



The Physician's Guide to **Mitochondrial Myopathies (MM)**

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55 Kenosia Ave.

Danbury, CT 06810

Phone: (203) 744-0100

Toll free: (800) 999-NORD

Fax: (203) 798-2291

Website: www.rarediseases.org

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Introduction

Welcome to the **NORD Physician Guide to Mitochondrial Myopathies**. The NORD Online Physician Guides are written for physicians by physicians with expertise on specific rare disorders. This guide was written by Michelangelo Mancuso, MD, PhD, Neurological Clinic, University Hospital of Pisa, Italy and Michio Hirano, MD, Columbia University Medical Center, New York, NY (see acknowledgements for additional information).

NORD is a nonprofit organization representing all patients and families affected by rare diseases. The information NORD provides to medical professionals is intended to facilitate timely diagnosis and treatment for patients.

This guide will focus on primary mitochondrial myopathy (PMM), namely genetic disorders of the mitochondrial respiratory chain affecting predominantly, but not exclusively, skeletal muscle.

Case Report

Since childhood, a 19-year-old woman complained of exercise-induced weakness and myalgia. She could not climb stairs or walk a block without stopping repeatedly. She also became short of breath with exertion. There was no family history of neuromuscular disorders. Neurological and cardiovascular examinations were normal. The electromyogram was normal. Laboratory investigations showed normal serum creatine kinase but elevated resting venous lactate (6.2 mmol/L, normal < 2.2). Histochemical analysis of a quadriceps muscle biopsy showed cytochrome c oxidase (COX)-positive ragged-red fibers (RRF), and biochemical analysis showed markedly decreased activities of both succinate–cytochrome c reductase and NADH–cytochrome c reductase, suggesting isolated complex III deficiency.

The patient harbored a stop-codon mutation at amino acid position 339 of the cytochrome *b* protein, resulting in premature truncation and the loss of carboxy-terminal 41 amino acids (10% of the total polypeptide length).

The patient has typical manifestations of a mitochondrial myopathy with exercise intolerance. Mitochondrial diseases are among the most frequent metabolic disorders and important causes of neuromuscular disease.

What Is Mitochondrial Myopathy (MM)?

While individual mitochondrial diseases are rare, mitochondrial myopathy is a common manifestation of mitochondrial diseases, the most frequent metabolic defect in humans with an estimating prevalence of 1–2 in 10,000 when all pathogenic mutations in mitochondrial DNA (mtDNA) and nuclear DNA (nDNA) are included.

This guide will focus on primary mitochondrial myopathy (PMM), namely genetic disorders of the mitochondrial respiratory chain affecting predominantly, but not exclusively, skeletal muscle. Secondary involvement of mitochondria is frequently observed in multiple neuromuscular diseases (i.e. inclusion body myositis, Ullrich and Bethlem myopathy, Kennedy disease) but is not discussed here.

Myopathy can present as the only clinical feature of a mitochondrial disease, or it may be associated with additional “mitochondrial red flags” – symptoms or signs such as diabetes, sensorineural hearing loss, optic atrophy, peripheral neuropathy, cardiomyopathy, cardiac arrhythmias, nephropathy, stroke-like episodes, seizures, ataxia, failure to thrive, developmental delay or regression, and dementia.

Because of the dual genetic control of the mitochondrial bioenergetic pathway, mitochondrial diseases like PMM can be classified genetically into two major groups: those due to mutations in nDNA and others caused by mutations in mtDNA. The first group follows the rules of Mendelian inheritance patterns while the second are typically maternally inherited, although they can be also sporadic (i.e. those due to mtDNA single deletion). There are three fundamental principals of mitochondrial genetics: (i) maternal inheritance: mtDNA is inherited only from the mother; therefore, only female patients may transmit the disease to the offspring; (ii) heteroplasmy and threshold effect: pathogenic mutations usually affect only a proportion of mtDNA; therefore, two populations of mtDNA, normal and mutated,

coexist; mutated mtDNA in a given tissue has to reach a minimum critical number before oxidative metabolism is impaired severely enough to cause dysfunction and phenotypic manifestation; (iii) mitotic segregation: during embryonic cell divisions, the degree of heteroplasmy can change so that tissues are affected differently.

