



A Look at Mitochondrial Disease

Mitochondrial disorders occur in 1 in 5,000 individuals. These rare conditions often are misunderstood and may be mistaken for other, more common diseases.

Mitochondria are in every cell in the body except in the blood cells, and they produce the majority of the energy of adenosine triphosphate (ATP). When mitochondria are not functioning properly, the result can be life-altering and affect almost any part of the body. We asked Hilary Vernon, MD, PhD, associate professor of genetic medicine in the department of genetic medicine at Johns Hopkins University, to explain the issue further and the research being done to find treatments.

MDA: How do mitochondrial disorders affect the body and what are some of the most common disorders?

Dr. Vernon: Every organ system requires energy and, in general, systems requiring more energy, like muscles, the brain, and the eyes, tend to be commonly affected.

The genetic information in mitochondria is located in two places. One is in the cells. There are 37 genes in mitochondria, and when we think of the most common disorders with the highest incidence for mitochondrial disorders, a couple are mitochondrial encephalomyopathy, lactic acidosis, and stroke (MELAS) and myoclonic epilepsy with ragged red fibers (MERRFs). There is also neuropathy that can cause isolated eye disease and other symptoms.

MDA: What are current treatments for mitochondrial diseases?

Dr. Vernon: Currently, there isn't a cure for mitochondrial disorders. There are disorders, such as nucleotide imbalance, where if you can directly supply the missing substrate you can improve mitochondrial dysfunction. Or where there is a defect in synthesis you can give something that can target the disorder. But, in general, with what most commonly affects mitochondrial energy production, there isn't a specific treatment targeted at that disorder. But we can attempt to manage the symptoms chronically and manage the acute systems.

MDA: What have been some of the advances in treatment and what treatment is in the early stages?

Dr. Vernon: There have been a number of clinical trials targeting different aspects of the disorders. There is the approach to increase mitochondrial biosynthesis or increase mitochondrial numbers and those are in clinical trials. There are some trials for agents to reduce oxidative stress. There are studies aimed at improving mitochondrial structure and function, intervening, for example, when it comes to the mitochondrial membrane. There are bigger picture studies focusing on replacing mitochondria, such as stem cell treatments. For example, with some disorders that affect the bone marrow, a bone marrow transplant can improve the disorders.

Directly targeting the cause of the disease, a number of gene therapy approaches are being evaluated. Because of the makeup of the mitochondria, it's difficult to get things in and out. There is a focus on defects of enzyme function and here mRNA therapy essentially is sending what would be the transcribed gene message into the cell and then the cell produces whatever is missing, and that can be activated in the cell and replace the missing enzyme.

MDA: How has treatment for mitochondrial diseases progressed and what is the outlook for the decades ahead?

Dr. Vernon: In the last 20 years, the clinical utility has improved, such as in large scale gene sequencing. Over time, many disorders have benefited from a sense of natural history in what to expect from treatment and how someone responds to therapies. This helps us understand how to match patients and it's informing why certain populations respond to a therapeutic agent and others don't.

In addition, companies used to not spend much time on rare and ultrarare diseases, but therapeutic interest has changed. Partly because of this, it's now a time of optimism.