Primary Mitochondrial Myopathies

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Synonyms of Primary Mitochondrial Myopathies

- PMM

General Discussion

Summary

Primary mitochondrial myopathies (PMM) are a group of disorders that are associated with changes in genetic material (e.g. depletions, deletions, or mutations) found within the DNA of mitochondria (mtDNA) or with genes outside the mitochondria (nuclear DNA), affecting predominantly the skeletal muscle. Mitochondria, found by the hundreds within every cell of the body, regulate the production of cellular energy and carry the genetic blueprints for this process within their own unique DNA (mtDNA). These disorders often hamper the ability of affected cells to break down food and oxygen and produce energy. Mitochondria provide more than 90% of the energy used by the body's tissues; mitochondrial disorders are characterized by a lack of sufficient energy for cells of the body to function properly. High-energy tissues like muscle, brain, or heart tissue are most likely to be affected by mitochondrial disorders. In most mitochondrial disorders, abnormally high numbers of defective mitochondria are present in the cells of the body. Mitochondrial diseases often affect more than one organ system of the body. Most mitochondrial diseases affect the muscles (myopathy). Sometimes, muscle disease is the only or predominant sign of a mitochondrial disorder, thus defined as PMM. There are no disease-modifying treatments for PMM; treatment is aimed to improving or resolving specific symptoms.

Introduction

Primary mitochondrial myopathies (PMM) are genetically defined disorders leading to defects of oxidative phosphorylation (see Causes section below) affecting predominantly, but not exclusively, skeletal muscle. Thus, secondary involvement of mitochondria, frequently observed in other neuromuscular diseases (e.g. Duchenne muscular dystrophy) is not considered PMM. Moreover, individuals with muscle disease symptoms but with other systems are affected (i.e. brain, liver, kidney, etc.) are not considered affected by PMM, and they may fit into a more straightforward clinical syndrome like Kearns-Sayre syndrome, MELAS syndrome, etc. NORD has individual reports on many different forms of mitochondrial disease. (For more information, choose the specific disorder name as your search term in the Rare Disease Database.)

Signs & Symptoms

The signs and symptoms of PMM are varied and how one of these disorders affects one person can be vastly different from how it affects another person. This is true for people with the same disorder, or even people within the same family and with the same genetic variation (mutation). PMM may present at any age, patients with severe generalized muscle involvement typically

present early in life, although individuals with milder forms of the disease, or symptoms confined to specific muscles tend to have later presentations. Generally, the earlier the onset (e.g. infancy or early childhood), the more severe a mitochondrial disorder will be.

Myopathy is defined as muscle disease. Mitochondrial myopathy is when muscle fibers cannot function properly because of an underlying defect in mitochondria. The most common presentation, which is estimated to affect about two-thirds of all people classified within this group, is progressive paralysis of certain eye muscles (progressive external ophthalmoplegia). This occurs slowly over time and limits the movements of the eyes so that affected individuals must turn their heads to see things in their peripheral vision. Sometimes, double vision (diplopia) may occur. Affected individuals often experience drooping of both their upper eyelids (bilateral ptosis). Ptosis is caused by paralysis of one of the muscles of the eyelid. Sometimes, this drooping can partially block vision. Other muscles involved in coordinating eye movements may be affected next, growing progressively weaker and eventually resulting in paralysis of certain eye movements. In severe instances, affected individuals may tilt their head.

Progressive external ophthalmoplegia can be a syndrome on its own unassociated with other signs or symptoms, or it can occur as part of a larger syndrome. In some people primary mitochondrial myopathy can cause weakness and paralysis of other facial muscles. This can lead to additional symptoms including difficulty swallowing or slurred speech. Some people can develop problems breathing (respiratory problems).

Some people may have involvement of the muscles of the arms and legs. The hips, shoulder girdle, or neck muscles can also be involved. Sometimes, only muscles in one area of the body are affected; sometimes in multiple areas of the body. Cramping, stiffness, weakness, and paralysis of the affected muscles can potentially develop. Muscle fatigue, muscle pain (myalgia), and muscle wasting can also develop. Exercise intolerance, which is a decreased ability to performed physical tasks, is a common symptom, and is sometimes the first noticeable symptoms in adults. Sometimes, symptoms of primary mitochondrial myopathy may only be present following exercise or physical activity. In severe instances, progressive muscle weakness in the legs can lead to the need for devices to help with walking (e.g. cane) or, eventually, a wheelchair.

