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—ROBERT C. GRIGGS, M.D.

Too Rare for Research?

AFTER SURGERY
CJ Soeby’s hairline shows the evidence of his surgery for hypothalamic hamartoma, a rare neurologic disorder.

People with rare diseases often experience significant delays in diagnosis and access to few, if any, treatment options.

BY AMY PATUREL, M.S., M.P.H.

When Jon Soeby snipped his newborn son’s umbilical cord, baby CJ grunted. Astonished, the doctor joked that CJ was already trying to talk. But CJ’s parents felt something was wrong.

Over the next several days, Jon and Lisa Soeby noticed CJ grunted for about one minute every 15 minutes around the clock. They went to three different pediatricians; each claimed CJ had colic. Finally, after Jon demonstrated how CJ’s “colic” occurred in precise 15-minute intervals, the third doctor ordered more tests. They revealed a walnut-sized tumor lodged in the newborn’s brain.

“It turned out CJ’s grunting episodes were actually seizures,” says Lisa. “We were told CJ has hypothalamic hamartoma (HH)—a disease so rare that we’d never find another family

with a child who has it.” The condition involves gelastic (laughing) seizures, developmental delays, rage behaviors, and endocrine problems (such as early puberty and thyroid disease). CJ’s doctors claimed there was nothing they could do and that CJ would be in a group home by the time he was five years old.

“If you’re the only person with a disease, or one of two people, it’s going to be hard to find someone who is an expert in your disease,” says Robert C. Griggs, M.D., professor of neurology at the University of Rochester School of Medicine, Fellow of the American Academy of Neurology (AAN), former AAN president, and former editor-in-chief of the AAN’s medical journal *Neurology*. “It’s also going to be difficult to find agencies who are willing to fund research on a condition that affects so few people.”

The result: Individuals with rare or “orphan” diseases (affecting fewer than 200,000 people in the United States) often experience significant delays in diagnosis and access to few, if any, treatment options.

GETTING A DIAGNOSIS

When Maia Pinkelman was born, she appeared to be a typical child. But by eight months old, she still wasn’t able to sit on her own.

“We walked into the pediatrician’s office thinking there’s just going to be some minor problem. We came out being told that our daughter had cerebral palsy,” says Maia’s mom, Anne Rutkowski, M.D., an emergency physician at Kaiser Permanente in Southern California. One week later, Dr. Rutkowski and her husband, Joe Pinkelman, received a call from the pediatrician. Maia’s blood work revealed that she didn’t have cerebral palsy but an unidentifiable muscle disease.

“We took my daughter to as many doctors as we could find to understand what she might have. Each of them told us that they’d never seen anyone like her before,” says Dr. Rutkowski, who began specializing in rare diseases after Maia was born and co-founded the patient advocacy group CURE Congenital Muscular Dystrophy (curecmd.org) with two other parents.

Eventually, Maia was diagnosed with a rare form of congenital muscular dystrophy called alpha dystroglycan-related dystrophy (dystroglycanopathy), which is caused by a genetic mutation. Many rare diseases are caused by genetic defects present from birth.

“As physicians, we’re good at identifying common diseases. But when a disease affects fewer than 200,000 people, as rare diseases do, many physicians will never see it,” says David Robertson, M.D., professor of neurology and pharmacology at Vanderbilt University, member of the AAN, and editor of *Spotlight on Rare Diseases*, the publication of the National Institutes of Health (NIH) Rare Disease Clinical Research Network (rarediseasesnetwork.epi.usf.edu). And it’s impossible to be an expert in a disease that you’ve never seen—hence the reason



HANGING OUT
Maia Pinkelman has been successfully treated with steroids for a rare form of muscular dystrophy.

Maia waited eight years for her diagnosis. Studies show that it often takes five years or longer to get an accurate diagnosis of a rare disease.

Maia’s parents spent much of those eight years trying to learn how to communicate with their daughter. “She is an engaging teen, but she has significant cognitive impairment and limited expressive capabilities,” says Dr. Rutkowski. “She can speak five words. Maia uses a talking computer and sign language to communicate.”