In mitochondrial disease the same genetic defect may result in different phenotypes in different individuals or families (intra- and inter- familial clinical heterogeneity) and, vice versa, homogeneous phenotypes may be an expression of different mutations. Some nosological well-defined syndromes are often associated with specific mutations. However, in most cases, phenotypes are heterogeneous and polymorphous, and may range from pure myopathy to multisystemic disorders, making it difficult to establish a precise genotype/phenotype correlation.

Although mitochondria are ubiquitous organelles, selective muscle involvement can occur because of mutations in muscle-specific nuclear genes, somatic *de novo* mtDNA mutations affecting myoblasts (the embryonic precursor of myocytes), or a heteroplasmic mutation that reaches the threshold only in muscle tissue.

Symptoms and Sign

PMM may present at any age, although typically the more severe phenotypes present earlier in life, and milder phenotypes present later in life. The commonest phenotype of PMM, observed in about two-thirds of all cases of PMM, is progressive external ophthalmoplegia (PEO). PEO is characterized by bilateral eyelid ptosis, often the presenting symptom, associated with a compensatory frontalis muscle contraction and, in severe cases, tilting of the head. Ptosis is accompanied by a slowly progressive, usually symmetrical limitation of eye movement (ophthalmoplegia) in all directions of gaze so that patients turn their heads to see a target at the periphery of the visual field; diplopia is sometimes reported by the patients. Intrinsic ocular muscles are not involved. A common misdiagnosis of patients with PEO is ocular myasthenia. PEO is often associated with other signs of skeletal muscle involvement, typically slow progressive axial and proximal limb weakness affecting predominantly the hip and shoulder girdle muscles often with muscle wasting. Muscle weakness may also cause difficulty swallowing (dysphagia) and respiratory failure. Distal muscle weakness may be present but rarely seen early in the disease.

From a genetic point of view, PEO may be autosomal dominant or recessive (due to nDNA mutations), sporadic (due to single large-scale deletion of mtDNA), or maternally inherited (due to mtDNA mutation).

PEO can be associated to multiple deletions and/or depletion of mtDNA, caused by nuclear gene defects and subsequent intergenomic signalling impairment. Autosomal dominant (AD) or autosomal recessive (AR) PEO with multiple deletions of mtDNA are caused by mutations in multiple nuclear genes: *POLG1* or *POLG2* (encoding mtDNA-specific polymerase gamma), *ANT1* (adenine nucleotide translocator1), *C10ORF2* (encoding a mtDNA helicase called Twinkle), *OPA1*, *TK2*, and other genes (a full list is available on www.mitomap.org). PEO is also the most frequent phenotype associated with a single sporadic large-scale deletion of mtDNA. The “common deletion” is 4.9-kb and accounts for about one-third of all single mtDNA deletions.

As already mentioned in the overview, myopathy can be the only clinical feature of a mitochondrial disease but also a component of other mitochondrial syndromes. For example, the association of PEO with pigmentary retinopathy, cerebellar ataxia, cardiac conduction block, cerebrospinal fluid (CSF) protein levels >0.1 g/L defines Kearns-Sayre syndrome.

Other manifestations of PMM are exercise intolerance with myalgia, muscle wasting, fatigue (defined as an overwhelming sense of tiredness, lack of energy and feeling of exhaustion), muscle cramps and recurrent rhabdomyolysis with myoglobinuria triggered by exercise as seen in cytochrome *b* deficiency or in the myopathic form of CoQ10 deficiency. Exercise-induced symptoms are common in PMM and reflect lack of energy production due to mitochondrial dysfunction in skeletal muscle, increased lactate production and phosphocreatine (PCr) depletion.

