Mitochondrial myopathies

Definition

Mitochondrial myopathies are a group of neuromuscular disorders that result from defects in the function of the mitochondrion, a small organelle located inside many cells that are responsible for fulfilling energy requirements of the tissue. These structures serve as "power plants" and are particularly important for providing energy for both muscle and brain function due to the large requirement for energy in these tissues.

People affected with one of these disorders usually have muscle symptoms such as weakness, breathlessness, exercise intolerance, heart failure, dementia, stroke−like symptoms, deafness, blindness, seizures, heavy eyelids or eye problems, and/or vomiting. Originally, mitochondrial myopathies were recognized based solely on clinical findings. Currently, there are genetic explanations that provide additional information that is usually consistent with the clinical diagnosis and can, in some cases, help determine the long−term prognosis. Mitochondrial myopathies can also result as secondary effects from other diseases.

Description

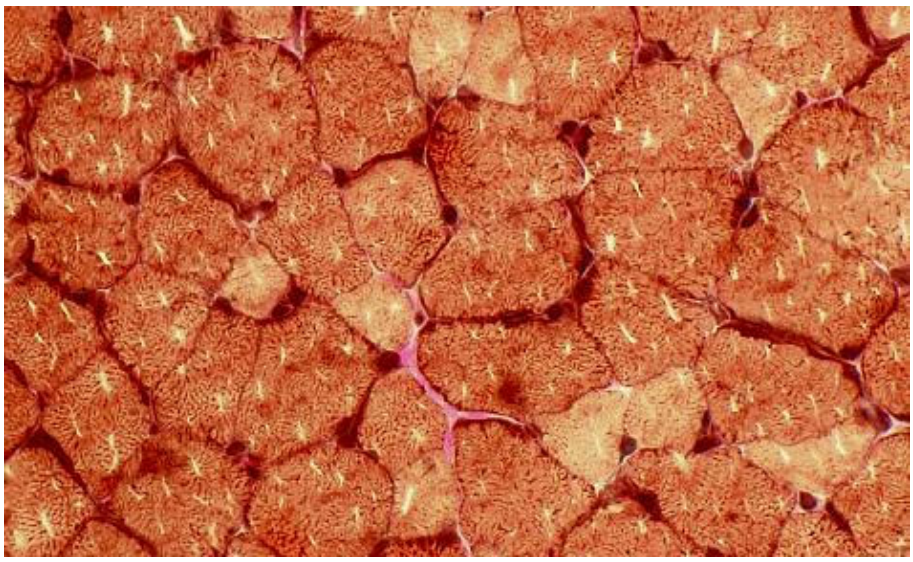
Myopathy means a disorder of the muscle tissue or muscle. Mitochondrial myopathies are, therefore, disorders of the muscle tissue caused by abnormalities of the mitochondria.

The following disorders are the most common mitochondrial myopathies, including:

- NARP: neuropathy, ataxia and retinitis pigmentosa
- KS: Kearns−Sayre syndrome
- Leigh's syndrome
- PEO: progressive external ophthalmoplegia
- MILS: maternally inherited Leigh's syndrome
- MELAS: mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes
- MERFF: **myoclonus epilepsy** with ragged−red fibers
- Pearson syndrome
- MNGIE: mitochondrial neurogastrointestinal encephalopathy
- LHON: Leber hereditary optic neuropathy

Demographics

The initial disease−causing or disease−related (pathogenic) alterations in mitochondrial DNA (mtDNA) were first identified in the early 1990s. Currently, more than 50 different single−base pathogenic mutations in the mtDNA sequence and more than 100 different pathogenic rearrangements within the genome have been identified. These include large deletions or duplications in the mtDNA sequence of bases. With the high mutation rate, it would seem that the prevalence of mitochondrial myopathies would be high; however, mitochondrial myopathies are relatively rare, having an incidence of



Fat accumulation in muscle. The focal ragged red fibers are consistent with mitochondrial myopathy.

approximately six out of every 100,000 individuals to as high as 16 out of 100,000 individuals. But there is evidence that, as part of the normal aging process, the accumulation of mtDNA mutations leads to neurological changes and abnormalities such as hearing loss or diabetes, which are normally considered to be

associated with aging.

Causes and symptoms

In most cases, the primary defect in mitochondrial myopathies results from mutations in important genes that determine (encode) the structure of proteins that function in the mitochondria. Mutations can be found in DNA from the nucleus of the cell. This DNA is known as nuclear DNA, which is the DNA that most people consider with respect to human genetic diseases, but DNA is also found in the mitochondrial genome. Mitochondrial myopathies can be caused by defects in nuclear and mitochondrial DNA.

