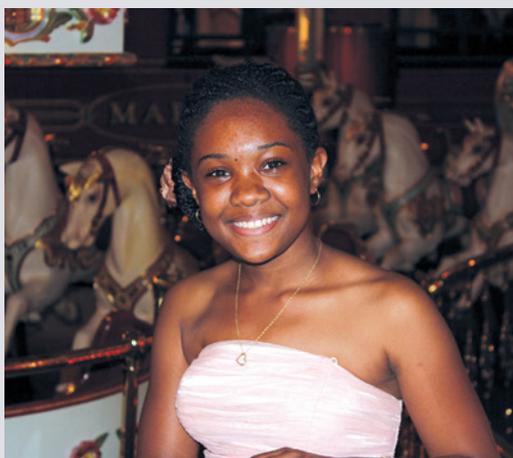


Surgical Procedure for Chronic Pancreatitis Transforms Young Person's World from Pain into Promise



Sydney

Fifteen-year-old Sydney is an active, academically high-achieving, and caring teenager living the full life of a tenth grader with school activities, playing her favorite sport of soccer, and pursuing her interests in medicine and theater production.

But just a few years ago, her life was dramatically different—marked by frequent attacks of abdominal pain so severe that they put her in the hospital for weeks at a time and kept her from going to school or engaging in any of the other typical activities of children her age. Her struggles with pancreatitis and her entire family's journey with managing the disease have not been easy. With the help of research on genetic factors

underlying this disease, however, much of which was performed by scientists with National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) support, and a surgical procedure called “total pancreatectomy-islet autotransplantation,” the future is bright for this young person who is eager to give back to the world of medicine and other children dealing with serious illnesses.

Living with Pancreatitis

The pancreas is an organ located behind the stomach that has many important functions. Specialized cells in the pancreas called islet cells produce hormones such as insulin and glucagon that are released into the blood to regulate the level of sugar (glucose) in the blood. The pancreas also produces fluid that is released through ducts into the intestine and contains enzymes and bicarbonate that are necessary for digestion of food. Usually, these powerful digestive enzymes are inactive until they exit the pancreas and enter the intestine. In cases of pancreatitis, however, digestive enzymes are activated prematurely while still inside the pancreas, resulting in damage and inflammation, and outward symptoms of abdominal pain, nausea, and vomiting. The acute form of the

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disease, often caused by gallstones as they pass through the duct connecting the pancreas and gallbladder to the intestine, resolves after a few days of treatment.

However, chronic pancreatitis is marked by frequent attacks of debilitating abdominal

pain that become worse over time, causing more long-term damage and preventing those affected from engaging in everyday activities such as attending school or work.

In Sydney's case, her pancreatitis symptoms started when she was 8 years old. "I just started having really bad stomach pain," she says. "I would go in and out of the hospital to figure out what was wrong, and for the longest time they didn't know what was going on."

She would be in the hospital for about 1 to 2 weeks at a time, and for as long as 7 weeks on one occasion, to manage the pain. During this time, she was unable to eat, but received intravenous (IV) fluids while her pancreas recovered from the attack. The disease took a heavy toll not only on Sydney, but on her whole family.

"As far as the pain, you know seeing my daughter was the most difficult part," says Sydney's mother, LaKindra. Sydney shares that feeling, saying "it was hard to see my parents see me in pain and then have two little brothers that needed help too."

Typically, pancreatitis is diagnosed through a combination of medical history, physical examination, blood tests for elevated levels of

digestive enzymes, and imaging tests showing the pancreas, gallbladder, and surrounding ducts.

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Pancreatitis can be hereditary. A few years after her symptoms of recurrent acute pancreatitis first started, the disease had progressed to chronic pancreatitis, and her doctors decided to do genetic testing to determine if Sydney's was a hereditary form of the disease. Chronic pancreatitis is rare in children, and in approximately 50 to 70 percent of cases, it is associated with a genetic mutation. People with hereditary forms of pancreatitis also have a 40 to 70 percent chance of developing pancreatic cancer later in life.

In the years preceding Sydney's diagnosis, NIDDK-supported science had advanced knowledge of the genetic factors underlying hereditary pancreatitis. In 1996, scientists reported the groundbreaking discovery of the first genetic mutation associated with hereditary pancreatitis, in a gene coding for the protein trypsinogen, an inactive precursor form of the digestive enzyme trypsin. Additional mutations associated with hereditary pancreatitis have since been discovered in the trypsinogen gene, in other genes that affect trypsinogen/trypsin, and in genes that have other functions.

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For example, mutations in the *serine protease inhibitor Kazal type 1* or “*SPINK1*” gene, which encodes a protein that inhibits trypsin, were identified in people with pancreatitis. Mutations in the gene associated with cystic fibrosis—called *CFTR*—were linked to pancreatitis. Depending on the nature and number of mutations, pancreatitis sometimes occurs in people with cystic fibrosis and sometimes in those who do not have cystic fibrosis, but have a *CFTR* mutation. *CFTR* encodes a protein that helps enzyme precursors like trypsinogen leave the pancreas and enter the small intestine.

