



Six-year-old Joshua Holdner is full of life. Keeping him that way is a day-to-day challenge.

Balancing Act

Long before Joshua Holdner got an accurate diagnosis of the rare condition that had been ailing him since birth, his mother, Teri, was getting a reputation. Her maternal instincts that something was seriously wrong with her infant son—and her tireless efforts to get him proper attention—were questioned by skeptical caregivers. One even opined that she, and not her sick child, required monitoring.

As a result, it took nearly a full year for the family to get to Duke Children's. There, the Holdners found out that their baby boy in fact had a rare genetic disorder called tyrosinemia type I. With the help of Duke's genetic and metabolic disorders team, they were able to snatch Josh back from the brink of death and give him a chance for a healthy, happy life.

Ironically, if Josh had been born just a year later, his condition would have been diagnosed and appropriate treatment begun within a week of his birth. In the 1990s, Duke pioneered a high-tech newborn screening technique known as tandem mass spectrometry. The method tests for 30 different congenital errors of metabolism—including tyrosinemia—with just a few drops of blood taken from a tiny needle prick on an infant's heel. At the time of Josh's birth, however, the test—while already being done on babies born at Duke—was not yet widely used (hospitals throughout North Carolina, as in many other states, now routinely perform the test on newborns).

Even without the test, Teri knew from the moment Josh was born that something was wrong. "He was so tiny—like one of those Keebler elves—and he just didn't look right," she recalls. "He would nurse for a second, then scream and throw up." When she detailed her concerns at her son's checkups, "They said he was just colicky. They gave him stomach drops, which didn't help. Then he started getting one ear infection after another—he was basically on antibiotics for five months."

Nailing a Diagnosis

At six months, Josh, always small, fell off the growth chart entirely. He couldn't sleep, couldn't raise his head, and alternated between screaming, projectile vomiting, and diarrhea. Two months later, Joshua became lethargic and non-responsive. Frightened for her son, Teri took him to a local hospital. The staff admitted that the results of Josh's blood labs looked odd, but didn't refer him on for further evaluation.

Determined to learn the truth, Teri found her way to Duke's Gordon Worley, MD, a developmental specialist who suspected a metabolic disorder. Referrals to Duke's pediatric neurology, nephrology, gastroenterology and endocrinology teams followed. After yet more blood tests and a liver biopsy, Joshua finally received a diagnosis: hereditary tyrosinemia type 1.

An extremely rare genetic metabolic disorder affecting just a few hundred youngsters worldwide, tyrosinemia type 1 is characterized by a lack of an enzyme that is needed to break down the amino acid tyrosine, which is found in many foods. Failure to properly break down tyrosine results in abnormal accumulations of substances within the body that are extremely toxic to the liver, kidneys, and central nervous system. Patients surviving beyond infancy are



at considerable risk for liver cancer. The grim diagnosis brought home a devastating truth: The foods with which Josh's worried mother had been trying to nourish her son were literally killing him.

Immediately, Duke geneticist Priya Kishnani, MD, obtained permission from the Duke Institutional Review Board to start Josh on a then-experimental drug called NTBC. (Surprisingly, the medication is actually an herbicide found by Swedish researchers in 1991 to prevent the formation of the toxic substances that accumulate in tyrosinemia type I.) Meanwhile, Duke nutritionist Anne Boney, who specializes in designing diets for kids with genetic metabolic disorders, put Josh on a very low-protein diet, supplemented by a special metabolic formula that is free of tyrosine and phenylalanine, another amino acid that can accumulate and cause problems for kids with the disorder.

"Within a week, my son began coming to life again," Teri says. "He was able to keep things down, to relax, and to sleep. It's a miracle that he made it as far as he did without diagnosis and treatment, but he wouldn't have been able to survive without Duke."

A Dietary Teeter-Totter

Josh will celebrate his 7th birthday this June. The party menu will not be the typical ice-cream-and-cake fare, as making sure Josh gets just the right nourishment each day continues to be a challenge. "It's a teeter-totter," Teri says. "Too much protein is dangerous; not enough and he won't grow." High-protein foods such as milk, cheese, and meat are out; even starchy foods such as pasta and potatoes contain protein (and therefore tyrosine) and must be weighed and measured to meet Joshua's dietary goals.

In 2002, the FDA approved the drug that Josh has been taking for the past several years, now called Orfadin, for treating his condition. It has proved to be a godsend for children with tyrosinemia type I, for whom liver transplantation was formerly the only alternative other than dietary treatment. "Basically, Orfadin changes a lethal disorder into something a child can live with," says Dr. Kishnani. "Still, its long-term effects are unknown."

So Josh continues to be closely monitored by the Duke team, receiving checkups every three months and regular imaging studies of his liver and kidneys. He's still small for his age, in the 5th percentile for height and weight. Teri relies heavily on the Duke team for day-to-day support and reassurance when snags or questions arise. "She's even called me from a restaurant, asking whether it's OK for Josh to eat something," Boney says. "As youngsters like Josh get older, you have to hope that the peer pressure they feel to eat certain foods will be balanced by their growing maturity and understanding of what those foods do to them."

Despite all these difficulties, Josh is a dynamo whose charisma and upbeat attitude charm everyone he meets. He's also a typical boy who loves to play with fire trucks and ride his skateboard. He even has a purple belt in Tae Kwon Do.



Seeking a Cure

Between caring for Josh and his older sister, Danielle, the Holdners have a full plate. Yet they have also thrown themselves into trying to find a cure for tyrosinemia. Through their Web site, www.joshuacure.com, and assorted special events, Teri proudly notes that the family has raised more than \$40,000 for research into the condition. "We belong to NORD [the National Organization for Rare Diseases], and \$35,000 is enough to start a research grant," she explains. With support from the Holdners, a Canadian doctor is seeking a way to prevent the liver tumors that are a common result of the disease.

"In our lifetimes, we have to do this," Teri says. "We adore Josh, and he's fought so hard to be here. Clearly, he was meant to be. We owe his life to Duke." 🍎