Molecular medicine comes to the rescue

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On Monday, August 14, Lilly Jaffe, a six-year-old North Shore suburban girl who had been diagnosed with type 1 diabetes when she was one month old, checked into the Clinical Research Center at the University of Chicago Medical Center. On Friday, August 18, she checked out, starting to make her own insulin, well on her way to insulin independence and ready to get in a few days of beach time in Michigan before starting first grade.

As she continued to do well, her insulin was reduced day by day. The following Wednesday, August 23, with her doctors' direction, Lilly's mother disconnected her insulin pump--the lifeline and security blanket she had relied on for years--for the last time.

"She is so proud," said her mother, Laurie Jaffe, "so happy, so excited. She's just thrilled, for the first time to be like her friends and her brother and sister."

"It is a miracle," she added. "We are humbled by the scientific brilliance and by the amazing grace of God that brought this cure to Lilly."

"It was awesome," said her doctor, diabetes specialist Louis Philipson, professor of medicine at the University of Chicago. "It was cool," he added, with uncharacteristic abandon, "way cool."

It was also lucky. Lilly suffered from an unusual form of diabetes caused by a genetic mutation rather than the errant immune system responsible for type 1 diabetes. Such "monogenetic" forms of diabetes in children

are just being recognized and studied.

Lilly is only the fourth such case treated in the United States and one of less than 100 in the world who have been successfully treated this way.

Researchers suspect there are about 2,000 people in the United States with neonatal diabetes who could benefit from the same treatment if precisely diagnosed and treated relatively early in life.

The take-home message, Philipson said, is that "anyone who has what appears to be type 1 diabetes with onset before the age of six months should be tested for this condition."

Conventional type 1 diabetes is an autoimmune disorder. For some reason the immune system turns on the insulin-making beta cells in the pancreas and destroys them. Patients lose the ability to make their own insulin. They have to restrict their diets, check their blood-glucose levels up to a dozen times a day, and give themselves frequent insulin shots.

Some, like Lilly, wear external insulin pumps. The pumps reduce the pain of frequent injections and can help smooth out glucose fluctuations, but still require constant attention and site changes every three days or so. Even those who practice "tight" control of blood-glucose levels are at increased risk for long-term complications including eye damage, nerve damage, and heart disease.

In the last two years, however, a team led by researcher Andrew Hattersley, of Peninsula University, Exeter, UK, has begun to study specific genes in patients diagnosed with diabetes before the age of six months--about one-tenth of a percent (1 in 1,000) of all type 1 diabetics. Nearly half of these patients, about one out of 200,000 newborns, turn out to have a mutation in one of two critical genes that work together to form a channel that regulates the flow of potassium ions in and out of

the insulin-producing beta cell.

In the normal beta call, glucose metabolism results in increased levels of ATP, a molecule that cells use to store energy. The increase in ATP causes the potassium channel to close. After it closes, potassium ions accumulate within the cell. When they reach a certain level, they trigger the opening of calcium channels. Calcium ions flow in and the cell responds by secreting insulin.

Mutations, such as Lilly's, that affect the potassium channel, make it less sensitive to the build-up of ATP. The channel remains open, allowing potassium ions to flow in and out rather than accumulate. As a result, insulin secretion is drastically reduced--in Lilly's case, to undetectable levels, even though she still had the normal number of insulin-producing cells

Drugs of the sulfonylurea class, developed decades ago to enhance insulin secretion in patients with type 2 diabetes--usually seen in adults--can close this ATP-dependent potassium channel.

A study by Hattersley and colleagues, published August 3, 2006, in the New England Journal of Medicine, showed that in 90 percent of patients with neonatal diabetes caused by mutations in one part of the potassium channel, high doses of sulfonylurea could restore normal insulin secretion. The only side effect was mild, short-term diarrhea in about ten percent of patients.

A second study, published in the same journal by a group from France and Houston, found that five out of nine patients with a mutation in a second gene that affects the same potassium channel could also be successfully treated with a sulfonylurea drug, allowing those patients to stop their insulin injections.

In short: Lilly's mutation prevents the cells that make it from secreting insulin. The sulfonylurea drugs correct that defect, and in Lilly's case empower her own cells to do what they are supposed to do.

Precise genetic diagnosis and targeted medication doesn't cure the disease but it vastly simplifies disease management and improves long-term prognosis. Patients still need to monitor blood glucose, although much less often. Instead of frequent insulin injections, they take pills twice a day.

"As long as they take their pills, it's like trading a severe case of type 1 diabetes for mild case of type 2," said Philipson, "a trade anyone would make. It's comparable to swapping influenza for the sniffles."

Lilly's journey began at a routine check-up one month after birth. A standard test showed glucose in her urine. Follow-up blood tests indicated diabetes.

"In a single day we plummeted from the joy of a new baby to the heartbreak and challenge of a new baby with diabetes," said her mother. "We were thankful that she was diagnosed early, and she has developed beautifully, but from that day on, our lives were forever changed. We could never let our guard down, having to monitor her closely and constantly. That meant glucose checks ten times a day, even at night, and three-to-five daily insulin injections, not to mention analyzing every bite she ate."