Encephalomyopathy

Encephalomyopathy (and not PMM as defined above) of infancy or childhood is when there are neurological problems along with problems affecting the muscles. The specific signs and symptoms of encephalomyopathy can vary greatly from person to person. Vision loss can occur because of involvement of the eye or the part of the brain that controls sight. Sensorineural hearing loss can also occur. This type of hearing loss occurs when the nerves within the ear cannot properly send sensory input (sound) to the brain, and is not caused by problems with the ear itself. The degree and production of hearing loss can vary. Additional symptoms of encephalopathy of infancy or childhood can include migraines, seizures, or poor coordination (ataxia). Some children may experience delays in reaching developmental milestones (developmental delays). Some children may fail to gain weight and grow as would be otherwise expected (failure to thrive) leading to poor growth. Some children may be shorter than would be expected for age and gender (short stature). Neurological involvement can lead to various problems including difficulty swallowing (dysphagia), difficulty speaking (dysarthria), and muscle weakness and muscle tightness (spasticity). Some individuals experience peripheral

neuropathy, which is a condition that occurs when nerves that carry messages to and from the brain and spinal cord to the rest of the body are damaged. Those affected may experience tingling, burning, numbness, and stabbing pain in the affected extremities. Mitochondrial diseases that cause neurological problems may be referred to as mitochondrial encephalomyopathies, and not primary mitochondrial myopathies.

Multisystem Mitochondrial Diseases
There are many genetic disorders that are classified as mitochondrial disease that can have mitochondrial myopathy as a feature. These disorders affect multiple organ systems of the body and include Barth syndrome; growth retardation, amino aciduria, cholestasis, iron overload, lactic acidosis, and early death (GRACILE syndrome); Kearns-Sayre syndrome; Leigh syndrome; maternally inherited deafness and diabetes (MIDD); mitochondrial DNA depletion syndrome; mitochondrial encephalomyopathy, lactic acidosis, and stroke-like (MELAS); mitochondrial neurogastrointestinal encephalomyopathy (MNGIE); mitochondrial recessive ataxia syndrome (MIRAS); myoclonus epilepsy with ragged red fibers (MERFF); neuropathy, ataxia, and retinitis pigmentosa (NARP); and Pearson syndrome. NORD has individual reports on many of these disorders. (For more information, choose the specific disorder name as your search term in the Rare Disease Database.)

Causes

Primary mitochondrial myopathies are caused by a variation (mutation) in a gene. Genes provide instructions for creating proteins that play a critical role in many functions of the body. When a variation of a gene occurs, the protein product may be faulty, inefficient, absent, or overproduced. Depending upon the functions of the particular protein, this can affect many organ systems of the body, including the brain. Most of the genes involved with primary mitochondrial myopathy involve proteins that are essential for the proper function, development, and health of mitochondria.

These genes contain instructions for creating (encoding) proteins that are part of the mitochondrial respiratory chain. This is a group of proteins involved in a process called oxidative phosphorylation. This cellular process uses oxygen combined with simple sugars and fats (obtained from food) to manufacture adenosine triphosphate (ATP), the main source of energy for a cell. A cell with too little ATP can build up unused sugars and fats and can generate potentially harmful substances such as lactate. The lack of energy supplied to tissue and the buildup of harmful substances causes the signs and symptoms of the disorder.

Genetic information is contained in two types of DNA: nuclear or autosomal DNA (nDNA), which is contained in the nucleus of a cell and is inherited from both biological parents. Mitochondrial DNA (mtDNA) is contained outside of the nucleus in the mitochondria of cells and is inherited exclusively from a child’s mother. Both changes in nDNA or mtDNA can cause PMM. Most mitochondrial proteins are encoded by genes that are part of the nuclear genome.

All human mtDNA comes from the mother. This because mtDNA that is found in sperm cells typically break off during fertilization. An affected mother will pass the mutation(s) on to all her children, but only her daughters will pass the mutation(s) on to their children. Sometimes, a mutation in mtDNA occurs spontaneously during the development of an embryo and there is no previous family history of the disorder. Each individual mitochondrion contains about 10 copies of mtDNA. This means that within the same cell, there may be mutated mtDNA and unaffected

mtDNA. This is called heteroplasmy. Generally, symptoms do not occur until mutations are present in a significant percentage of the mitochondria. The uneven distribution of unaffected and mutated mtDNA in different tissues can affect different organ systems in members of the same family. Thus, affected family members may exhibit a variety of different symptoms and varying degrees of severity.

Genetic diseases due to nDNA mutations (also called autosomal inheritance) are determined by two genes, one received from the father and one from the mother. PMM can be inherited in an autosomal recessive pattern, an autosomal dominant pattern, or it can occur spontaneously during the development of the embryo without any family history of the disorder.