Hypotonia, floppy infant syndrome, respiratory insufficiency and reduced or absent deep tendon reflexes are common in early onset forms of MPP (i.e. the myopathic form of mitochondrial depletion syndrome typically due to *TK2* mutations).

Diagnosis

The diagnostic process of PMM may require a complex approach that includes routine and special laboratory tests, exercise physiology study,

muscle biopsy for morphology and biochemistry, and molecular genetic screening. It is important to carry out a comprehensive evaluation taking account of the multisystem manifestations of mitochondrial disease.

The diagnostic process should start from patient and family history and physical and neurologic examination. A family history must be taken meticulously, with special attention to the “mitochondrial red flags”. Clear evidence of maternal inheritance directs attention to mtDNA mutations, whereas Mendelian inheritance indicates mutations in nDNA-encoded proteins; parental consanguinity suggests autosomal recessive inheritance.

The neurological examination should be conducted very carefully with a focus on evaluation of extraocular motility, limb muscle strength and signs of central nervous system involvement.

Laboratory tests may reveal high blood lactate concentrations, elevated blood lactate-to-pyruvate ratio (typically >20:1) and mild to marked elevation of serum creatine kinase. A simple, non-invasive screening tool for PMM (but also useful for metabolic myopathies) is the forearm exercise test, which, in PMM, can reveal an exaggerated increased production of lactate with muscle activity. Because plasma levels of lactate and pyruvate are not very sensitive biomarkers for PMM diagnosis, novel biomarkers that are more sensitive, specific and reproducible are strongly needed. In this scenario, in the past 4 years two biomarkers in blood, FGF-21 and GDF-15, have demonstrated a good sensitivity and specificity (especially GDF-15). Electromyography (EMG) may identify myopathic motor unit potentials and early recruitment, which are non-specific signs of myopathy; however, EMG can also be normal in mitochondrial myopathy, especially when the myopathy is restricted to the extraocular muscles. At specialized academic centers, ³¹P-nuclear magnetic resonance spectroscopy allows non-invasive evaluation of muscle metabolism in vivo and in patients with PMM can reveal signs of oxidative metabolism impairment such as low phosphocreatine/inorganic phosphate (PCr/Pi) ratio at rest and slow post-exercise recovery and delay in post-exercise adenosine diphosphate (ADP) recovery. In addition, near-infrared spectroscopy has been used to demonstrate reduced oxygen extraction with forearm muscle exercise in PMM patients. Cardiopulmonary exercise testing may reveal reduced exercise capacity and early anaerobic threshold in PMM patients; however, these findings are non-specific and can be difficult to distinguish from abnormalities seen in deconditioned patients.

Molecular studies on peripheral circulating cells or other easily accessible tissues (like urinary sediment, oral mucosa, hair follicles and cultured skin fibroblasts) can be performed. Genetic studies on blood cells are more useful in nDNA than in mtDNA-associated myopathy because, as a result of the mitotic segregation, mtDNA mutations (especially mtDNA deletions) are more easily detected in muscle than other tissues. Curiously, urine sediment often contains mtDNA mutations at higher levels of heteroplasmy than blood, buccal swabs, or even fibroblasts so screening urine for mtDNA mutations is recommended before invasive muscle biopsies.

