Child's Play

A six-year-old with hereditary spastic paraplegia keeps moving forward.

BY STEPHANIE STEPHENS

A fiercely determined Brianna Bernard maneuvers her walker down the hallway of the medical office, grinning ear-to-ear for the camera. The lens loves the exuberant six-year-old, who is ready to take on the world *and* her hereditary spastic paraplegia (HSP).

HSP is considered a rare disease, defined by the National Institutes of Health (NIH) as one that affects fewer than 200,000 Americans. HSP refers to a group of inherited neurologic disorders that cause progressive weakness and spasticity, or stiffness, in the lower extremities, mostly the leg and hip muscles. The long-term prognosis for people diagnosed with HSP varies: Some become very disabled, while others experience only mild disability. Some may eventually need the help of a cane, walker, or wheelchair.

Brianna uses a walker. "Are you taking pictures of me *and* of my walker?" she asks in the video made by her parents, Karen and Allen Bernard of Columbus, OH. Next, the camera cuts to Brianna at home in a pretty pink dress, marching down the hall with a cane in her right hand. Her feet turn inward, and her legs buckle at the knees as she struggles to maintain her balance.

The precocious first-grader keeps walking, just as she has every day since she was first diagnosed with HSP at 15 months. "HSP doesn't affect Brianna's health, just her legs, and her overall condition hasn't deteriorated," her mother says.

FINDING A DIAGNOSIS

Brianna's mom recalls that her daughter hit all her growth milestones within the normal age range up until her first birthday. When she tried to stand, however, it was on her toes, and she couldn't walk independently.

At 15 months, her parents consulted an orthopedic surgeon who advised them to "wait it out" until Brianna reached age two. Sensing something was wrong and not willing to wait, they sought a second opinion from a pediatrician, who ordered a magnetic resonance image (MRI) scan of her brain and spine that ultimately appeared perfectly normal.

Then, right after her second birthday, the Bernards consulted another orthopedic surgeon, who diagnosed Brianna with cerebral palsy based on the physical presentation of her legs and her unusual gait. Karen was perplexed by the diagnosis. She knew that cerebral palsy is caused by a brain injury or malformation that occurs during the brain's development before, during, or after birth. And both her pregnancy and scheduled C-section delivery had been normal.

The surgeon told the Bernards that nothing could be done about Brianna's condition, but they remained undeterred. They visited the cerebral palsy clinic at Nationwide Children's Hospi-

WALKING TALL "I might come in last, but I'm going to do it anyway," said Brianna Bernard before participating in the children's one-mile fun run at the Marine Corps Marathon in Washington, DC, this past October.

NEWTON SPORTS PHOTOGRAPHY

tal, where a neurologist ordered additional diagnostics, including genetic tests. Those revealed that Brianna carried a gene mutation responsible for HSP: SPG3A, also known as atlastin-1.

In pursuit of more answers, the tenacious parents searched the Internet and sought out Craig Blackstone, MD, PhD, a senior investigator in the Neurogenetics Branch of the NIH who is also a member of the American Academy of Neurology (AAN).

During a phone call, Dr. Blackstone invited both parents to come to the NIH to be tested for the SPG3A mutation. The couple accepted, and their results came back negative.

"That's when they took a biopsy from Brianna," her dad recalls. "Those few cells are now liters of cultured motor neurons Dr. Blackstone is using to study SPG3A." (Motor neurons are nerve cells that carry information from the central nervous system to the muscles to cause movements.)

Dr. Blackstone told them Brianna had a spontaneous, *de novo* genetic mutation, meaning it had arisen completely on its own, with no family history of HSP and with neither parent carrying the mutation.

A GENETICALLY DIVERSE CONDITION

The journey toward receiving a diagnosis of HSP normally includes an initial assessment of clinical symptoms by a neurologist. Usually, those symptoms include spastic gait impairment—an abnormal way of walking—and lower extremity spasticity and weakness, says Brianna's neurologist, John K. Fink, MD, the director of the neurogenetic disorders program and a professor of neurology at the University of Michigan Medical School.

In patients diagnosed with the condition, there may be a family history of HSP among first-degree relatives, or, as with Brianna,

ONE OF A KIND Brianna, pictured here at the Columbus Marathon in 2013 with parents Allen and Karen, had a spontaneous, "de novo" genetic mutation that caused her condition.

there may be no family history at all, says Dr. Fink, who is also a Fellow of the American Academy of Neurology (FAAN).

"Years ago, only specialized centers could do the gene testing, but now [more sophisticated and faster methods] for gene analysis can be obtained commercially from different companies," Dr. Blackstone says.

HSP is a genetically complex disorder. "More than 70 different genes—and the number is rising—cause HSP, and this is more than almost any disease. We couldn't test for many forms of HSP and similar diseases even five or 10 years ago, since the affected genes were not yet known," Dr. Blackstone says. [See sidebar, "Genetic Types of HSP."]

The fact that genetic diseases can now be identified so early in life affords the advantage of precious time. "Many patients develop symptoms in their late teens or 20s and 30s, and genetic tools can tell us who is at risk early on," Dr. Fink says. "We want to understand HSP at its fundamental level and to develop interventions that can prevent the appearance and progression of symptoms."