They had given up on a diagnosis until Maia experienced a sudden loss of strength that left her unable to walk or lift her head off the bed. At that moment, the Pinkelmans redoubled their efforts. Dr. Rutkowski sent an e-mail describing her daughter’s condition to Francesco Muntoni, M.D., of Dubowitz Neuromuscular Centre in London, who has expertise in diagnosing muscle diseases—a man she found

through a physician friend of her mother.

Within half an hour, Dr. Muntoni e-mailed back suggesting that Maia might have a mutation in the protein-O-mannosyltransferase 1 (POMT1) gene. (Protein-O-mannosyltransferase 1 is an enzyme that places a sugar onto a protein in the muscle cell surface.) A laboratory at the University of Iowa confirmed those suspicions through a blood test. Maia became the first person in the United States identified with a mutation in POMT1 gene. One year later, she began taking steroids, which has stalled the disease progression, Dr. Rutkowski says.

“But even when there’s not a pill or a cure, getting a genetic diagnosis is really important because it can help a family understand and anticipate complications,” says Dr. Rutkowski. “A genetic diagnosis also contributes to our knowledge of a particular disease,” she adds—including how many people have it, what the signs and symptoms are, and how it might be treated.

“Knowing my daughter’s diagnosis enabled us to try a medication, which in her case worked and has maintained her ability to move around,” Dr. Rutkowski says.

Many families turn to the Internet to find experts and thereby get a diagnosis. Going to the Internet can be dangerous, as many Web sites are not trustworthy, and lists of symptoms can convince someone that he or she has any number of serious illnesses. But for people with rare diseases, scouring the Internet is a logical first step, according to Dr. Robertson.

“We have a patient who found her diagnosis—a disease that only 19 people in the world have—by Googling two of the hallmark symptoms,” Dr. Robertson says.

MONEY FOR RESEARCH

When patients finally do receive a diagnosis for a rare disease, finding treatment usually presents another challenge. Developing a new drug is costly, and since rare diseases affect relatively small numbers of people, companies are not always able to recover the expense of making the drug without government assistance.

Passed into law in 1983, the Orphan Drug Act offers incentives to companies who develop new drugs to treat a rare disease. Such incentives include tax credits for the costs of clinical research, unique opportunities to apply for grant funding, help designing clinical trials, and a seven-year period of marketing exclusivity after an orphan drug reaches the

American market, during which time no other sponsor may obtain approval of the same drug for the same use except under limited circumstances (though the FDA may approve a different drug for the same indication).

“Thirty years ago, you couldn’t get the pharmaceutical industry to pay attention to rare diseases,” says Dr. Griggs. “But with these new incentives and tax breaks, it has been possible for companies to pay for the cost of developing drugs for these diseases.”

The incentives appear to be paying off. During the decade before 1983, only 10 new treatments were developed by the pharmaceutical industry (“pharma”) to treat rare diseases. Since 1983, 2,200 treatments have entered the research pipeline, and more than 360 have been approved for marketing.

Similar to the Orphan Drug Act, the Humanitarian Device Exemption (HDE) allows a medical device to be marketed without requiring evidence of effectiveness. A device is eligible for a humanitarian exemption if, among other criteria, it is designed to diagnose or treat a disease or condition that affects fewer than 4,000 individuals in the United States per year. This enables patients who might benefit from the device to gain access to it while it’s still under investigation—a critical point for those affected by a rare disease since they have few, if any, approved treatment options.

However, cautions Dr. Robertson, people with rare diseases who are experiencing painful or debilitating symptoms may be willing to try anything—including unproven experimental drugs, procedures, and devices—to treat their condition. With-

out sufficient data, there’s no way to know whether these treatments will have negative effects over the long haul. For this reason, experts recommend having a frank discussion with one’s neurologist about the potential risks and benefits of any treatment.

RAISING AWARENESS

Building awareness of rare diseases can help attract young scientists, draw attention from pharma, and secure funding from the federal government. And when it comes to publicity, celebrity support can make a huge difference. Take Pro Football Hall of Famer and former Buffalo Bills quarterback Jim

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—ANNE RUTKOWSKI, M.D.