Muscle biopsy is often necessary for the diagnosis of PMM and the gold standard to demonstrate mitochondrial dysfunction in vivo. The hallmark pathological features of PMM are ragged-red fibers (RRF), accumulation of structurally altered mitochondria, and cytochrome c oxidase (COX, or complex IV) negative fibers. In muscle sections, modified Gomori trichrome stain can show RRF, which contain high percentages of mutated mitochondrial genomes. RRF are signs of pathological proliferation of structurally altered mitochondria, probably an attempt to compensate for the respiratory chain dysfunction. Further alterations are made evident by the histochemical stains for mitochondrial enzymes succinate dehydrogenase (SDH or complex II) and COX. SDH staining can show the presence of subsarcolemmal or diffuse accumulation of mitochondria ("ragged blue fibers") and alterations of the intermyofibrillar reticulum when typically RRF are not present. Thus, SDH staining is more sensitive than modified Gomori trichrome stain in detecting excessive mitochondrial proliferation. COX staining can show the presence of COX-negative fibers. Anti-COX subunit antibodies allow the comparison of nuclear protein synthesis (COX IV) and mitochondrial protein synthesis (COX I, II and III) in single fibers, leading to the detection of the site of the dysfunction (nuclear or mitochondrial). Importantly, normal muscle histology does not rule out PMM, especially in patients with primary coenzyme Q10 deficiency. Biochemical spectrophotometric investigations can be performed in tissue homogenates to measure the activity of respiratory chain (RC) enzymes. A mutation in a nDNA or mtDNA gene encoding a structural subunit of the RC commonly results in deficiency of the solitary affected enzyme, whereas the impairment of mitochondrial protein synthesis (mutations in tRNA, single or multiple deletions, and mitochondrial depletion) reduces the activity of respiratory complexes I, III, and IV while sparing complex II (SDH) which is entirely encoded by nuclear DNA. Genetic studies can

be performed on muscle biopsy, to detect single or multiple deletions of mtDNA, quantitate total mtDNA content, or to sequence the entire mtDNA for point mutations.

Treatment

There is currently no available disease-modifying therapy for PMM; therefore, treatment of PMM focuses on symptomatic management of disease manifestations and use of a combination of vitamins and supplements (often described as “mito-cocktails”).

Several agents (mostly nutritional supplements) have been investigated with double-blind, placebo-controlled studies. These include riboflavin (vitamin B2), thiamine (vitamin B1), L-carnitine, creatine, coenzyme Q10 (CoQ10), dichloroacetate, dimethylglycine, and the combination of creatine, coenzyme Q10 and alpha lipoic acid. None has demonstrated a striking efficacy in clinical trials, although numerous non-blinded studies and small series have suggested modest efficacy.

Although extremely rare, PMM caused by CoQ10 deficiency will sometimes respond to high dose of CoQ10 supplementation; therefore a trial on this agent is appropriate for patients who have a possible phenotype of these conditions.

There has been great interest in exercise regimens and their benefit on both biochemical and clinical end-points in PMM. Aerobic, endurance, and resistance training programs have been studied. It is likely the benefits of exercise in PMM are due to reversal of deconditioning, which is a common feature of many muscle diseases. Furthermore, in PMM exercise seems to alter the underlying pathology by promoting mitochondrial biogenesis. There are multiple clinical studies indicating that aerobic exercise programs are safe and beneficial for many aspects of PMM, including strength, fatigue, and quality of life.

Other management considerations in MPM include the avoidance of agents which may worsen the patient's condition. Statins often cause toxic effects on skeletal muscle, although the precise mechanisms remain unclear. Statins should therefore be used cautiously in PMM, with careful monitoring of symptoms and the serum creatine kinase. Antiretroviral agents are known to cause reversible and dose-dependent mitochondrial toxicity. Valproic acid is known to interfere with mitochondrial function and in clinical practice

may aggravate symptoms in patients with PMM, and valproate-induced hepatotoxicity may be more common in PMM patients.

Investigative Therapies

Information on current clinical trials is posted at www.clinicaltrials.gov or www.mitoaction.org/study.

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

NORD does not endorse or recommend any particular studies.

