A Mother’s Love

One woman’s scientific journey to treat her daughter’s epilepsy.

By Gina Shaw

“There are three million people with epilepsy in this country, and one-third of them—a million!—are dealing with uncontrolled seizures like Savannah. They’re at the mercy of epilepsy.”

—Tracy Dixon-Salazar, Ph.D.
Savannah Salazar went to bed one night in 1995 as a typical toddler. At two and a half years old, she could count to three and knew most of her colors, although she still mixed up black and brown. As far as her parents could see, she was developing pretty much the same way her four-year-old brother had.

And then, in the middle of that night, everything changed. Her parents, Ruben Salazar and Tracy Dixon-Salazar (who is now Dr. Dixon-Salazar), awoke to a sound every parent dreads: their daughter was choking. “She was gagging, hacking, and making frothing noises,” Dr. Dixon-Salazar recalls. “I thought my child was dying. By the time the paramedics came, Savannah was okay. But I’ll never forget what one of them said next: ‘Her airway is clear, but what you’ve just described sounds like a seizure.’”

Savannah didn’t go to the hospital that night. Her exhausted parents tried to go back to bed. But when Savannah had another seizure a couple of weeks later—and a total of four within a period of two months—the family embarked on a seemingly endless roller coaster of scans, tests, and doctor visits: blood tests, magnetic resonance imaging (MRI), computed tomography (CT) scans, electroencephalography (EEG)—but they all came back normal.

For a while, it looked like the seizures were going away as mysteriously as they had appeared. “All of the seizures occurred in the middle of the night, when Savannah was sleeping,” says Dr. Dixon-Salazar. “After those first four seizures, she went six months where she didn’t have any seizures. I don’t think we missed any because she was sleeping with us at that point. We were hypervigilant, and the seizures were hard to miss.”

But then they came back. And they got worse. Much worse. The first few had been tonic-clonic seizures, which often begin with a stiffening of the limbs (the tonic phase) followed by jerking movements (the clonic phase). But then Savannah began having hundreds of seizures of different types in a typical week. (See box, “Seizure Types.”)

MORE THAN SEIZURES
For two years, the Salazars had no diagnosis for Savannah’s condition. “We knew she was having these spells, but all her eight EEGs were normal, and the doctors were reluctant to be definitive about what her condition was without better information,” Dr. Dixon-Salazar says. Apart from the patient history and the neurologic examination, the EEG is the most influential tool in the diagnosis of seizures and epilepsy. It provides a record of ongoing electrical activity in the brain.

When Savannah was five, she started kindergarten, and her parents began to realize that more was wrong than just the seizures. “My son couldn’t read when he started kindergarten, but by the end he was reading little books with rhyming words and sight words,” says Dr. Dixon-Salazar. “But we saw that Savannah just wasn’t adding to what she could do. When she got around her peers and people started measuring progress more, we realized that she wasn’t typical.”

The delays, along with new changes on Savannah’s EEG, finally helped to identify her condition as Lennox-Gastaut syndrome (LGS), which has three primary defining characteristics: multiple seizure types, a distinctive brain wave pattern that doctors call a “slow spike-and-wave,” and mental and developmental delays that can range from mild to profound. It usually develops between about 3 and 8 years of age. (See box, “Lennox-Gastaut Syndrome.”)

“It is one of the severe pediatric epilepsies,” says Jacqueline French, M.D., director of the Epilepsy Study Consortium, professor of neurology at New York University Langone Medical Center, and Fellow of the American Academy of Neurology (AAN). “There are a number of them, unfortunately. Lennox-Gastaut syndrome is a group term.”

Sometimes LGS has a structural cause. For example, children with lissencephaly, a rare brain disorder in which the folds in the surface of the brain (otherwise known as gyri) fail to develop, can go on to develop LGS. The condition can also develop after birth trauma, head injury, or exposure to toxins (such as maternal consumption of alcohol during pregnancy leading to fetal alcohol syndrome). Infantile spasms, which typically begin in babies less than a year old, can also sometimes progress to LGS.

But none of those things were true of Savannah. The mystery of what had happened to her daughter haunted Dr. Dixon-Salazar. She began a quest for answers. “I couldn’t wrap my brain around the fact that nobody could tell me why one day my daughter was absolutely fine and the next day she was not fine. I had to know,” she says.
Seizure Types

Seizures are divided into two major groups: primary generalized seizures and partial seizures. Each group contains several seizure types, often defined by degree and whether the individual remains conscious or not.

**PRIMARY GENERALIZED SEIZURES** usually begin with a widespread electrical discharge that involves both sides of the brain at the same time. Types of primary generalized seizures include:

- **Absence seizures**, which are brief episodes of staring during which awareness and responsiveness are impaired.
- **Atypical absence seizures**, which are periods of staring during which the individual is somewhat responsive.
- **Myoclonic seizures**, which are brief, shock-like jerks of a muscle or a group of muscles.
- **Atonic seizures**, during which muscles suddenly lose strength. For example, eyelids may droop, the head may nod, and the person may drop things and fall to the ground.
- **Tonic seizures**, during which muscle tone is greatly increased and the body, arms, or legs make sudden stiffening movements.
- **Clonic seizures**, which involve rhythmic jerking movements of the arms and legs, sometimes on both sides of the body. Tiredness or confusion does not usually follow these seizures.
- **Tonic-clonic seizures**, also known as grand mal seizures, involve the entire body and are what most people think of when they hear the word “seizure.” People often lose consciousness during tonic-clonic seizures.

