REVIEW

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Mitochondrial cytopathy in adults: What we know so far

ABSTRACT

Mitochondrial cytopathies are a diverse group of inherited and acquired disorders that result in inadequate energy production. They can be caused by inheritable genetic mutations, acquired somatic mutations, exposure to toxins (including some prescription medications), and the aging process itself. In addition, a number of well-described diseases can decrease mitochondrial energy production; these include hyperthyroidism, hypothyroidism, and hyperlipidemia.

KEY POINTS

The mitochondrial cytopathies vary considerably in their manifestations, leading to uncertainty about diagnosis and classification.

There are no absolute diagnostic criteria for mitochondrial cytopathies, and most screening tests are neither specific nor sensitive, which can lead to false-positive and false-negative diagnoses.

MITOCHONDRIAL CYTOPATHIES—disorders of the energy-producing organelles of the cells—are an increasingly recognized cause of human illness. Although this field is still in its infancy, several syndromes have been identified and linked to specific mutations in mitochondrial DNA. These probably represent only a few of the mitochondrial function disorders.

This paper addresses:

- How mitochondrial diseases arise
- The presentations and diagnosis of the various known mitochondrial diseases
- Possible treatments (there are no cures).

The challenge for the primary care physician is to identify patients who may have a mitochondrial cytopathy and to coordinate management. The challenge for the subspecialist diagnostician is to provide an accurate diagnosis and assist the primary care physician in caring for the patient.

MITOCHONDRIA: POWERHOUSES OF THE CELL

Mitochondria, contained in all human cells except mature erythrocytes, perform the vital task of generating adenosine triphosphate (ATP), the molecule the cell uses for the bulk of its energy needs (FIGURE 1).

MITOCHONDRIAL DISEASES ARE REMARKABLY DIVERSE

A problem that has vexed the study of mitochondrial diseases ever since the first reported case (in 1962)[1] is that their manifestations are remarkably diverse.[2] Although the underlying characteristic of all of them is lack of adequate energy to meet cellular needs, they vary con-

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Discovery of mitochondrial diseases

THE FIRST DESCRIPTION of a mitochondrial disease was in 1962, when Luft and colleagues reported a case of a 35-year-old euthyroid woman with myopathy, excessive perspiration, heat intolerance, polydipsia with polyuria, and a basal metabolic rate 180% of normal.[1] Study of her muscle cells revealed an increase in the number of mitochondria, which were larger than normal and exhibited a wider range of sizes than normal. The ultrastructure of the mitochondria revealed electron-dense inclusions, subsequently termed *paracrystalline* inclusions, which are coagulated and nonfunctional enzyme complexes. Functional mitochondrial studies in this patient (a technique called *polarography*) demonstrated that oxidation and phosphorylation were not coupled, meaning that in the absence of ADP and inorganic phosphate, food substrates could be oxidized without ATP being produced. Since then, however, only one other patient has been reported with a similar presentation, although uncoupling is occasionally seen in our patients.

It was soon recognized that excessive accumulation of abnormal mitochondria were present on light microscopy. This feature was termed *ragged red fibers* because of its appearance when muscle tissue was prepared with a modified Gomori trichrome stain. Ragged red fibers were soon associated with the syndrome of chronic progressive external ophthalmoplegia (CPEO), a condition affecting adults that causes ptosis and paralysis of eye muscles. The term *CPEO plus* was used to describe a syndrome with additional features including systemic myopathy (TABLE 2).

In the late 1970s and 1980s, as more cases with varying features were reported, debate ensued as to whether the new cases represented diseases already defined (a position taken by "lumpers") or whether they were in fact different diseases (a position taken by "splitters"). The term *Kearn-Sayre syndrome* (KSS), it was agreed, described only the combination of CPEO, cardiac conduction defect, and sensorineural hearing loss. Acronyms for other diseases followed, and overlap of clinical features led to the inclusive but incomplete term *mitochondrial myopathies*.

In the 1980s and 1990s the mitochondrial genome was mapped, and many, but not all, of the disease acronyms could be linked to specific point mutations or common deletions in the mtDNA. Common methods of evaluating and classifying patients and their diseases included complementary but distinct methods of molecular genetic analysis and biochemical analysis. This led to increased confusion about how best to classify these diseases, which still plagues attempts to develop a rational classification system for mitochondrial disease, because genetic defects could not be found in many patients with severe biochemical defects such as severe electron transport defects. As it became apparent that many organ systems other than muscle could be primarily involved, *mitochondrial cytopathy* became the preferred term for this group of diseases.

siderably from disease to disease and from case to case in their effects on different organ systems, age at onset, and rate of progression, even within families whose members have identical genetic mutations. No symptom is pathognomonic, and no single organ system is universally affected. Although a few syndromes are well-described, any combination of organ dysfunctions may occur.[3]

These diseases most often affect the central and peripheral nervous systems, but can affect any organs or tissues that are postmitotic at birth (ie, in which the cells have stopped dividing), including the muscles, liver, kidneys, heart, ears, eyes, and endocrine system (TABLE 1).