Kelly and his wife, Jill. They created Hunter's Hope Foundation (huntershope.org) in 1997 after their infant son, Hunter, was diagnosed with Krabbe leukodystrophy, an inherited and fatal neurologic disease.

In 2004, the organizations celebrated a significant milestone in its Comprehensive Universal Newborn Screening Awareness Campaign when New York State expanded their Newborn Screening Program, changing the total number of diseases screened at birth from 11 to 44. In 2006, Krabbe disease was added to the list of diseases included in newborn screening, making New York the only state that screened for Krabbe. Since then, Illinois, New Mexico, and Missouri have begun newborn screening for Krabbe along with four other similar diseases: Pompe, Gaucher, Niemann-Pick, and Fabry, demonstrating the power of celebrity to educate law makers and institute change.

Fortunately, you don't need someone with Kelly's name recognition to make progress in the world of rare diseases.

"A celebrity can certainly help raise support and awareness of a rare disease," says Dr. Griggs. "But I wouldn't underestimate the ability of non-celebrity patients and advocates to make an impact in terms of finding the cause and treatment for their disease."

However, some doctors worry about the cost of screening newborns for rare diseases and believe a more selective approach, when possible, is best. "A number of rare diseases seem to be confined largely to certain groups," explains Dr. Robertson. "Familial dysautonomia in Ashkenazi Jews is an example. The number of patients now being born with familial dysautonomia (which affects the development and function of nerves throughout the body) is in steep decline because of genetic testing. But genetic screening is not as cost-effective for very rare diseases distributed throughout the general population."

FINDING TREATMENTS

Only 200 of the diseases classified as rare have approved treatments. Many rare diseases don't even have consensus guidelines, a document that outlines how a given disease is treated.

"Developing consensus guidelines is a major first step for rare diseases. Care is often inconsistent, with little oversight and less accountability than for more common conditions," says Dr.

Rutkowski. "Without guidelines, doctors may be less proactive in their care. For example, they may be less likely to order genetic testing."

Instead, families may only be offered supportive care to manage the symptoms, even when a treatment that might change the course of the disease is available. In the case of hypothalamic hamartoma (HH), supportive care means trying to control seizure activity. Unfortunately, antiepileptic drugs (AEDs) may not be effective in a child who has HH.

Nevertheless, CJ was on AEDs for three years. "He was throwing up all kinds of colors and was absolutely numb," says Lisa. "I knew we had to try something different."

After CJ was diagnosed with HH at three months old, the Soebys moved to Phoenix, AZ, to be near Barrow Neurological Institute (BNI). For three years, while CJ was on AEDs, they scoured medical libraries and consulted with neurologists. Because HH was so rare, information was scant. It wasn't until they found families with children who shared the same diagnosis in an Internet chat room that the

Soebys realized they weren't alone—and that there was hope.

They learned about an 11-year-old girl in Melbourne, Australia, who was about to undergo surgery to remove her HH tumor. The neurosurgeon who would perform the surgery had been practicing on cadavers for six months, going deep into the brain to remove the tumor without damaging surrounding structures. This young girl would be his fifth live patient.

"The surgery was hugely successful—the girl's last seizure was right before the procedure," says Lisa. "We approached the doctors at Barrow and asked them to perform the same operation on CJ, but they said it was too risky. So we went to Australia, where they had a different point of view."

According to Dr. Robertson, people with rare or incurable diseases may be vulnerable to the aggressive promotion of risky, experimental treatments with unproven benefits. (See "To China for Stem Cells" at <http://bit.ly/yCxi2i> for an example.) On the other hand, says Dr. Robertson, some countries may be farther along in their investigation of a particular disease than others because their researchers have seen more of it.

After consulting with their neurologist about the risks and

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—LISA SOEBY

benefits of the surgery, the Soebys decided to try it. They flew to Australia, where CJ's four-hour surgery was a success. He became seizure-free and has experienced no complications, according to the Soebys. When the family returned from Australia, they brought CJ back to the doctors at BNI and urged them to reconsider offering the surgery to patients.

