New treatment cures baby of often-fatal metabolic disorder

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Shou Yang (left) dotes on her baby, Dean Thao, in March after his liver transplant. The operation was the final step in a first-of-its-kind treatment for a rare metabolic disorder that was pioneered at Packard Children's.

(PhysOrg.com) -- Physicians at Packard Children's Hospital believe they are the first to cure an infant of a serious disorder using prenatal infusions followed by liver transplant after his birth.

As he was being born at Lucile Packard Children's Hospital, Dean Thao received infusions of a medication — never before given prenatally — for a rare metabolic defect that usually causes permanent brain damage, and often death. Thanks to medical geneticists at the hospital who identified the defect at 34 weeks gestation, the doctors were prepared to begin treatment when Dean's mother went into labor and continued to

guard and treat his condition over the next three months until, on March 8, he got a new liver.

Now, baby Dean is believed to be the first case of ornithine transcarbamylase deficiency to be cured with this novel one-two punch of an approach to treatment.

Replacing Dean's liver is a perfect example of "gene therapy with a scalpel," said Gregory Enns, MB, ChB, director of Packard Children's biochemical genetics program. "Our job was to keep his brain as safe as possible — through labor, to birth and then to transplant — so that he'd have the best chance of a good outcome."

Ornithine transcarbamylase, or OTC, deficiency is a genetic disorder that appears in one in 40,000 births. Because of a genetic defect, the body's metabolic machinery is jammed, with the liver failing to function properly. The result can be sudden spikes of ammonia, from normally small amounts naturally occurring in the body to levels that are toxic. Although the disease has its primary metabolic effect in the liver, it is the brain that bears the brunt of OTC deficiency.

Doctors have rescued children with OTC deficiency and other metabolic disorders before by using specialized medication infusions, intensive nutritional support and liver transplantation. Indeed, Enns, who is also associate professor of pediatrics at the medical school, has worked with Packard Children's liver transplant team to treat eight children with OTC deficiency.

But often by the time Enns and others intervened after birth, the children's brains had suffered damage. More than half of kids surviving OTC-deficiency crises have brain damage, and about 80 percent have developmental issues. "The neurological outcome is typically poor," Enns said. "We've a number of children with urea cycle disorders with

normal intelligence, but often the damage is already done at the time of diagnosis, because these disorders are so severe and strike so quickly."

The solution, Enns said, would be to switch out the liver with one that has intact genes — before the brain takes a hit.

With OTC deficiency, a crisis often occurs in the first day or so of life. Parted from the mom's nutrient stream, the baby's metabolism kicks into high gear. Diagnosis is by symptoms: lethargy, poor feeding and coma, in rapid order. Prenatal diagnosis is still quite uncommon. So when an amniocentesis a few months before Dean's delivery confirmed that he had the disease, Enns was ready to implement a bold, new approach.

Shoua Yang, who lives in Fresno, Calif., came to Stanford worried she had a fetus at risk. Her mother had lost two sons, though no one had attributed the deaths to genetics. When Yang lost her own firstborn son 10 years ago, she was told the cause was OTC deficiency. But it was easier to leave it as "God's will," she said, than to acknowledge the gene defect. She went on to have two daughters and a son, all healthy. When she became pregnant with Dean, her midwife Renee Halstead, MD, of Women's Specialty Center in Clovis, Calif., advised an amniocentesis. "She was hard to say no to," said Yang. "She pushed me to get tested. Now, I'm so thankful.

"I needed to find out," she added, "for my girls."

The disorder is caused by a defect on the X chromosome. That means OTC deficiency fully affects only boys, as males have only one X chromosome. In girls, with two X's, the normal one can compensate for the bad one. Yang's daughters could be carriers. But the vital question was this: Was she passing the OTC gene to this new son.

"Our prenatal and biochemical genetics team is among a select group

nationally that has the expertise to identify and care for OTC deficiency," said Enns. "We had to sequence the gene in the mom, then look for it in the fetus." The mutation had to be found and sought in the fetal cells obtained. And indeed, the amnio showed it was there.

To prevent an ammonia spike during Yang's labor on Nov. 17, Enns and his colleagues put part one of their plan in motion, first infusing a solution of sodium phenylacetate and sodium benzoate, along with arginine hydrochloride, into Yang's bloodstream to safely capture the toxin. These infusions help to "scavenge" excess ammonia in urea cyle disorder patients. Enns said this was the first time the combination of infusions was carried out during labor, as far as he knows.

After the birth, mom and baby stayed close to Packard Children's at the Ronald McDonald House to await a donor liver and transplant, which would effect the cure. Yang fed Dean a special low-protein formula and watched for low body temperature or tiredness that could indicate another ammonia spike — he had a mild one in December that was treated quickly at the hospital.

On March 8, Yang was told that a matching liver for Dean was available. Carlos Esquivel, MD, PhD, director of transplantation, led the surgical team in a four-hour procedure. According to medical literature, Enns said, this makes Dean the first documented infant with OTC deficiency to undergo a liver transplant after continuous treatment with this combination of medications and monitoring from before birth.

Now, with regular outpatient visits to clinics at Packard Children's to check Dean's progress, Yang and her growing boy are looking to what will hopefully be a normal life back home with his siblings. "We're looking forward to happy days ahead," said Yang.

Dean's experience is definitely a new standard of care, "but only

specialized institutions are able to do this," said Enns, who plans to publish the case. "You need the experience. It's setting the bar high, but it does set a goal in place.

"Our focus was to provide treatment that would keep his brain healthy — so far things are looking great," he said. "Though he'll always need medications to help avoid transplant rejection and there may be other issues, he has an excellent chance at a full, active life."

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