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State, Federal Efforts Under Way to Identify Children With “Bubble Boy Syndrome”

Bridget M. Kuehn

THE STORY OF DAVID VETTER, A BOY with severe combined immunodeficiency (SCID) who lived in a protective bubble from his birth in 1971 until his death in 1984, captured the public's attention decades ago. Therapies developed since then can often improve or restore immune function, enabling children with SCID to lead relatively normal lives. Yet many children with the disorder are not identified quickly enough to receive such lifesaving treatment.

But state and national efforts are under way to change this pattern. In May, Kathleen Sebelius, Secretary of the Department of Health and Human Services (DHHS), included SCID in a panel of 30 genetic disorders for which the department recommends states screen all infants at birth. The recommendation may prompt more states to join Wisconsin, Massachusetts, and California in screening newborns for the disorder. Wisconsin's screening program, which began in 2008, has identified a child with SCID and several others with related immune deficiencies.

The addition of SCID to the screening panel is the latest step toward developing a more consistent system of newborn screening across the country. States are responsible for establishing newborn screening programs, and there has long been considerable variation among states. In 2001, the Health Resources and Services Administration Maternal and Child Health Bureau commissioned the American College of Medical Genetics (ACMG) to create a standardized panel of newborn screening tests based on evi-

dence available for each disease. The ACMG recommended 29 conditions for inclusion on the panel. In 2005, this panel was endorsed by the Advisory Committee on Heritable Disorders in Newborns and Children, a group that

that although the panel has become universally accepted, some states have encountered technical issues that have prevented them from implementing screening for certain conditions.

EARLY THERAPY CRUCIAL

In February, the DHHS Secretary's Advisory Committee on Heritable Disorders in Newborns and Children recommended that SCID be added to the panel, based on a standardized evaluation procedure (<http://www.hrsa.gov/heritabledisorderscommittee/correspondence/feb2010letter.htm>). The procedure takes into account such factors as whether the condition is readily recognizable by physical examination, whether early intervention offers better clinical outcomes, and whether a reliable test exists. SCID is the first of 9 disorders that have been considered by the committee to be added to the panel.

Children with SCID may have any of several gene defects that impair the action of T cells and B cells, which are vital to fighting infection. Without such protection, they are so vulnerable to infection that they may develop opportunistic infections such as pneumocystosis or may develop diarrhea after vaccination with the rotavirus vaccine, which is now contraindicated for these children (Centers for Disease Control and Prevention. *MMWR Morb Mortal Wkly Rep.* 2010;59[22]:687-688). Jennifer Puck, MD, professor of pediatrics at the University of California, San Francisco (UCSF), and senior immunologist at the UCSF Benioff Children's Hospital, explained that about 20% of cases occur in children who have a family history of the disorder,



A test for severe combined immunodeficiency has been added to a recommended panel of newborn screening tests for genetic disorders. The tests use a blood spot collected at birth.

advises the secretary of DHHS. At that time, only 38% of babies were born in states that tested for at least 21 of the conditions, according to the March of Dimes.

To help promote wider adoption of the panel, the March of Dimes has run state-by-state advocacy campaigns. The emergence of tandem mass spectrometry machines, which make it possible to test for many diseases at a reasonable cost, has also aided an expansion in screening. Now 42 states and the District of Columbia screen for all 29 conditions, and every state screens for at least 26, said Alan R. Fleischman, MD, senior vice president and medical director of the March of Dimes in White Plains, NY. Fleischman explained



which often leads to earlier identification. However, the other 80% of cases are sporadic and may not be identified until severe complications develop.

"They collect infections and never really get over anything," Puck said. "These infections may be fatal even before physicians think about the possibility of an immune disorder."

Even when a diagnosis is made based on infections and immune abnormalities, it may come too late. A recent case study described a 4-month-old girl who developed a mouth ulcer, fevers, recurrent ear infections, weight loss, a respiratory illness, and persistent lymphopenia (Adeli MM and Buckley RH. *Pediatrics*. 2010;126[2]:e465-e469). She was ultimately diagnosed with SCID by a specialist; however, she died after developing parainfluenza 3 and adenovirus before she could receive a bone marrow transplant.