"Six months later, our surgeon from Melbourne came to Barrow to perform the procedure on six children," says Lisa. "All of them were from our online support group, which had grown to include more than 100 families from all over the world."

Today, BNI has successfully treated more than 150 HH patients from all over the world. While the surgery does not cure the disease—and many patients require subsequent surgeries—it has stopped or significantly reduced seizures for many of these patients, improving their quality of life.

PUSHY PARENTS

The Soebys' experience illustrates the need for advocacy to accelerate treatments for rare diseases, particularly in terms of bringing the right people to the table.

"The only way that significant advances are made for any rare disease is by building a network of doctors, allied health professionals, people with the disease, scientists, and advocacy groups, all working together with the federal government," says Dr. Rutkowski. "Only when you achieve that level of support and collaboration are you able to move research into the disease forward."

Such collaboration allows experts to identify common symptoms, define appropriate treatments, establish consensus guidelines, and translate those guidelines into lay language so families are armed with the necessary tools to really understand what proactive care means. That way, if a physician isn't taking the appropriate steps, the family knows it.

"If your doctor is unresponsive, you have to be willing to move on to the next one," says Lisa. "And if that one doesn't do it for you, again, be willing to move on to the next one. You have to find a physician who is willing to partner with you to understand your child's condition."

As awareness grows, diagnosis of diseases like HH is increasing, which suggests that some rare diseases may not be quite as rare as once thought, just misdiagnosed. And as with any uncharted medical territory, educating neurologists and other doctors to recognize the symptoms and provide a correct diagnosis is a critical first step in offering hope to patients with rare diseases.

The Soebys say they were lucky that CJ's seizures followed such a regular pattern, making them hard to miss. But other families aren't as fortunate. Some children with HH have infrequent seizures or other symptoms such as developmental

Finding Help for a Rare Disease

Despite tremendous advances in recent years, many doctors still don't know what to do when presented with a rare disease.

"With 6,000 to 7,000 rare diseases, how can you be an expert in all of them?" asks Dr. Rutkowski. "This is where the team approach becomes so critical"—and where patient advocates are so important.

- ▶ **DO YOUR RESEARCH:** Visit clinicaltrials.gov to learn about ongoing research studies for people with the disease and search reliable Web sites like the National Institutes of Health (nih.gov), the Centers for Disease Control and Prevention (cdc.gov), the National Institute of Neurological Disorders and Stroke (ninds.nih.gov) or the Web sites of patient advocacy groups.
- ▶ **CONTACT THE NATIONAL ORGANIZATION FOR RARE DISORDERS (NORD; 800-999-6673; rarediseases.org):** NORD has genetic counselors and registered nurses on staff who can help locate information about the disease and determine what type of doctor would be an appropriate starting point.
- ▶ **VISIT A TEACHING FACILITY:** Teaching hospitals that are affiliated with a university are more likely to have experience with rare diseases than community hospitals. If you need help locating a teaching hospital, contact NORD—they can point you in the right direction.
- ▶ **FIND OUT IF THERE'S A PATIENT ORGANIZATION FOR YOUR DISEASE:** Search the Patient Organizations Database on NORD's Web site to find organizations for people with a particular rare disease.
- ▶ **TAKE NOTES:** Keep a notebook at home and jot down any questions or concerns so you won't forget to mention them when you see the doctor.

delays and endocrine issues that can be confused with more common conditions.

Understanding all of a disease's signs and symptoms is crucial to better diagnosis and treatment. "As advocates, we need to help the medical community come up with the best set of diagnostic tools possible," Lisa says.

Today, CJ is an active 14-year-old. He's in a regular classroom and participates in boy scouts, sports, and bowling—a far cry from the group home predicted back in 1997.

"My goal is to encourage parents to be involved and not be afraid to challenge the medical community," says Lisa. "You have to be your child's best advocate. Trust your instincts and join the proud ranks of 'Pushy Parents.'" NN



For more information on rare diseases, see Resource Central on page 37.