Understanding **Primary Mitochondrial Myopathy**

Our muscles need energy to function. That energy comes from our mitochondria.

Mitochondria are tiny structures inside almost every cell in our bodies. Each person has trillions of them working to convert oxygen and food into a special type of energy called adenosine triphosphate, or ATP. 90% of the energy our muscles need comes from ATP.

Some cells have a single mitochondrion while others contain hundreds of them. Someone who does not have enough healthy mitochondria, in one or several muscle groups, is said to have mitochondrial myopathy, or mitochondrial disease.

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Mitochondria provide our muscles with the energy they need to function.

ATP is the main source of energy for our cells. It is comprised of adenine, a ribose sugar and three phosphate groups linked together by two high-energy bonds.

Amino acids combine in different patterns to create the essential proteins we need to live, grow and reproduce.

Proteins perform specific functions depending on what amino acids are used to construct them and the order in which they are connected.

DNA (deoxyribonucleic acid) is a long molecule that contains genes. Changes in nuclear DNA (nDNA) or mitochondrial DNA (mtDNA) can cause Primary Mitochondrial Myopathy (DMM).

Genes contain special instructions for creating specific proteins that each have a unique purpose. Humans have over 22,000 genes. Some genes are linked to energy production.

Gene mutations are changes to genes that may impair instructions for making proteins. This may result in too many or too few proteins being produced, or for them not to work properly.

Primary Mitochondrial Myopathies are complex -- to diagnose and treat. The importance of getting an early and accurate diagnosis cannot be underestimated.
- Dr. Samantha Marin

Myopathy literally translates to muscle disease	myo = muscle pathose = disease

Types of Mitochondrial Myopathy

Primary Mitochondrial Myopathy, or PMM, is inherited. It is usually diagnosed when changes, known as mutations, are identified in the genes of our DNA responsible for creating ATP.

Secondary Mitochondrial Myopathy, or SMM, causes similar dysfunction in the mitochondria but the mutations occur in genes not involved in energy production. SMM can either be inherited or develop as a result of exposure to environmental toxins.

Symptoms of Mitochondrial Myopathy

The two most common symptoms of mitochondrial myopathy are muscle weakness and exercise intolerance that leads to unusual feelings of exhaustion. Patients often also have symptoms in their organs. In fact, people with mitochondrial diseases often have symptoms affecting three or more organs. This is because organs like the brain, nerves, heart, pancreas, liver, eyes, and kidneys have high energy needs.

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Mitochondrial Syndromes

Mitochondrial disease symptoms may include impaired hearing and vision, ataxia (challenges with balance, coordination and speech), seizures, learning disabilities, heart defects, diabetes, and poor growth.

Symptoms affect everyone differently and can vary from mild to life-threatening. Younger people tend to have more debilitating conditions. Children with mitochondrial disease may have difficulty developing certain skills such as sitting, crawling, walking, speaking and learning.

Because most people with a mitochondrial myopathy experience symptoms that affect multiple systems at the same time, common symptoms are grouped together and referred to as syndromes. Some of these symptoms are outlined below:

Syndrome	Symptoms
Barth Syndrome *Infancy or early childhood (sometimes adulthood)*	• Enlarged heart • Increased rate of infections • Delays in growth before puberty • Low muscle tone (hypotonia) • Muscle weakness • Specific facial appearance (round face, full cheeks, pointed chin, large ears, deep-set eyes) • Certain laboratory findings, for example: high lactate, low white blood cell count, low cholesterol, increased 3-methylglutaconic acid and 2-ethyl hydracrylic acid in urine or blood, increased monolyso-cardiolipin: cardiolipin ratio • Mainly impacts males
CPEO Chronic Progressive External Ophthalmoplegia *Adolescence or early adulthood*	• Weakness of the eye muscles leading to decreased ability to move the eyes • Ptosis (weakness of the eyelid muscle leading to drooping of the eyelids)
KSS Kearns-Sayre Sydrome *Before age 20*	• Weakness of the eye muscles leading to decreased ability to move the eyes • Ptosis • Abnormal pigment in the back of the eye (pigmentary retinopathy) which may affect vision • Failure to thrive • Abnormal heart rhythm • Ataxia • Certain laboratory findings such as increased protein in cerebrospinal fluid
Leigh Syndrome Note: when inherited through mtDNA, it may be called MILS or Maternally Inherited Leigh Syndrome *Infancy (3 – 24 months) or early childhood*	• Rapid loss of developmental skills, including head control, sitting, standing, or walking following earlier normal development • Decreased level of consciousness • Difficulty breathing • Weakness • Seizures • Low muscle tone (hypotonia) • Ataxia • Abnormal movements • Enlarged heart muscle • Failure to thrive • Certain laboratory findings such as high lactate