Such transplantation can reconstitute the immune system of a child with SCID, but success rates are highest with the youngest recipients. A long-term follow-up study on a cohort of 161 patients with SCID who received bone marrow transplants at Duke University Medical Center in Durham, NC, found an overall survival rate of 77% (Railey MD et al. *J Pediatr*. 2009;155[6]:834-840). The survival rate for the 48 infants transplanted before 3.5 months of age was 94% compared with a survival rate of 70% among the 113 who received a transplant at an older age.

Gene therapy is also a proven treatment for a subset of patients with SCID who have an adenosine deaminase deficiency, Puck noted. One study looked at 10 children with this deficiency who had not responded to other therapies. These children received therapy to replace the *ADA* gene via an infusion of the child's bone marrow that had been treated with a retroviral vector containing the *ADA* gene. The treatment improved the children's immune function and quality of life (Aiuti A et al. *N Engl J Med*. 2009;360[5]:447-458).

However, gene therapy for other types of SCID remains experimental, Puck said. For example, a follow-up

study of 9 patients with X-linked SCID, which involves the absence of the cytokine receptor common γ chain, identified serious adverse events after gene therapy to correct this immune problem (Hacein-Bey-Abina S et al. *N Engl J Med*. 2010;363[4]:355-364). According to the authors, the therapy initially corrected the immune systems of 8 of the children. However, 4 of the 9 developed leukemia, and one died. Three patients survived leukemia and 4 others had sustained immune reconstitution. Puck noted that more recent trials of gene therapy for SCID have used safer vectors.

SCREENING SUCCESS

The development of a high-throughput test for SCID in 2007 also made SCID screening feasible. In 2005, Puck and her colleagues at UCSF determined that polymerase chain reaction assays could be used to detect T-cell receptor excision circles (TRECs), small bits of DNA that form during the development of T cells, in dried blood spots taken from newborns at birth (Chan K and Puck JM. *J Allergy Clin Immunol*. 2005;115[2]:391-398). They found that the number of these TRECs could be used as a surrogate to measure the number of T cells and that the test could identify infants with SCID, who have very few TRECs or none at all.

Based on this idea, Wisconsin and Massachusetts developed high-throughput versions of the test and began using them to screen for SCID and related disorders. Wisconsin has demonstrated that its test can be effectively used by a state newborn screening program to identify children with severe T-cell-related immune deficiencies (Routes JM et al. *JAMA*. 2009;302[22]:2465-2470). In the first year of such screening, 71 000 infants in Wisconsin were tested; 17 had at least one abnormal result, and 8 were found to have T-cell lymphopenia. None of the infants had SCID specifically, but rather had related immune deficiencies, including 2 with DiGeorge syndrome and one who had a mutation in the *Rac2*

gene and was successfully treated with a cord blood transplant.

To date, Wisconsin has screened more than 200 000 infants, and identified one infant with SCID and several others with related immune deficiencies, according to Charles D. Brokopp, DrPH, director of the Wisconsin State Laboratory of Hygiene in Madison. Some of the children have undergone successful bone marrow transplants, Brokopp confirmed.

Brokopp said the testing is also cost-effective. The tests cost about \$5 to \$6 per infant, or about \$400 000 per year, in Wisconsin. Based on data collected by the Children's Hospital of Wisconsin, in Milwaukee, the medical costs of care for a child with SCID who is not identified at birth is about \$2 million compared with about \$250 000 to \$300 000 for a child who is identified early and undergoes a transplant. Based on these estimates, Brokopp noted that early identification and treatment of a single child with SCID could more than pay for screening for the whole state.

However, there are up-front costs for states that wish to begin testing for SCID. Because the test is the first newborn screening test to rely on a molecular assay, Fleischman explained, state screening laboratories must purchase new equipment and train staff to use it, and may even have to hire additional staff. To overcome these challenges, some states are considering creating regional centers to conduct the testing. Louisiana is planning to have the Wisconsin State Laboratory of Hygiene test its samples, Brokopp said.

"The people who run these programs are anxious to comply [with the DHHS recommendation]," Fleischman said. "But they are developing these plans in an environment of tight state budgets and need the support of the public."

As testing becomes more widespread, it may provide a clearer picture of the incidence of SCID—estimated to be between 1 in 50 000 births to 1 in 100 000 births—and related disorders. Puck explained that 50 to 100 cases are identified in the United States each year,



but that an unknown number of children with SCID may die from infections without being diagnosed.