Sydney’s doctors sequenced her DNA and found that she carried two of the genetic mutations that had been discovered a few years before as risk factors for pancreatitis: in the *SPINK1* and *CFTR* genes. This knowledge gave Sydney’s family and doctors more information to go on in understanding her disease. But because hereditary pancreatitis in children is so rare, it was difficult for Sydney’s family to find information that would help them decide with their health care team about the best course of treatment for her. Also, options tailored to the needs of pediatric patients were limited.

As Sydney’s father, Robert, says, it was “almost impossible” to find information about treatments for people with chronic pancreatitis who had the same kind of genetic mutations as Sydney. “It was almost a word-of-mouth kind of thing trying to get your hands on any data so that you could try to see exactly what other possible treatments have been tried on other patients with like symptoms,” he says.

Treatment for chronic pancreatitis typically focuses on relieving pain and managing any complications, such as blocked ducts within the pancreas. For example, a technique called endoscopic retrograde cholangiopancreatography (or “ERCP”) allows doctors to view the pancreas, gallbladder, and surrounding ducts, as well as treat any narrowing or blockage of the ducts using small plastic tubes called stents. Another procedure called a celiac plexus block involves injection of a local anesthetic directly into a group of nerves leading to the pancreas. Pancreatic enzymes are also usually prescribed to be taken with meals so that the pancreas does not have to work so hard in assisting digestion.

In Sydney’s case, her pain was managed through a combination of ERCP, celiac plexus blocks, and taking two powerful narcotic pain relievers. But, with the concern about possible addiction from long-term narcotic pain reliever use, her parents sought alternatives.

“There is practically no one that supports pediatric patients for pain management, so literally we had to work with doctors that did not specialize with pediatric patients,” says LaKindra.

They worked with the staff at the nearby University of Chicago Medicine Comer Children’s Hospital, where Sydney tried different approaches to manage her pain, including more holistic approaches such as aromatherapy and guided imagery. The family also sought out acupuncture services outside the hospital for Sydney to help with the pain.

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Unfortunately, by 2011, all the pain management techniques had stopped working for her. Then, at only 11 years old, she was hospitalized six times that year and was in school only part time. Also, for several months during that year, she was unable to eat, receiving her nourishment exclusively through total parenteral nutrition or “TPN” via an IV tube delivering a high-calorie mix of nutrients directly into her bloodstream. Her family decided it was time to pursue another option with the potential to relieve Sydney’s pain more permanently.

Choosing a Life Without Pain

Sydney’s family credits the talented health care professionals they encountered near their home in Chicago with correctly characterizing her disease and quickly putting them on a path to a long-term solution.

“The stars were all aligned and God was in our favor because we had doctors who were more than willing to say ‘I don’t know what’s going on, but let me direct you to someone else,’” says LaKindra.

From their local community hospital, they were sent to a physician at the University of Chicago who had seen another pediatric patient with chronic pancreatitis. This patient had undergone a procedure called a total pancreatectomy-islet autotransplantation (TP-IAT) at the University of Minnesota Masonic Children’s Hospital.

In the TP-IAT procedure, the pancreas is surgically removed and its insulin-producing islet cells, which regulate blood sugar, are collected and infused back into the body through a large vein going into the liver, where the cells are able to implant and function. This surgery serves the dual purpose of removing the source of pain and increased cancer risk while preserving some insulin production, so as not to cause diabetes. The TP-IAT procedure had been used in adults since 1977 and in children since 1996. The surgery is more successful, in terms of achieving independence from insulin medications for diabetes, the earlier it is done after a diagnosis of pancreatitis and when performed in young patients under 12. Currently, about 15 U.S. medical centers perform the TP-IAT procedure. The NIDDK has supported some of the clinical research on TP-IAT use for treating chronic pancreatitis in adults and children.

Sydney’s family weighed the pros and cons of having the procedure, including Sydney being free of the pancreatic attacks and less likely to develop

pancreatic cancer later, but also the serious risks of any surgical procedure and also the possibility

of developing diabetes if the transplanted islets did not produce enough insulin.

“It was a group decision. We included Sydney in it, but leading up to that we all felt really on the same page that ‘hey, we really didn’t have an option.’ The alternative just was unacceptable,” says Robert.

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They were helped through this difficult decision process by other families coping with the disease. “It’s really a close-knit community of people kind of relying on each other and forming support groups, so that was really instrumental in strengthening us and helping us make it through,” he says.

Sydney’s family traveled with her to Minneapolis to stay in a hotel close to the University of Minnesota and prepare for the TP-IAT surgery. The family was hopeful that the surgery would help her, but also unsure of what the outcome might be. “It was a lot of anticipation,” says Sydney.

On November 14, 2011—which coincidentally was the same day as the annual World Diabetes Day—Sydney had the surgery performed by a surgical team at the University of Minnesota, including her surgeon, endocrinologist, pediatric gastroenterologist, and others.