Two years ago Lilly had two nighttime seizures, caused by low glucose. "It's sobering," said Jaffe, "dealing with that kind of fragility and intensity day after day."

An insulin pump helped prevent further seizures, but over the summer the Jaffes worried about Lilly's imminent transition from half-day

kindergarten, with frequent visits with the school nurse, to a full school day in first grade.

Meanwhile, on June 17, the University of Chicago brought Andrew Hattersley to Chicago to lecture on "Molecular genetics: a new clinical tool for the diabetes clinic."

Philipson helped organize and attended his talk. Nine days later, on June 26, he included a brief summary of Hattersley's work in a presentation he gave to the local chapter of the Juvenile Diabetes Research Foundation. After the talk, Michael Jaffe--a member of the JDRF's executive committee and Lilly's father--approached Philipson and told him about his daughter.

Philipson told his colleague Graeme Bell, professor of medicine and human genetics at the University who had been involved in the first such US case, two years ago at Loma Linda Hospital in California, just published in July. They agreed to test Lilly's DNA. Bell FedExed a DNA sampling kit to the Jaffes.

"Lilly spit in the cup and we sent it back and tried to forget about it," said Laurie Jaffe. "This disease is an emotional roller coaster. We had been through enough. We were determined not to get too excited."

Because of the early age of onset, their pediatric endocrinologist, Deborah Edidin, had suspected that Lilly might not have the usual kind of Type 1 diabetes. Prior to the recent Hattersley publications, however, there was no compelling reason to reconsider the diagnosis. (Edidin was constantly involved in the next stages and visited with Lilly and Philipson at the University.)

When the DNA test came back positive for the exact mutation--known as Kir6.2--the mood of the Jaffe household brightened. "We suddenly

began to read all the studies," said Mrs. Jaffe. "We were blown away by the possibilities."

The next barrier was logistical. Her parents and her doctors did not want to delay, but Lilly didn't fit any normal patient categories. It could take months to design a formal study, to get funding and approval. On the other hand, the drug was already approved, but not for this use.

"Dr. Philipson," said Laurie, "and his colleagues in the Clinical Research Center at the University of Chicago moved heaven and earth to get permission and the resources to treat Lilly and we will be forever grateful for those efforts."

Treatment required a team of pediatric endocrinologists who cared for the child 24 hours a day while she was in the hospital, skilled nursing to measure frequent blood glucose levels, recognize signs and symptoms of hypoglycemia and adjust the insulin level in her pump as the oral medication was taking effect. Laboratory technicians provided immediate glucose analyses around the clock. Dieticians cooked appropriate meals. A research pharmacist prepared the medication. Proximity to the Comer Children's Hospital provided access to resources such as the ChildLife playroom, which made her week in the hospital a little more fun.

"The level of complexity and novelty of this protocol," said Roy Weiss, professor of medicine at the University and director of the CRC, "could not have been performed on a routine medical floor."

That week, the Jaffes cut short their vacation at their beloved Michigan cottage and settled in at a nearby hotel. Lilly was admitted to the CRC on a Monday and "we began to give her low doses of sulfonylurea and gradually to reduce her insulin," said Philipson. They doubled the sulfonylurea dose each day.

"It was an intense experience," recalled Laurie. "Our hopes were so high, but we didn't know if it was going to work. Lilly was really scared, at first, spending the night in a hospital with everyone focused on her. I stayed there with her and we did a lot of praying."

"What we witnessed during that week was the gradual unfolding of a miracle," she said. "By Friday Lilly was skipping down the hallway."

"It was a gradual transition," Philipson said, "but by the fourth or fifth day, we knew it was working. Can you imagine how good that felt?"

Philipson let Lilly leave the hospital that Friday and the Jaffes returned to their vacation home on Lake Michigan, where Lilly's pump was removed the following Wednesday.

"It was surreal to remove the battery from her pump and store it away," said her mother. "We always believed that day would come, we just thought it would be 10 years down the road."

For the first time in more than six years, Lilly no longer gets insulin. She takes five sulfonylurea pills twice a day, for now. That will be reduced to two as her team settles on the optimal dose.

"Lilly has always been an active child, involved in soccer and ballet," said her mother, "but now she has the freedom to be a normal active child. She can go to sleepovers or playdates without Mom coming along to do blood sugar tests and operate her pump. She can eat snacks without counting carbohydrates or testing her blood. Just like all of us, it is important that Lilly continue a healthy, physically active lifestyle for her health, but this will greatly enhance her long-term prognosis."

"We hope and pray that Lilly's story will bring hope to all those who suffer with diabetes," added Lilly's parents. "This was Lilly's unique

'cure' but there are many other 'cures' on the horizon.

"Lilly will still see her friend the school nurse every day," said Laurie, "but from now on she'll just wave, and say 'Hi.'"

Source: University of Chicago Medical Center