Clinical course

Symptoms in adults tend to develop over years, and therefore it is distinctly uncommon for these diseases to be diagnosed when symptoms first begin. The early phase can be mild and may not resemble any known mitochondrial disease. In addition, symptoms such as fatigue, muscle pain, shortness of breath, and abdominal pain can easily be mistaken for collagen vascular disease, chronic fatigue syndrome, fibromyalgia, or psychosomatic illness.

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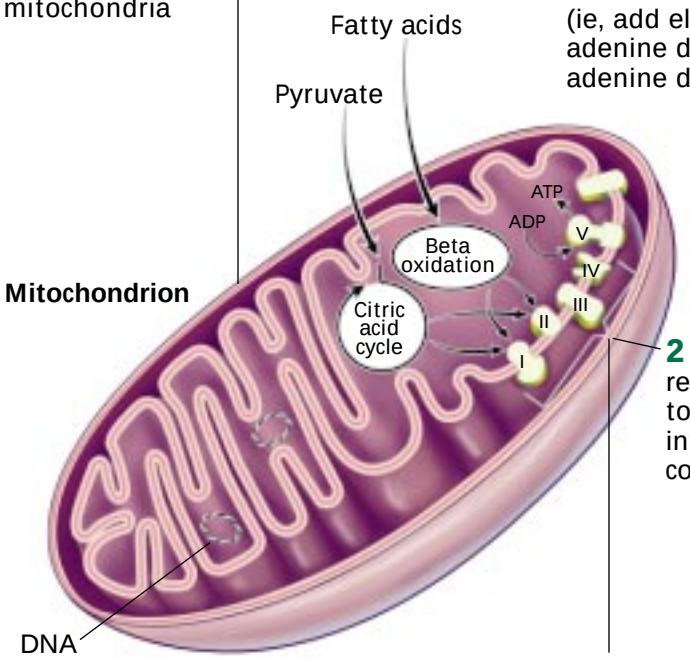
How mitochondria synthesize ATP

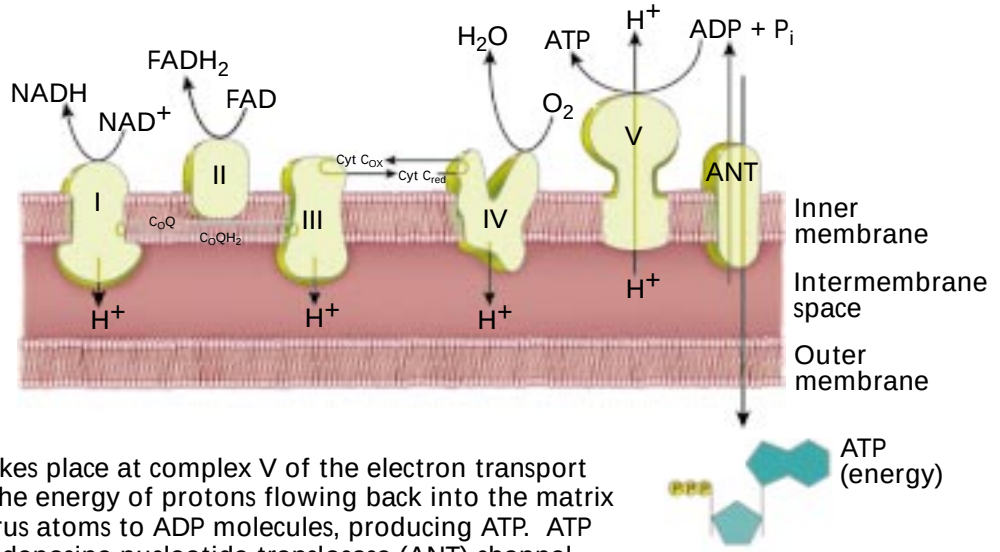
Mitochondria synthesize adenosine triphosphate (ATP) from adenosine diphosphate (ADP) and inorganic phosphate in a process called *oxidative phosphorylation*. Simply put, they burn food in the presence of oxygen to produce ATP. The process, greatly simplified, has three main steps.