**PARTIAL SEIZURES** begin with an electrical discharge in one limited area of the brain. They can have many different causes, including traumatic brain injury (TBI), brain infection, stroke, tumor, or changes in the way an area of the brain was formed before birth. Types of partial seizure include:

- **Simple partial seizures** are localized to one area on one side of the brain, but may spread from there; consciousness remains intact.
- **Complex partial seizures** can begin in any lobe of the brain, but cause altered awareness due to spreading of seizure activity.
- **Secondarily generalized seizures** begin in one part of the brain, and then spread to involve both sides of the brain with associated loss of consciousness.

**BECOMING A NEUROSCIENTIST**

Over the course of the next 15 years, her determination to help Savannah and other children like her transformed Tracy Dixon-Salazar from a stay-at-home mother of two—who admittedly had not done all that well in high school and had never been to college—to a Dr. Dixon-Salazar, a Ph.D. neuroscientist and genetic researcher.

It started simply enough, with hours spent at the library. “Every question I was able to answer led to 50 more questions,” Dr. Dixon-Salazar says. “For the first few years, I nearly always had a medical encyclopedia next to me. I would look up every other word I encountered. Naively, before I realized that this was scientific language, I thought it was because I had had a poor vocabulary.”

So she took a few English classes at Grossmont Junior College in San Diego, where the family lived. “Then I started taking science classes. I took a psychology class that covered neuroscience, which are periods of staring during which the individual is somewhat responsive. Dr. Dixon-Salazar learned about “H.M.,” perhaps the most famous patient in the history of neurology, who had most of his hippocampus (a region of the brain that plays an important role in forming new memories) removed in an attempt to treat his epilepsy. Forever after, he was unable to form memories of new events.

She also took a genetics course and marveled when, in the late 1990s, several genes associated with certain forms of epilepsy were identified. “I thought, this is where the answers lie!” Dr. Dixon-Salazar recalls. “I was constantly filtering everything I learned: could this explain Savannah or somebody else like Savannah?”

By this time, her daughter was having hundreds of seizures a day. “I’d do my homework in bed with her,” says Dr. Dixon-Salazar. “She’d seize, and I’d stop doing my homework to help her. I’m not brilliant. I just kept going because I had to. I wanted to have something to show for this. I don’t give up.”

Juggling child care with her husband (“I always thought he’d throw his hands in the air and give up!”) and piecing together grants, scholarships, and stipends, Dr. Dixon-Salazar worked her way through a degree in physiology and neuroscience at the University of California-San Diego (UCSD).

She considered medical school, but the thought of treating patients like Savannah broke her heart. By then, none of the 26 drugs and multiple other therapies had done anything to reduce Savannah’s seizures. “I didn’t want to treat kids and then 26 drugs later, there’s still nothing that’s working,” Dr. Dixon-Salazar explains. So she dove into a Ph.D. program at UCSD with the goal of advancing epilepsy research. “I felt like the war against epilepsy—and I very much feel like this is a personal war—is being fought, in some ways, in the research lab,” she says.
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—TRACY DIXON-SALAZAR, PH.D.

Dr. Dixon-Salazar was realistic about her chances of helping her own daughter. “I always thought anything I could do in epilepsy research would help the next generation. Savannah had had so many seizures and was so damaged. As I learned more and more about the brain and how it changes, I realized how much seizures mess with the brain’s normal set point. I thought, wow, her poor brain must have a completely different set point after 10,000 seizures,” she says.

After finishing her Ph.D., Dr. Dixon-Salazar decided to work in the lab of Joseph Gleeson, M.D., a neuroscientist investigating genetic causes and treatments for childhood brain diseases. Dr. Gleeson sequences the exome, which is made up of the protein-encoding parts of all the genes. Dr. Dixon-Salazar began her work in Dr. Gleeson’s lab at a particularly tough time at home. “Savannah had started puberty my last year of graduate school. Her seizures were becoming more and more unpredictable and severe,” she says.

At least once a week and sometimes as often as three times a week, Savannah was also going into nonconvulsive status epilepticus, a stupor-like state that can last for hours and even days unless interrupted with rescue medication or hospital treatment. “We’d wake up every morning and put a hand on her chest to see if she was breathing,” Dr. Dixon-Salazar recalls. “We knew this wasn’t going to end well. Savannah was going to die. Either a seizure would kill her, or an accident, or sudden unexpected death in epilepsy. It was just a matter of time.”

Dr. Gleeson saw Dr. Dixon-Salazar struggling and suggested they sequence Savannah’s exome—which means evaluating all of her DNA. The desperate mother leaped at the chance.