Disorders inherited in a recessive pattern occur when an individual inherits two variants in a gene for the same trait, one from each parent. If an individual receives one normal gene and one gene for the disease, the person will be a carrier for the disease, but usually will not show symptoms. The risk for two carrier parents to both pass the altered gene and, therefore, have an affected child is 25% with each pregnancy. The risk to have a child who is a carrier like the parents is 50% with each pregnancy. The chance for a child to receive normal genes from both parents is 25%. The risk is the same for males and females.

Less often, PMM can be inherited in an autosomal dominant pattern. Dominant genetic disorders occur when only a single copy of an abnormal gene is necessary for the appearance of the disease. The abnormal gene can be inherited from either parent, or can be the result of a new mutation (gene change) in the affected individual. A new mutation occurs spontaneously and there is no previous family history of the disorder. The risk of passing the abnormal gene from affected parent to offspring is 50% for each pregnancy. The risk is the same for males and females.

Affected Populations

Mitochondrial diseases are one of the most common forms of metabolic disease. They are estimated to affect about 1 in 5,000 people in the general population of the United States. Within the mitochondrial diseases, PMM are very common but real epidemiological studies are not available yet. This is also because PMM often go misdiagnosed or undiagnosed so determining their true frequency in the general population is difficult. These disorders affect both men and women, children and adults, and individuals of all ethnic and racial groups.

Related Disorders

Symptoms of the following disorders can be similar to those of PMM. Comparisons may be useful for a differential diagnosis.

The list of disorders that can have signs and symptoms to mitochondrial disease is long. Any disorder that can cause progressive, multisystem disease may need to be differentiated from mitochondrial diseases.

Some disorders cause damage to or hamper the ability of mitochondria. This is referred to as secondary mitochondrial disease. The list of disorders that cause secondary mitochondrial dysfunction is constantly increasing and includes spinal muscular atrophy, Friedreich’s ataxia, Charcot-Tooth-Marie disease type 2K, hereditary spastic paraplegia 7, inclusion body myositis, Wilson’s disease, and some forms of muscular dystrophy including Duchenne muscular

dystrophy and limb-girdle muscular dystrophy. (For more information on these disorders, choose the specific disorder name as your search term in the Rare Disease Database.)

Diagnosis

A diagnosis of PMM is based upon identification of characteristic symptoms, a detailed patient and family history, a thorough physical and clinical evaluation, and a variety of specialized tests. The characteristic signs and symptoms of primary mitochondrial myopathy are common to many different types of disorders. The diagnostic workup requires a complex approach that includes routine and special laboratory tests.

Clinical Testing and Workup

Initial tests may be conducted to assess the extent of disease in various organ systems and detect evidence of a potential mitochondrial disease. These tests do not confirm a diagnosis of PMM.

A physical exam can include tests that measure strength and endurance. A neurological exam can include tests that assess reflexes, vision, speech, and intellectual abilities. These tests can support a diagnosis of PMM or a mitochondrial disease, or rule out other conditions.

Laboratory tests can include metabolic screening tests including a complete blood count, urine analysis and, if a brain involvement is suspected, cerebrospinal fluid (CSF) analysis. These tests measure for certain substances including lactate and pyruvate levels in the blood or CSF, creatinine kinase (an enzyme that is found in elevated levels when muscle is damaged), ammonia, plasma amino acids, plasma carnitine, urinary organic acids, and plasma acetyl-carnitine profile. Lactate is often elevated in mitochondrial disorders and is known as lactic acidosis. A fasting blood glucose test can be ordered to confirm diabetes.

A test that assesses the health of muscles and the nerves that control muscles (electromyography) may be recommended. During this exam, a needle electrode is inserted through the skin into an affected muscle. The electrode records the electrical activity of the muscle. This record shows how well a muscle responds to the nerves and can determine whether muscle weakness is caused by the muscles themselves or nerves that control the muscles. A nerve conduction study, in which motor and sensory nerves are electrically stimulated to assess a nerve’s ability and speed in conducting nerve impulses, may also be performed. Electromyography and nerve conduction studies can rule out other conditions. Electromyography can support a diagnosis of PMM, but not everyone with a mitochondrial disorder will have changes detectable by this test.

A test called an electroencephalography (EEG) may be recommended for individuals with seizures or signs of encephalopathy. An EEG records the brain’s electrical impulses.

Specialized imaging techniques like computerized tomography (CT) scanning and magnetic resonance imaging (MRI) may be recommended, especially for individuals with central nervous system involvement. During CT scanning, a computer and x-rays are used to create a film showing cross-sectional images of certain tissue structures. An MRI uses a magnetic field and radio waves to produce cross-sectional images of particular organs and bodily tissues. These tests can show characteristic findings in the brain that can support a diagnosis of specific mitochondrial disorders or indicate another type of neurological disorder.