Mitochondrial DNA (mtDNA) is much smaller than nuclear DNA (nDNA). Nuclear DNA has approximately 3.9 billion base pairs in its entire sequence; mtDNA has only 16,500 pairs. Although mtDNA is much smaller in size, each cell contains anywhere from 2?100 mitochondria, and each mitochondria has 5?10 copies of its genome.

Unlike nDNA that is twisted into a double helix, mtDNA has a circular structure. Mitochondrial DNA also has a high mutation rate, almost 20 times that of the nDNA. All of these factors are important in understanding the role of mtDNA mutations in the development of inherited or other mitochondrial myopathies.

A unique feature of mtDNA is that out of the more than 1,000 mtDNA genomes within the cell, a new mutation in one of the mtDNA genomes can be replicated each time the cell divides, thus increasing the number of defective mtDNA genomes. Because the distribution of the newly replicated mtDNA into the two daughter cells is random, one of the daughter cells may contain mtDNA that is not mutated (a condition referred to as homo−plasmy), while the other daughter cell inherits both mutation genomes (known as heteroplasmy, or a mixture of mutated and normal genomes). Knowing the percentage of heteroplasmy for different mutations is often helpful in determining whether the disorder will manifest symptoms, as well as how severe they might be. As a result of the heteroplasmic nature of mitochondrial myopathies, the range of symptoms and severity of symptoms is often highly variable.

Mitochondrial myopathies are caused by mutations in either the nDNA or the mtDNA. These mutations generally affect tissues that have a high demand for metabolic energy production. Some disorders only affect a single organ, but many involve multiple organ systems. Generally, nDNA mutations result in clinical symptoms that develop during early childhood, while mtDNA mutations (either directly or as secondary effects from a nDNA mutation) lead to clinical manifestations that develop in late childhood or early adulthood. The genes that comprise the mtDNA genome encode proteins that function inside the mitochondria. For example, sugar broken down from food is used for fuel to manufacture a specific molecule, adenosine triphosphate (ATP), which is used by the cell to accomplish a variety of essential functions. ATP is produced by charged particles called electrons that come from digested food products to harness the energy. This is accomplished through five highly organized protein complexes. The first four complexes (complex I, II, III, and IV) are part of the electron transport chain and function to move the electrons towards the fifth complex (complex V), which produces the ATP molecule. A defect in any one of these complexes can lead to mitochondrial myopathies. Both DNA from the nucleus and the mitochondria are required to assemble the many subunits that make up these complexes.

The process of producing ATP requires oxygen. This is essentially why humans cannot live without it. In the absence of a properly functioning electron transport chain, precursor molecules as well as unused oxygen begin to accumulate. One molecule in particular, called lactic acid, accumulates normally during strenuous exercise when tissue demands for energy cannot be met, resulting in muscle fatigue. This occurs essentially by

accumulation of lactic acid, or lactic acidosis. Persons with a deficiency in the electron transport chain, therefore, have symptoms similar to an athlete's muscle fatigue, but without the factor of strenuous exercise. Both muscle contraction and nerve cell stimulation requires ATP; thus, these cells are particularly sensitive to defects in mitochondrial function. Furthermore, oxygen that is not metabolized can be converted into toxic compounds called reactive oxygen species (ROS). ROS can lead to many symptoms that an individual with a mitochondrial myopathy will experience.

Inheritance and medical significance

Mitochondrial DNA is inherited almost entirely from the maternal sex cell (the egg). Therefore, mutations or alterations in the mtDNA can be transmitted from a maternal sex cell to all the mother's children, regardless of gender.

Heteroplasmy, or the condition of having both normal and mutated mtDNA genomes, has several clinically important implications. If mtDNA molecules are deleted, they are generally not transmitted from the mother to her offspring for reasons that are currently unclear. If the mtDNA is duplicated (or various sequences are repeated with the same sequences such that the total size of the genome increases by exactly the number of repeated bases) or there is a mutation that only affects one base in the sequence, there usually is some of the mutant mtDNA molecules that get transmitted. Additionally, a phenomenon called the mitochondrial genetic bottleneck occurs during the production of the mother's sex cells (eggs). This term refers to a reduction in the number of mtDNA molecules followed by an amplification of this reduced mtDNA that occurs during maturation of the mother's eggs. The result is considerable variability in the amount of mutated mtDNA molecules that each of the offspring inherits. However, in general, mothers that have a higher amount of mutated molecules are more likely to have offspring that are more severely affected compared to mothers that have a lower mutant load.