The screening results will also facilitate study of these immune conditions and how best to treat them. Puck noted that the National Institute of Allergy and

Infectious Diseases and the National Institutes of Health's Office of Rare Diseases have established a network of centers that study rare immune deficiencies. She said the consortium's work should allow clinicians to determine which treatments are best for patients

based on the gene variants underlying the condition. Additionally, these efforts may lead to new insights about which genes and pathways are crucial for proper immune function.

"It will show us the nonredundant pathways in immunity," she said. □

Oversight of Fast-Track Drug Approval by FDA Stuck in Low Gear, Critics Say

Mike Mitka

SINCE 1992, THE US FOOD AND Drug Administration (FDA) has offered an accelerated approval process designed to make available new drugs to treat dire conditions that lack alternative therapies. To achieve speed, the FDA allows approval based on a lower standard than required for the regular approval process. That laxity in initial oversight is supposed to be followed by rigorous postmarketing studies that validate the efficacy and safety of the drug.

But the system does not always work as planned. A company with a product that was approved this way and that is already generating revenue has little incentive to conduct a postmarketing

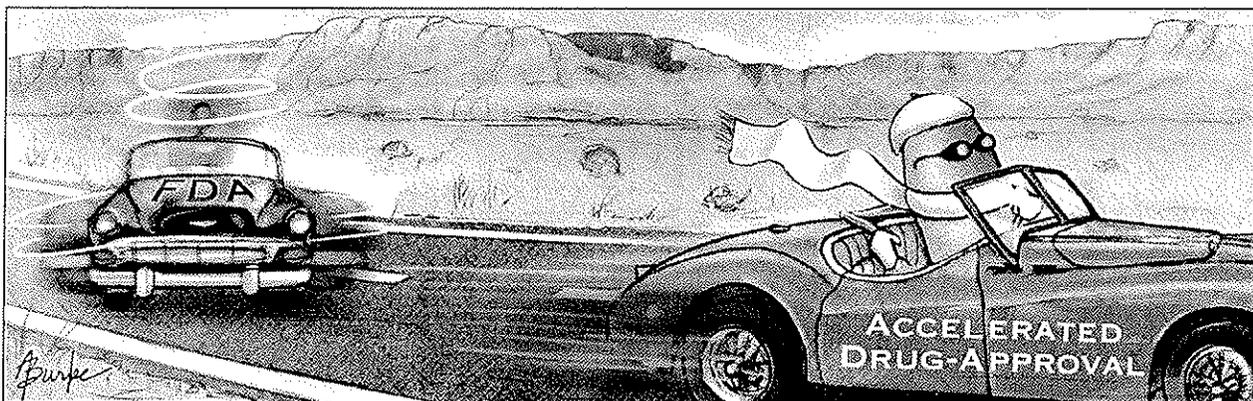
study that may or may not validate the drug. And even if a company cannot produce a postmarketing trial showing efficacy, the FDA will still have a hard time removing a drug from the market, as patients, who may believe the drug is helping them, make their worries known to the agency, the media, and elected officials.

The case of one such drug, midodrine hydrochloride, exemplifies this conundrum. Midodrine was granted accelerated approval in 1996 to treat orthostatic hypotension, a condition marked by a drop in blood pressure that causes dizziness or fainting when a person stands. To date, no postmarketing study showing the drug's efficacy has been accepted by the FDA. On August 12, the FDA announced that it had begun a process that could ul-

timately lead to midodrine becoming the first drug removed from the market because of the manufacturer's inability to produce rigorous postmarketing data confirming efficacy (<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm222580.htm>).

The FDA's announcement prompted an immediate outpouring of concern and worry from some of the 100 000 patients already taking the medication or its generic equivalents. In press accounts, these patients, and some of their physicians, said the drug was the only therapy that allowed them to overcome the effects of orthostatic hypotension and live normal lives.

This public concern prompted the FDA to clarify its decision, and in a September 10 update, the agency ex-



Some charge that officials with the US Food and Drug Administration are too lenient in requiring the proper rigorous follow-up studies needed to confirm the efficacy and safety of pharmaceuticals entering the market through the accelerated approval process.