Syndrome	Symptoms
MDS Mitochondrial DNA Depletion Syndrome *Infancy to adulthood*	• Impaired energy production affecting muscle, liver, brain and kidneys May experience: • Intractable seizures • Liver problems • Ataxia • Weakness and numbness in the limbs • Hearing loss • Difficulty with eye movements and drooping eyelids • Difficulty gaining weight
MELAS Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like Episodes Syndrome *Childhood to early adulthood Sometimes onset may be as late as 40 years*	• Dementia • Seizures • Migraine headaches • Stroke-like episodes • Recurrent vomiting • Weight loss • Exercise intolerance and weakness • Hearing loss
MNGIE Mitochondrial Neurogastroin-testinal Encephalomyopathy *Infancy to adulthood, usually before age 20*	• Difficulty moving food through the digestive tract • Peripheral neuropathy (numbness and weakness in limbs, hands and feet) • Ptosis • Ophthalmoplegia • Hearing loss • Leukoencephalopathy (abnormal white matter in brain)
MERRF Myoclonus Epilepsy with Ragged Red Fibres *Childhood to adulthood*	• Muscle twitching (myoclonus) • Seizures • Ataxia • Muscle weakness and exercise intolerance • Hearing loss • Dementia • Enlarged heart muscle
NARP Neuropathy, Ataxia, and Retinitis Pigmentosa *Infancy to adulthood*	• Peripheral neuropathy • Muscle weakness • Ataxia
Pearson Syndrome *Infancy*	• Anemia that usually requires frequent transfusions • Signs of pancreas dysfunction

Diagnosing Mitochondrial Myopathy

There are many factors that make diagnosing mitochondrial myopathy difficult. It affects anyone from children to the elderly, impacts each person differently, and many family physicians are not familiar with the disease.

The process leading to a diagnosis can be long. It usually begins with your physician taking a medical history, conducting a thorough physical evaluation, measuring your strength and endurance, and possibly ordering a series of specialized tests outlined below.

Test	
CT or CAT Scan Computed (Axial) Tomography	Using computers and rotating X-ray machines, the CT creates images to provide detailed information about soft tissues, blood vessels, and bones in various parts of the body.
ECG or EKG Electrocardiogram	This fast and simple test records the electrical signals in your heart. Electrodes connect to the ECG machine through wires placed on certain spots on your chest, arms and legs. Specialists will be looking for signs of arrhythmia or cardiomyopathy.
Echo Echocardiogram	An echocardiogram is similar to an ECG but looks for irregularities in the structure of your heart using ultrasound. This test is used to look for signs of cardiomyopathy.
Electromyography	This test assesses the health of muscles and nerves. An electrode is inserted through the skin into an affected muscle. The machine records electrical activity of the muscle and can determine whether muscle weakness is caused by the muscle itself or the nerves that control the muscle. This is often done at the same time as a nerve conduction study (see next page).
Genetic Testing	Genetic testing can determine whether someone has a genetic mutation in the nDNA or mtDNA that causes mitochondrial disease using blood, muscle or saliva samples. *Note: there is no genetic test that completely rules out a genetic condition.*
Laboratory tests	Blood or urine are standard tests used to detect problems with various organs, including the liver and kidney. These tests also look for elevated lactic acid levels, which is common for those living with mitochondrial disease.

Many people are misdiagnosed or go undiagnosed for years. Sadly, most patients will see a variety of specialists over a period of years, before receiving the diagnosis and care they need.