Inheritance and the nuclear genome

Not all mitochondrial proteins are produced by the mitochondrial genome. In fact, the majority is produced by the nuclear genome. Therefore, mitochondrial myopathies can be caused by mutations in both the nDNA and the mtDNA. This has important implications for genetic counselors that assess the recurrence risks in families with affected offspring. If the defect is of nuclear origin, it is typically recessive. In this case, there is a 25% chance of having an affected baby if both parents are carriers. There are also dominant disorders leading to mitochondrial myopathies that are characterized by a carrier parent passing on the mutant nuclear gene to 50% of the offspring. There are many mitochondrial myopathies that do not have a mtDNA mutation, and there are no nDNA mutations known.

Scientists are increasing their understanding of the intercommunication between the nucleus and the mitochondria. The identification of nDNA mutations that cause mitochondrial myopathies was first made when a nuclear gene involved in mtDNA replication was found to be defective in a disorder involving a patient with a mitochondrial myopathy.

Symptoms of mitochondrial myopathies are largely variable from person to person, even within the same family, and are dependent on the amount and type of genetic mutations present. These disorders can occur in infancy, childhood, or adulthood. In general, individuals with mitochondria dysfunction have abnormalities in the central nervous system. Defects can involve seizures, movement disorders, **headaches**, and cognitive (thought) disorders such as developmental delay or dementia (forgetfulness, senility). People with mitochondrial myopathies can also have hearing loss.

It is common that symptoms become apparent in a specific cluster of abnormalities and are thus considered a syndrome. For example, Kearns−Sayre syndrome can be recognized clinically due to similar symptoms that patients have. These symptoms include ocular abnormalities (degeneration of the retina and external opthamaloplegia, or droopy eyelids), dysphagia (swallowing problems), progressive myopathy, and various central nervous system abnormalities such as hearing loss. Confirmation of this disorder can be performed by genetic analysis that looks for large deletions in mtDNA.

Due to the nature of the genetic and biophysical defects, mitochondrial myopathies have symptoms related to muscle weakness and atrophy. Droopy eyelids and loss of the ability to control eye movements indicate muscle wasting, which leads to paralysis, and compensatory attempts at correcting eye movements by tilting the head. Visual loss often occurs.

Muscle wasting, or myopathy, is not restricted to the eyes. The face and neck can also be affected, leading to incomprehensible speech and swallowing difficulties. Overall musculature wasting pervades many affected individuals, requiring wheelchairs and, in severe cases, assisted living requirements. Exercise−induced pain can also result.

Diagnosis

The diagnosis of mitochondrial myopathies is initially clinical, which means that it is based on the observable clinical manifestations that the patient shows versus results obtained from genetic analysis or laboratory tests. The physician will make careful observations of the affected child and interview the parents, in particular the mother, as it is common that she has the same mtDNA mutation, though usually at a lower percent load. Persons with mitochondrial myopathies are referred to a clinical geneticist for management and further evaluation, particularly in the absence of a confident clinical diagnosis. If there is a positive test after a genetic evaluation, genetic counseling is critical for understanding the nature of the disease and the implications for future offspring.

Diagnostic criteria

Any multi−system progressive disorder should lead a physician to suspect a mitochondrial disorder. A diagnosis can be particularly difficult if there is only one symptom. The diagnostic criteria for mitochondrial myopathies involve phenotypic evaluation (or evaluation of observable traits), followed by laboratory evaluation. A clinical diagnosis can be confirmed by laboratory studies, muscle biopsy, and molecular genetic evaluation, in which a geneticist analyzes the mtDNA. If a mtDNA mutation is detected, diagnosis is much more straightforward. In the absence of a mtDNA mutation, diagnosis becomes difficult.

There are several classical clinical manifestations that warrant DNA studies, such as in the case of MELAS, MERRF or LHON. Other disorders such as MNGIE require nDNA studies. In the absence of specific clinical criteria characteristic of a mitochondrial myopathy, blood plasma or cerebral spinal fluid is measured for lactic acid concentration, ketone bodies, plasma acylcarnitines, and organic acids in the urine. These are metabolites that are typically abnormal in an individual with a mitochondrial myopathy. If they are abnormal, a muscle biopsy is performed. Molecular genetic testing can often confirm a clinical diagnosis with or without positive laboratory results.

Treatment team

Treatment for patients with mitochondrial myopathies is best performed by a neurologist and a clinical geneticist or specialist that has experience diagnosing, treating, and managing patients with mitochondrial myopathies.