“When you sequence someone’s exome, you end up with about 100,000 genetic mutations, things that are different when compared to a normal sequence,” says Dr. Dixon-Salazar. “We winnowed it down by getting rid of things that are common. If 50 percent of the population has this mutation, it’s obviously not associated with epilepsy. We were able to get the number down to 300 high-impact genetic changes, unique to her, that were in the areas of genes that could potentially be driving her epilepsy. Then we clustered them according to function. What do those genes do? And which of those might be treatable?”

THE PAYOFF

At first, nothing popped out. Then, Dr. Dixon-Salazar spotted a set of 25 mutations in a group of genes regulating how calcium enters Savannah’s brain cells; many of the changes she saw were thought to increase the levels of calcium going into the cells. “Calcium: I might be able to work with that,” she recalls thinking. And then she remembered something: over the years, Savannah’s doctors had recommended several times that she take calcium supplements, because her antiepileptic drugs leached calcium away from her bones. But every time they gave her the supplements, the seizures got worse.

Dr. Dixon-Salazar identified a drug called verapamil—a calcium...
channel blocker commonly used to treat people with heart problems—that specifically targets the type of channel where many of Savannah’s mutations were located. After carefully checking Savannah’s heart function, her doctors agreed to try the medication.

“It was really, really scary. It could have made her worse,” says Dr. Dixon-Salazar. “She had tried at least three other drugs that some people swear had helped their epilepsy, but for her they did the opposite. One made her psychotic, causing her to try to injure herself. And after she’d failed so many drugs, the chances that a new one would work were low. But they weren’t zero. And we had to keep trying.”

They started her on a low dose of the drug. Almost immediately, Dr. Dixon-Salazar noticed a difference. “She went a day without needing the rescue medication for status epilepticus. And then another day, and then a week, and then three weeks,” she says. “She had been having about 300 seizures a month before we started the medication. A month later, it was about 25.”

For months, the Salazars told no one except Savannah’s treating physician. “We were afraid to talk about it,” Dr. Dixon-Salazar says. “Around three months, I sort of mentioned it to Dr. Gleeson. He said, ‘Wow, that’s really exciting!’”

But Savannah’s parents were still wary. She’d had brief honey moons with a few other drugs, which didn’t stop the seizures but reduced them a little, before they stopped working. And a special high-fat diet called the ketogenic diet had almost eliminated the seizures for nearly three months before Savannah’s condition began to deteriorate again.

Finally, after a year, Dr. Dixon-Salazar began to believe that the treatment would keep working. And today, two years later, 20-year-old Savannah is still doing well. “We can’t seem to get rid of those last 18 to 25 seizures a month, but those are always at night. She can go without the helmet. We’re not constantly waiting for that seizure where she busts her face on the one piece of furniture we have in the house. She’s much more awake, she’s talking more, she’s bossing us around,” she says.

The damage done to Savannah’s brain by nearly two decades of relentless seizures is almost certainly irreversible. She functions at about the level of a five-year-old. “She’s not going to all of a sudden catch up, but now that the seizures have lessened, she can start to learn and form new memories,” Dr. Dixon-Salazar says. “And we’re not living under this constant umbrella of fear which [uncontrolled] epilepsy creates.”

Savannah’s mutations are specific to her, but genetic research like this holds promise for other children with LGS, according to Dr. French. “The Epilepsy Phenome-Genome Project recently completed a very large study that assessed the genes of many children who had LGS without an obvious cause. The study found a number of spontaneous gene mutations involved. Now it’s the job of scientists to figure out what those genes do so we can determine the abnormalities in the brain and possibly target specific therapies.”

Dr. Dixon-Salazar’s work with Dr. Gleeson is likely to have an impact well beyond LGS and epilepsy. In addition to Savannah, their team sequenced the exomes of more than 100 patients with different neurodevelopmental diseases in an effort to find as yet unidentified genetic causes of their disorders.

They discovered at least two new genes: one that causes a disorder of the cerebellum known as Joubert syndrome, and another associated with a rare condition involving microcephaly (a small brain) and childhood-onset diabetes. In a surprising number of cases (about 10 percent), they also found that a known disease-causing gene—one that had been previously ruled out—was actually responsible for the child’s condition.

But as much as she loved the lab, Dr. Dixon-Salazar recently decided that it was time to shift her focus. In 2013, she joined the staff of Citizens United for Research in Epilepsy (CURE; visit their website at cureepilepsy.org), managing the organization’s research portfolio with a team of scientists. “It’s all about finding a cure for one of the epilepsies in the next five years, more if possible. There are three million people with epilepsy in this country, and one-third of them—a million!—are dealing with uncontrolled seizures like Savannah. They’re at the mercy of epilepsy. It just comes in unannounced and uninvited and it rocks your world. I want to change that.”

FOR MORE INFORMATION

- For more Neurology Now articles on epilepsy, go to http://bit.ly/L2KnVM.
- For articles on epilepsy from Neurology Today, another publication from the American Academy of Neurology (AAN), go to http://bit.ly/3d6iZk.
- To read a Patient Page on epilepsy from Neurology, one of the AAN’s medical journals, go to http://bit.ly/1eAjyoY and search “epilepsy.”