A test called magnetic resonance spectroscopy can be used to detect lactate, which is elevated in the brain or muscles at rest in some affected individuals. This noninvasive test is a specialized

imaging technique that allows physicians to assessed changes in brain or muscle tissue biochemistry.

If initial tests suggest PMM, then a muscle biopsy and molecular genetic testing are recommended. A muscle biopsy involves taking a small sample of affected muscle tissue that is studied under a microscope. The visual appearance of muscle tissue under a microscope can be indicative of mitochondrial disease or another disorder that affects the disorder. Chemical tests conducted on the muscle tissue sample can also indicate a diagnosis.

Molecular genetic testing is necessary to confirm a diagnosis of PMM. Molecular genetic testing can detect variations in the genes known to cause these disorders, but is available only as a diagnostic service at specialized laboratories.

Standard Therapies

Treatment

Treatment of mitochondrial diseases may require the coordinated efforts of a team of specialists. Pediatricians, surgeons, physicians who specialize in diagnosing and treating disorders of the central nervous system and brain (neurologists), physicians who specialize in diagnosing and treating disorders of the bones, muscles, tendons, and ligaments (orthopedists), physicians who specialize in diagnosing and treating disorders of the heart (cardiologists), physicians who specialize in diagnosing and treating disorders of the eye (ophthalmologists), physical therapists, social workers, and other healthcare professionals may need to systematically and comprehensively plan treatment.

Genetic counseling may be of benefit for affected individuals and their families. Psychosocial support for the entire family is essential as well. The organizations listed in the Resources section of this report provide support and information for individuals with mitochondrial disorders.

There is no cure or disease-modifying treatment for PMM. Treatment is supportive and based on the specific type of PMM that is present and is directed toward the specific symptoms that are apparent in each individual.

Some individuals with mitochondrial disease have responded to a combination of vitamins and supplements – this is sometimes referred to as “mito-cocktails.” Common ingredients include riboflavin (vitamin B2), thiamine (vitamin B1), L-carnitine, creatine, coenzyme Q10, and antioxidants. These treatments are developed in close consultation with the entire medical team and preferably medical professionals with experience in treating mitochondrial disorders. In some individuals, these vitamins and supplements do not bring about any improvement in mitochondrial function.

Exercise has shown some benefit for people with primary mitochondrial myopathy. Researchers have studied aerobic, endurance, and resistance training programs. Aerobic exercise has shown benefit in improving strength and lessening fatigue. Exercise programs have been shown to improve quality of life in many affected individuals.

In rare instances, affected individuals have coenzyme Q10 deficiency and some of these individuals may respond to therapy with high doses of coenzyme Q10 supplementation.

Additional therapies are supportive and generally follow standard guidelines. For examples, seizures may be treated with anti-seizure medications called anti-epileptics or anti-convulsants.

Eyelid drooping can be treated with eye crutches or surgery. Hearing loss can be treated with hearing aids called cochlear implants.

Following an initial diagnosis, a developmental assessment may be performed and appropriate occupational, physical, and speech therapies be instituted. Periodic reassessments and adjustment of services should be provided with all individuals. Additional medical, social, and/or vocational services including specialized learning programs for affected children may be necessary.

Investigational Therapies

Gene therapy is also being studied as another approach to therapy for individuals with mitochondrial diseases. In gene therapy, the defective gene present in a patient is replaced with a normal gene to enable the produce of the active enzyme and prevent the development and progression of the disease in question. Given the permanent transfer of the normal gene, which is able to produce active enzyme at all sites of disease, this form of therapy is theoretically most likely to lead to a "cure." However, at this time, there remain some technical difficulties to resolve before gene therapy can be advocated as a viable alternative approach.

The U.S. Food and Drug Administration (FDA) has granted orphan drug status to elamipretide for the treatment of PMM. Elamipretide is a peptide, and is designed to restore energy production within mitochondria. Elamipretide is currently in clinical trials.

Information on current clinical trials is posted on the Internet at https://clinicaltrials.gov/. All studies receiving U.S. Government funding, and some supported by private industry, are posted on this government web site.

For information about clinical trials being conducted at the NIH Clinical Center in Bethesda, MD, contact the NIH Patient Recruitment Office:

Toll-free: (800) 411-1222
TTY: (866) 411-1010
Email: prpl@cc.nih.gov

Some current clinical trials also are posted on the following page on the NORD website: https://rarediseases.org/for-patients-and-families/information-resources/info-clinical-trials-and-research-studies/

For information about clinical trials sponsored by private sources, contact: http://www.centerwatch.com/

For information about clinical trials conducted in Europe, contact: https://www.clinicaltrialsregister.eu/