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Resources

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PO Box 55322

Birmingham, Alabama, USA

Email: contact@mitoresearch.org

<http://www.mitoresearch.org>

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<http://www.mitosoc.org>

United Mitochondrial Disease Foundation

8085 Saltsburg Road Suite 201

Pittsburgh, PA 15239

Phone: (412) 793-8077

Toll-free: (888) 317-8633

Email: info@umdf.org

<http://www.umdf.org>

MitoAction

PO Box 51474

Boston, MA 02205

Phone: (888) 648-6228

Email: info@mitoaction.org

<http://www.MitoAction.org>

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National Organization for Rare Disorders (NORD)

55 Kenosia Avenue

Danbury, CT 06810

Telephone: (203) 744-0100 or (800) 999-NORD

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Acknowledgements

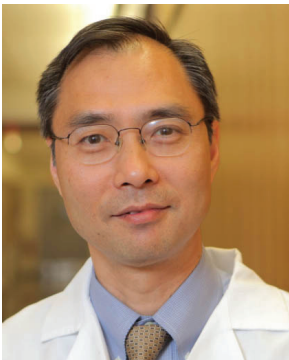
NORD is grateful to the following medical expert for reviewing this Physician Guide:



Dr. Michelangelo Mancuso is the head of the Centre of Neurogenetics and expert for mitochondrial diseases and rare diseases at the Neurological Clinic of the University Hospital of Pisa. Scientific activity of Dr. Mancuso has mainly been conducted in the field of mitochondrial and neuromuscular diseases. Sectors of interest are epidemiological and clinical-molecular correlation studies in mitochondrial diseases,

assessment of biological and genetic markers in amyotrophic lateral sclerosis, Alzheimer's disease and other genetic neuromuscular and neurodegenerative disorders. His research has been presented in national and international congresses and published in more than 150 full papers in peer-reviewed scientific journals.

Dr. Mancuso is actively involved in multiple projects mainly focusing on mitochondrial diseases. He is an active member of the Italian Network of Mitochondrial diseases and of the International Consortium of Mitochondrial diseases experts for the development of the International Database for Mitochondrial diseases. Dr. Mancuso has coordinated clinical trials on mitochondrial diseases, and has been invited to publish several reviews focusing on mitochondrial therapy.



Dr. Michio Hirano is a Professor of Neurology, Director of the H. Houston Merritt Neuromuscular Research Center, and Chief of the Neuromuscular Medicine Division at Columbia University Medical Center. He is also the Clinical Principal Investigator of the National Institutes of Health (NIH) U54 funded North American Mitochondrial Disease Consortium (NAMDC), which is comprised of 17 centers of mitochondrial

disease clinical expertise in the United States and Canada. NAMDC is a member of the Rare Disease Clinical Research Network (RDCRN) sponsored by the NIH National Center for Advancing Translational Studies (NCATS). NAMDC features a clinician-populated mitochondrial disease clinical registry, a mitochondrial disease biorepository, pilot studies, natural history studies, and a clinical trial.

Dr. Hirano's research focuses on genetic neuromuscular and mitochondrial diseases. His laboratory has identified causative mutations for more than 10 diseases including mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), LAMP-2 deficiency, and primary coenzyme Q10 deficiencies. In addition, to characterize the pathogenesis and develop therapies for human diseases, his laboratory studies cell and mouse models. Dr. Hirano has also led clinical trials including the phase I safety study of hematopoietic stem cell transplantation for MNGIE and a phase II study of idebenone for MELAS.

This NORD Physician Guide was made possible by an educational grant from [Stealth BioTherapeutics](#).

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- Advocacy for health-related causes that affect the rare-disease community
- Publications for physicians and other medical professionals

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National Organization for Rare Disorders (NORD)

55 Kenosia Avenue
Danbury, CT 06810
Phone: (203) 744-0100
Toll free: (800) 999-NORD
Fax: (203) 798-2291

www.rarediseases.org
orphan@rarediseases.org

NORD is grateful to the following medical experts for serving as authors of this Physician Guide:

Dr. Michelangelo Mancuso

Head of the Centre of Neurogenetics
Neurological Clinic of the University Hospital of Pisa

Dr. Michio Hirano

Professor of Neurology
Director of the H. Houston Merritt Neuromuscular Research Center
Chief of the Neuromuscular Medicine Division at Columbia University Medical Center

This NORD Physician Guide was made possible by an educational grant from Stealth BioTherapeutics.