“I remember us praying before I went in to surgery,” recalls Sydney. “And I remember my mom coming in, in like this bunny surgical suit and making me laugh.” LaKindra accompanied Sydney into the surgery room initially; then the family waited anxiously outside over the next 14 hours while the surgery took place.

The Long Road to Recovery

Sydney’s recovery in the following months after the TP-IAT surgery was slow and full of challenges.

Beginning immediately upon returning to her hospital room after her surgery, now without a pancreas, Sydney’s recovery would require many interventions in the weeks and months that followed, to help her maintain her blood sugar, manage pain, and help with some difficulty she experienced breathing.

“Everything had to be sustained by a lot of pumps, a lot of medications, managing her blood sugar, managing her pain, managing her breathing... she doesn’t remember any of that, but it was quite painful for her as well,” recalls Robert.

Nutrition was also a major challenge during this time. Sydney remained on the IV TPN for a few months following the surgery. For weeks, Sydney

had to have her blood sugar monitored around the clock until the

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transplanted islet cells showed signs that they were functioning normally in their new home inside the liver. Until then she was considered to have “brittle diabetes,” a condition in which blood sugar levels fluctuate unpredictably. Even after beginning to eat by mouth again, she was taking both short- and long-acting forms of insulin, in addition to pancreatic enzymes, with her meals, and closely counting her carbohydrates, to provide intensive control of her blood sugar while her islet cells recovered.

The family stayed at a hotel nearby after Sydney was released from the hospital and then at the Ronald McDonald House for about a month while

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she fully recovered. During that time, they had to continue managing Sydney's blood sugar and pain, with help from nurses who came by on a regular basis.

Sydney also experienced a few complications from the surgery, including internal bleeding and infection with the bacterium *Clostridium difficile*, which put her back in the hospital after returning home to Chicago. And for a long time after the surgery, Sydney experienced pain and itching in the scar covering her surgical site.

But a bright spot from that difficult recovery period came when, while in the hospital, Sydney was

able to meet another child who went through the procedure around the same time.

The two became "inseparable" afterwards and remain good friends.

"We share this special bond...all kids that have this surgery, there are so few of us that we all share this bond and we connect instantly," says Sydney. The family also offers support to others going through the procedure.

A New Quality of Life

Now, 4 years after the TP-IAT surgery, Sydney is back in school full time and studying diligently, even attending a math and science camp during her summer break. She no longer

experiences abdominal pain, takes minimal insulin medication and lower doses of the pancreatic enzymes with her meals, and only has to check her blood sugar after exercising. She also continues to take special care through her diet, including daily vitamin supplements.

"Now I'm totally normal," she says. "I'm doing whatever a normal teenager does—I go to school, I do my sports, my clubs, and just try and do everything I didn't get to do from that period that I was sick."

"We believe this is what the surgery has given her, that quality of life," adds LaKindra. Though in Sydney's case, the decision to have the

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surgery also meant a lifelong commitment to managing her blood sugar—a tradeoff they

willingly accepted to give Sydney a life free of chronic pain. Sydney, her family, and her health care team take care to preserve the function of the islet cells transplanted into her liver, which cannot replicate like islet cells within the pancreas.

"She has a set number of islet cells for the rest of her life," says Robert, adding "There aren't any long-term data right now," for children undergoing the surgery and islet cell transplantation. Sydney returns to the University of Minnesota each year for a check-up with her doctors and sees her local doctors every 6 months to make sure everything is still on track.

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Sydney's experience with pancreatitis and the TP-IAT surgical procedure has strengthened her interest in science and the medical profession. "Now that I've experienced what some kids have to go through when you're in a situation where they don't have that much information for kids having this, it just touched my heart and I was like 'you know, I could really make a difference, I could really help,'" she says.

For someone who has overcome formidable health challenges at such a young age and even found inspiration in them, anything is possible.

Hope Through Research

The NIDDK has supported research related to pancreatitis conducted by individual investigator-led teams, as well as larger, multi-center studies, such as the North American Pancreatic Study Group, which in 2012 performed the first genome-wide association study of pancreatitis, discovering additional genetic factors involved in the disease. The Institute has also sponsored

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workshops in recent years to foster new ideas and collaborations that can further advance pancreatitis research. For example, a 2013 workshop co-sponsored by the NIDDK and the National Cancer Institute (NCI) focused on pancreatitis, diabetes, and pancreatic cancer; a 2014 workshop focused on opportunities for research on TP-IAT use as a treatment for chronic pancreatitis; and a 2015 workshop focused on the development of biomarkers to facilitate early diagnosis of pancreatic disease.

Also in 2015, a new Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer was established with support from the NIDDK and the NCI. The Consortium's work will include conducting studies of people with chronic pancreatitis to improve understanding

of disease processes and related outcomes such as diabetes and pancreatic cancer development. These efforts offer hope through

research to advance knowledge of pancreatic disease and improve its management.