"Knowing about genetic disease from the time a person is born gives us the ability to intervene and alter disease progress before significant disability develops," Dr. Blackstone adds.

To listen to a podcast from Dr. Craig Blackstone about advances in HSP, go to **bit.ly/blackstone-HSP**

HOW HSP PROGRESSES

HSP can begin in childhood and progress no further, as it does in some patients with the genetic mutation for the disease. Or it can begin in infancy and progress though adulthood, gradually worsening. "Uncomplicated" HSP involves spasticity and weakness in the lower extremities and occasionally bladder disturbances. "Complicated" HSP may involve cognitive impairment or dementia, muscle wasting, seizures, peripheral nerve problems, visual impairment, or lack of coordination.

At present, the underlying nerve degeneration in HSP cannot be prevented, stopped, or reversed, but there are treatments that can alleviate the symptoms. For example, benzodiazepines and muscle relaxants, including implanted pumps of baclofen, and injections of botulinum toxin (Botox) can reduce spasticity. There are also medications that can reduce urinary urgency. Stretching, physical and occupational therapy, and recreational exercise can help patients improve and

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> —CRAIG BLACKSTONE, MD, PHD

maintain muscle flexibility, strength and balance, and range of motion. Orthotics, including shoe inserts or braces, as well as canes and walkers, can help make walking easier.

Children with HSP require a different approach and treatment than adults because of their ongoing growth and development, says Mauricio Delgado, MD, FAAN, director of neurology at Texas Scottish Rite Hospital for Children and a professor of neurology at the University of Texas Southwestern Medical Center in Dallas. "That may affect the timing and type of interventions required to help their function, activities, and participation."

"Symptomatic therapies [that treat the symptoms but not the cause of the disease] do have some benefit, but they don't result in dramatic improvement from the current medications," says Dr. Blackstone. "That's why more research is so critical."

Texas Scottish Rite Hospital for Children has established a pediatric HSP clinic and a clinical database that currently includes 130 children, Dr. Delgado says. "The goal is to improve our understanding of pediatric-onset HSP, standardize assessments, and identify the best treatments for these patients. Collaborations with other institutions to identify the genetic cause of childhood-onset HSP are ongoing, but more research funding is needed to support these efforts."

Genetic Types of HSP

Every child receives half of their genes from their mother and half from their father. The 70-plus genetic mutations that cause HSP and determine its symptoms can be transmitted by one of three main patterns of inheritance:

- **AUTOSOMAL DOMINANT**: In this most common form of inheritance, a person only needs to receive an abnormal gene from one parent who may have the disease. It's often seen in multiple generations, although *de novo* mutations can also occur.
- **AUTOSOMAL RECESSIVE**: This form requires the presence of mutated genes from both parents. Mothers and fathers must both carry a mutation that they pass on, although they typically have no symptoms themselves. Recessive disorders tend to occur in only one generation, most often when relatives marry other relatives.
- **X-LINKED**: This form of inheritance occurs in males who are hemizygous for the gene mutation, meaning they have a mutation only on their X chromosome (men also have a Y chromosome; women do not). Women have two X chromosomes and are therefore much less likely to be affected, since two copies of an abnormal gene would be required for the disorder to develop.

WHERE THE RESEARCH IS HEADING

Dr. Fink is encouraged by the pace of advancing research, which is focusing on three main areas. First, scientists are transforming skin samples from adults with HSP into cellular models of disease in the laboratory, and then using advanced techniques to test how they respond to various agents. Second, they are conducting human clinical trials to determine whether drugs showing promise in related conditions that have similar symptoms will have an effect on HSP. And third, they are studying animals that have been genetically modified to express HSP mutations and symptoms in order to explore the causes of the disease and potential treatments.

"None of us thinks of ourselves as just working on rare diseases, because we know we can apply the knowledge of what we find to other neurological conditions," says Dr. Blackstone. "Even though these individual diseases are rare, spasticity of the legs is not. It can occur when long neurons get damaged by stroke or spinal cord injuries, for example. We want to apply what we learn from HSP more broadly to patients with similar types of nerve damage."

The more science brings rare diseases together and links them in a common thread, the more likely it becomes that new therapies will emerge and interest major pharmaceutical companies. "It's an economic reality," Dr. Blackstone says.

Meanwhile, Brianna's reality involves trying to walk without assistance as much as possible. "She's not sick and she's otherwise healthy, smart, and beautiful," her mom says. "We focus on that and keep moving forward."

Recently, Karen participated in the Marine Corps Marathon in Washington, DC, while Brianna walked and ran in the children's one-mile fun run. The youngster prepped by running up and down her street, showing the same characteristic resolve that won her a leadership award at the end of kindergarten last year. "I might come in last, but I'm going to do it anyway," she says.

In fact, she didn't come in last, says her mom. "There were three girls behind her who walked the mile run." NN

FOR MORE INFORMATION:

- Learn more about HSP from The National Institute of Neurological Disorders and Stroke (NINDS) here: **bit.ly/NINDS-HSP**
- The Spastic Paraplegia Foundation offers resources and help for finding clinics and genetic testing sites: **sp-foundation.org**

COURTESY OF THE BERNARD FAMILY