MITOCHONDRIAL DISEASE — A CASE STUDY

A TALE OF TWO BROTHERS

Mitochondrial disease is one of the mysteries of modern medicine. A shape shifter of maladies, it can produce many different symptoms, affect different organ systems and respond in different ways to treatment. But our understanding of mitochondrial disease is growing — and nowhere is progress occurring more rapidly than at Mitochondrial Medicine, a program at Children's Hospital of Philadelphia (CHOP). The story of two brothers illustrates the complexities and long journey for answers many patients experience.

Mystifying Symptoms

Now in their 40s, M. and J. first showed signs of mitochondrial disease as young adults — although it would be years before they knew just what was afflicting them.

As a college junior, M., previously healthy and well-adjusted, began exhibiting behavioral changes — drinking heavily and struggling with his coursework. At age 24, he developed double vision and was unable to track moving objects. Despite extensive tests, his doctors struggled to find a cause. Eventually, M. suffered a psychotic break, characterized by violent outbursts. He would scream, "Get this thing out of my head!"

Meanwhile, younger brother J., known for his outgoing personality, began experiencing similar issues. He had double vision and showed changes in behavior, growing more withdrawn and neglecting personal hygiene. After collapsing at a college party, J. was hospitalized with dangerously low magnesium and potassium levels. But again, no underlying cause could be found.

The distraught family ultimately sought help from a neurologist, who spent the next two years working to unravel the brothers' mysterious health problems. It was he who first suspected mitochondrial disease.

The Batteries of the Cell

Mitochondria are specialized compartments within all of the body's cells, except for mature red blood cells. Scientists often liken mitochondria to batteries, as they are responsible for generating the energy cells need to function properly. They are especially important in high-energy-demanding organs like the heart and brain. All told, mitochondria are responsible for creating 90% of the body's energy.

Mitochondrial disease occurs when mitochondria anywhere in the body malfunction. Because so many different organ systems can be implicated, mitochondrial dysfunction can cause a wide range of symptoms, including fatigue, weakness, exercise intolerance, developmental disabilities, seizures, stroke, vision or hearing loss, feeding and growth difficulties, hormone imbalances, and serious problems with heart, liver or kidney function. The average mitochondrial patient seen at CHOP, whether a child or adult, presents with 16 different symptoms.

Answers at Last

J.'s and M.'s doctor suspected both brothers had a form of mitochondrial disease known as Leigh syndrome, which causes progressive neurologic deterioration and often early death.

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Even with the same disease, the brothers were affected differently — M. with primarily psychologic issues, J. with a range of functional symptoms. Although they began treatment, it was another eight years before the tentative clinical diagnosis would be confirmed by definitive genetic testing.

J. ultimately underwent whole exome sequencing, an analysis of all 20,000 genes in the body. The testing uncovered a mutation in the *SURF 1* gene. Further testing of the entire family revealed that both parents were single mutation carriers of the *SURF 1* gene. Their sons inherited a copy of the defective gene from each parent, with late-onset manifestations of Leigh syndrome.

Little Known, But Not Rare

Mitochondrial disease is not extremely rare. Worldwide, it affects at least 1 in 4,300 people. Every 30 seconds, a child is born who will develop mitochondrial disease by age 10.

This new field of medicine was discovered less than 30 years ago, by Doug Wallace, PhD, a mitochondrial pioneer who is now Director of the Center for Mitochondrial and Epigenomic Medicine at CHOP.

While all of the possible causes are not yet fully understood, primary mitochondrial dysfunction is known to be genetic — and may result from mutations in any of more than 300 different genes located either in the nucleus or mitochondria of cells. Any known inheritance pattern may therefore be seen among the many different types of mitochondrial disease.

The Roberts Individualized Genetic Medicine Center at CHOP provides the full spectrum of genetic testing — including exome and genome sequencing — and works to assist clinicians with analysis and interpretation of results. Today, genetic testing is often the first-line test performed to evaluate for and establish a specific diagnosis when mitochondrial disease is suspected.

Expert, Personalized Care

Finally, M. and J. had answers, but their journey was far from over. A quest for research studies in which they could participate led them to CHOP, where J. was accepted into a trial in 2016. The hospital's Mitochondrial Medicine program, led by Marni Falk, MD, is a world leader in diagnosis and treatment of the disease, which usually presents in childhood but, as happened in this family, may not develop until adulthood.

Eventually both brothers were enrolled in research studies at CHOP, requiring frequent visits to Philadelphia. As a result, they are now cared for by the Mitochondrial Medicine program's multidisciplinary team, which includes physicians, genetic counselors, nurses, a nurse practitioner, social worker, physical therapists, a dietitian, exercise physiologist, and laboratory and clinical researchers.

There is no cure for mitochondrial disease. In some cases, it is managed with medication, along with carefully monitored diet and exercise plans. As each case is unique, a personalized approach to treatment is essential.

There is still much to learn about mitochondria, how they function and how they can go awry. The Mitochondrial Medicine program at CHOP is at the forefront of discovery. Areas of focus include the development of more precise lab tests to diagnose and guide management, as well as less invasive testing methods that use exercise, MRI, nanosensors and ophthalmologic assessments to better assess mitochondrial function as it changes over time and in response to candidate therapies. Pre-clinical modeling is done to better understand the impact of different genetic and chemical causes of mitochondrial disease, evaluate candidate therapies and treatment combinations, and develop highly individualized treatment plans to bring back to the patients.

With close adherence to their medication plans and improved eating and exercise habits, M. and J. are feeling the best they have in years. Their parents note they are more alert and focused. While their disease prognosis remains serious, they have shown good overall stability and are better informed about how to manage and optimize their well-being.

As their mother Barbara says: "After 20 years ... we are in the right place. When we ask questions, we get answers from real knowledge, based on international research. Without CHOP, we wouldn't feel so comfortable about our sons' future."

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