Treatment

There is no cure for mitochondrial myopathies. Therefore, treatment is solely for the purposes of minimizing pain and symptoms, and increasing mobility. Due to the wide variability in the disorders, treatment is usually individualized. Although the diseases are rare, many of their clinical symptoms are common and treatable. There are medications and lifestyle modifications that can help treat conditions such as headaches, diabetes, stroke−like symptoms, and seizures that are often associated with mitochondrial myopathies.

Medications are tailored to reduce the specific symptoms that the patient is experiencing (anticonvulsant medication may be required, for example, for an individual suffering from seizures). Dietary supplements are often used, although they have not been investigated in longterm studies. Creatine, coenzyme Q 10, and carnitine are naturally occurring supplements that are thought to enhance ATP production.

Recovery and rehabilitation

Because there is no cure for mitochondrial myopathies, the focus is on maintaining optimum function for as long as possible, rather than recovery. Physical therapy helps extend the range of muscle movement. Occupational therapy helps with positioning and mobility devices, and trains the affected individual in strategies designed to accomplish self−care and activities of daily living. Speech therapy can help children and adults that have difficulty in speaking, as well as how to safely eat and swallow food. Hearing and visual aids (glasses) are often necessary and helpful.

Clinical trials

As of early 2004, there were few clinical trials to develop therapies to treat mitochondrial myopathies. There was one study to investigate the role of dichloroacetate to lower lactate levels in patients diagnosed with MELAS at the National Institutes of Health (NIH). Lactic acidosis has been shown to be associated with nerve cell and muscle cell impairment in patients that have MELAS. Decreasing the levels of lactate might help prevent severe lactic acidosis.

Prognosis

Mitochondrial myopathies are extremely variable in the symptoms produced, and so the prognosis for those affected with mitochondrial myopathies also varies. The adverse affects on muscle function are often progressive, and persons often show physical deterioration over time. Occasionally, affected persons are mentally delayed. It is difficult to determine the exact course that each individual will endure, and in many cases the symptoms are relatively mild. Life expectancy for a person with a mitochondrial myopathy depends on many different circumstances, including the percentage of mtDNA that is mutated, the type of mutation,

and the tissue in which it is mutated. If it is a nDNA defect, the physical and developmental effects depend on the gene that is mutated, the location of the mutation in the gene, the importance this gene has on the function of the mitochondria, and whether there are compensatory mechanisms. Overall, the prognosis is dependent on the involvement of vital organs.

Special concerns

Perhaps one of the most problematic issues that patients with mitochondrial myopathies experience is the absence of a causative explanation for why the symptoms developed. This is especially challenging for determining recurrence risks for parents considering future pregnancies. Mitochondrial myopathic disorders can pose challenges for the entire family, especially since many affected children and adults are not born with the disorder, but the condition progressively worsens with time. Support groups are available through various national disease foundations and local community organizations.

Resources

BOOKS

Staff. *The Official Parent's Sourcebook on Mitochondrial Myopathies: A Revised and Updated Directory for the Internet Age.* San Diego: Icon Group International, 2002.

PERIODICALS

Chinnery, P. F., and D. M. Turnbull. "Epidemiology and Treatment of Mitochondrial Disorders." *Am J Med Genet* (2001) 106: 94?101.

Thorburn, D. R., and H. H. Dahl. "Mitochondrial Disorders: Genetics, Counseling, Prenatal Diagnosis and Reproductive Options." *Am J Med Genet* (2001) 106: 102?14.

OTHER

"Mitochondrial Myopathies: Facts About Mitochondrial Myopathies." *Muscular Dystrophy Association.* March 10, 2004 (May 23, 2004). <http://www.mdausa.org/publications/mitochondrial_myopathies.html>.

"NINDS Mitochondrial Myopathies Information Page." *National Institute of Neurological Disorders and Stroke*. March 10, 2004 (May 23, 2004). <http://www.ninds.nih.gov/health_and_medical/disorders/mitochon_doc.htm>.

ORGANIZATIONS

National Organization for Rare Disorders (NORD). P.O. Box 1968 (55 Kenosia Avenue), Danbury, CT 06813−1968. (203) 744−0100 or (800) 999−NORD (6673); Fax: (203) 798−2291. orphan@rarediseases.org. <http://www.rarediseases.org>.

United Mitochondrial Disease Foundation. 8085 Saltsburg Road Suite 201, Pittsburgh, PA 15239. (412) 793−8077; Fax: (412) 793−6477. info@umdf.org. <http://www.umdf.org>.

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