe. Lab technicians verify these results with both enzyme and genetic tests. What investigators have found has been surprising.

Of the 228 infants who tested positive for Krabbe, 24 were found to have genetic markers associated with the disease. So far, however, only four of those children have developed Krabbe symptoms, whereas the other 20 continue to appear healthy. In the vast majority of cases, symptoms of Krabbe appear in early infancy and quickly worsen. A few reports in patient registries describe infants who developed symptoms—albeit mild ones—later in life. The 20 New York infants who screened positive for genetic markers of Krabbe but have not yet shown symptoms may have this late-onset form of Krabbe.

When Should Doctors Screen?

According to guidelines proposed by the World Health Organization in 1968, doctors should screen for a medical condition only if:

- ✓ **The condition is an important health problem.**
- ✓ **Doctors can effectively treat the condition.**
- ✓ **Patients have access to diagnostic services and treatment.**
- ✓ **Doctors can recognize a latent stage and early symptoms.**
- ✓ **Doctors have devised an accurate test for the condition.**
- ✓ **The general population understands the rationale behind such tests.**
- ✓ **Doctors understand how the disease develops.**
- ✓ **Doctors agree on which patients should be treated.**
- ✓ **Screening is affordable.**
- ✓ **Doctors plan to continue screening new generations of children.**

But researchers do not understand late-onset Krabbe well enough to know when, if ever, any of these children will develop symptoms. Only when clinicians detect nerve damage in a battery of invasive neurological exams, including brain imaging and a spinal tap, can they be sure that a child has Krabbe. And only then are they certain that treatment justifies its inherent risks. Studies have shown that early stem cell transplants sometimes stop the disease from progressing, although around 30 percent of children do not survive the procedure and all who do still have trouble speaking and moving their limbs.

Many of the 20 children whose tests suggest late-onset Krabbe but who are not yet sick continue to get neurological exams about every four to six months. Some researchers call these children “patients in waiting.” As Jennifer Kwon, a neurologist at University of Rochester Medical Center, puts it, “There’s this whole group of children nobody expected to find.” The problem, Kwon says, is that parents of patients in waiting do not know what to do with the information they receive from doctors or even what to expect. Parents begin to worry excessively, become overprotective, pursue risky tests and procedures, and avoid routine ones. “It’s a huge burden for parents to carry around this knowledge that many of them didn’t ask for,” agrees Melissa Wasserstein, a pediatrician at Mount Sinai Hospital. “Every time their child so much as trips and falls, they’re thinking, ‘Oh, my God, does this mean the start?’”

Patricia K. Duffner, who directs the research arm of Hunter’s Hope at the University of Buffalo, counters that many parents prefer to know about their child’s risk because, if symptoms appear, they will not lose time searching for a diagnosis.

Other experts argue that forcing parents to participate in a public health program when the benefits of screening may not outweigh the emotional trauma is unfair. “So far what’s come out of the Krabbe program is we’ve done a lot of screening, we’ve scared a lot of parents and we haven’t truly helped a kid,” says Lainie Friedman Ross, an ethicist and pediatrician at the University of Chicago. According to the doctors who cared for the four New York infants with early-onset Krabbe, one family refused a transplant and the baby died; a second baby died from complications of a transplant; and a third child’s affliction continues to progress despite a successful transplant. Only one baby has clearly benefited from screening. At three years, though, he is the size of a one-year-old and recently lost his ability to walk.

Ross fears that newborn screening is destined for another rapid, premature expansion as genome-sequencing technologies become inexpensive enough to use routinely. “With these new test platforms, there is the potential to test for hundreds of conditions we don’t fully understand,” she says. “If adults can refuse these tests, why should we force them on children?”

Jeff Botkin, a medical ethicist at the University of Utah School of Medicine, has similar concerns. “I think people sometimes forget that we’re talking about the state mandating these tests. That’s a big deal. If we’re going to say to parents, ‘You don’t have a choice,’ there ought to be clear justification for doing a test. We shouldn’t just add these things because we can.” ■

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