Test	
MRI Magnetic Resonance Imaging	MRI machines use a magnetic field and computer-generated radio waves to create detailed 3D images of organs and tissues that can be evaluated by a specialist.
MR Spectroscopy Magnetic Resonance Spectroscopy	Using the MRI machine, this test measures levels of phosphocreatine and ATP. Muscles of people with mitochondrial disease are often depleted of these molecules.
Muscle Biopsy	This procedure involves removing a small sample of muscle, usually from the thigh. The sample is then treated with a dye. Muscle fibres affected by mitochondrial disease show as a distinct red and have a ragged appearance.
Nerve Conduction Study	This test evaluates the ability and speed of nerve impulses and can be used to rule out conditions other than PMM.
Neurological Test	This test uses tuning forks, flashlights and/or reflex hammers to evaluate motor and sensory skills, hearing, vision, speech, coordination, and balance.
Spinal Tap or Lumbar Puncture	A needle is inserted between two vertebrae to remove a small amount of cerebrospinal fluid (CSF) to measure folinic acid, protein and/or lactic acid levels. CSF surrounds and protects the brain and spinal cord. Elevated lactic acid or protein levels as well as low folinic acid may indicate mitochondrial disease.

Clear Communication Leads to Better Care

It is your role as a patient, or advocate for your loved one, to ensure that you provide your health care team with accurate information so they can make an early and accurate diagnose. Once you have the diagnosis, a care plan can be created specifically for you.

Protecting Future Generations

The risk of passing mitochondrial disease on to a child depends on many factors, including whether the disease is caused by genetic mutations in nDNA or mtDNA. These risks should be discussed with a doctor or genetic counsellor.

Treating Mitochondrial Myopathy

At this time, there is no cure for mitochondrial disease. The goal of current therapies is to relieve symptoms and improve quality of life. Most therapies involve nutritional supplements and exercise programs with a special diet being a possible solution for some. In many cases, those living with the disease may need devices and therapies to help them breathe, eat, move and learn.

Nutritional supplements

Recommended supplements contain natural substances involved in ATP production in our cells and include:

Creatine: Creatine phosphate typically provides a burst of ATP, which is required for strenuous muscle activity.

Carnitine: Carnitine helps improve the efficiency of ATP production by recruiting molecules into mitochondria to clean up some of the toxic by-products of ATP production. This is sold as L-carnitine.

Coenzyme Q10 (CoQ10 or ubiquinone/ubiquinol) is an antioxidant and component of the process that makes ATP. For those mitochondrial diseases that are caused by CoQ10 deficiency, supplementation may be helpful.

Mito Cocktail: This is a combination of supplements. The components of the cocktail may vary depending on the condition being treated and may include creatine, L-carnitine, alpha-lipoic acid, riboflavin, and CoQ10.

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Exercise

Research shows that some patients with mitochondrial myopathy may see lower fatigue, improved health, and better quality of life when they exercise according to a plan designed specifically for them. Moderate endurance exercise can help increase aerobic fitness. Resistance training can increase strength. It is important to note that new programs should be introduced slowly and that overexertion should be avoided.

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Hope on the Horizon

Scientists have recently identified many genetic mutations that cause mitochondrial myopathy. This means that diagnostic tests may better predict who is most at risk so the onset of disease can be prevented and treatments can be designed.

There are exciting possibilities on the horizon, including:

- treatments that recruit healthy mitochondria or encourage healthy mitochondria to multiply and outnumber damaged or dysfunctional mitochondria
- repairing or bypassing defective mitochondria
- stimulating development of new and healthy mitochondria
- mitochondria replacement therapy (MRT) which could potentially prevent the passing on of mitochondrial mutations from parent to child

Also encouraging news is that the U.S. Food and Drug Administration (FDA) has granted Fast Track designation to two drugs to facilitate and expedite the development of investigational treatments that show potential benefits for those with mitochondrial myopathy. We hope these options will soon extend to Canada.

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MitoCanada is the Canadian charity dedicated to creating a world where all lives are powered by healthy mitochondria. Visit us at: www.MitoCanada.org.