Cell with mitochondria

1 The citric acid cycle breaks down pyruvate (a product of glucose metabolism) and **the beta oxidation spiral** breaks down fatty acids. Both use the energy released to reduce (ie, add electrons to) the electron carriers nicotinamide adenine dinucleotide (NAD^+), yielding NADH, and flavin adenine dinucleotide (FAD), yielding $FADH_2$



2 The electron transport chain (also called the respiratory chain) uses the energy from the electrons to pump hydrogen ions (protons) into the intermembrane space. The electron transport chain comprises five complexes designated I through V.



3 ATP synthesis takes place at complex V of the electron transport chain, which uses the energy of protons flowing back into the matrix to attach phosphorus atoms to ADP molecules, producing ATP. ATP exits through the adenosine nucleotide translocase (ANT) channel, where ATP is exchanged for ADP.

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FIGURE 1

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TABLE 1

Problems associated with mitochondrial cytopathies

ORGAN SYSTEM	POSSIBLE PROBLEMS
Muscles	Hypotonia, weakness, cramping, muscle pain, ptosis, ophthalmoplegia
Brain	Developmental delay, mental retardation, autism, dementia, seizures, neuropsychiatric disturbances, atypical cerebral palsy, atypical migraines, stroke and stroke-like events
Nerves	Neuropathic pain and weakness (which may be intermittent), acute and chronic inflammatory demyelinating polyneuropathy, absent deep tendon reflexes, neuropathic gastrointestinal problems (gastroesophageal reflux, constipation, bowel pseudo-obstruction), fainting, absent or excessive sweating, aberrant temperature regulation
Kidneys	Proximal renal tubular dysfunction (Fanconi syndrome), may result in loss of protein (amino acids), magnesium, phosphorous, calcium, and other electrolytes
Heart	Cardiac conduction defects (heart blocks), cardiomyopathy
Liver	Hypoglycemia, gluconeogenic defects, nonalcoholic liver failure
Eyes	Optic neuropathy and retinitis pigmentosa
Ears	Sensory-neural hearing loss, aminoglycoside sensitivity
Pancreas	Diabetes and exocrine pancreatic failure
Systemic	Failure to gain weight, short stature, fatigue, respiratory problems including intermittent air hunger

mtDNA is inherited solely from the mother

No rules accurately predict the course of these diseases: they are usually thought to be progressive, but some patients' conditions remain stable over time, and others even improve spontaneously.

WHY THE DIVERSITY?

Reasons for the diversity in the manifestations of these diseases may involve the mitochondria's unique genetic makeup. Alone among the organelles, mitochondria possess their own DNA, a remnant of their long-ago past as free-living organisms. Approximately 1.5 billion years ago the aerobic mitochondria took up residence inside the anaerobic ancestor of the modern eukaryotic cell, and although most of the mitochondrial genes migrated to the nucleus eons ago, 37 of them—some of which encode absolutely vital functions—still reside within the mitochondria themselves.[4]

A fertilized ovum contains several hundred mitochondria, each of which contains several copies of the mitochondrial genome (in double-stranded loops exactly 16,569 base pairs in length). All of the mitochondria and the mitochondrial DNA (mtDNA) come from the ovum itself: the sperm, with its mitochondria in its tail, contributes none.[5]

If a percentage of these mtDNA carry defects, when the ovum divides, one of the daughter cells may receive more of the defective mtDNA and the other may receive less. With successive cell divisions, the defect may become more concentrated in one of the developing organs or tissues. Since the process in which defective mtDNA becomes concentrated in an organ is random, this may account for the differing manifestations among patients with the same genetic defect. And the more defective mtDNA becomes concentrated in any given organ, the worse the disease manifestation.[3,6]

Mitochondrial diseases may also arise from processes other than germline mutations in mtDNA. A case of a somatic (acquired) mutation causing mitochondrial disease was recently reported.[7] Some mtDNA mutations

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may cause disease only when the bearer is exposed to an environmental toxin: aminoglycoside-induced ototoxicity is a case in point.[8] Mutations may accumulate with aging, or with chronic hypoxia, as occurs, for example, following cardiac ischemia.[9]

WHY ARE POSTMITOTIC TISSUES VULNERABLE TO MITOCHONDRIAL DISEASE?

Postmitotic tissues such as those in the brain, muscles, nerves, retinas, and kidneys, are vulnerable for several reasons. They all tend to have a high demand for energy. Furthermore, their diseased cells cannot be replaced by healthier neighbor cells, a process that would occur in tissues with cellular turnover, such as the skin or mucosa.

In dividing tissues such as mucosal membranes, cell populations with healthy mitochondria would have a selective advantage over those with diseased mitochondria. Over time, cells with diseased mitochondria would disappear from the population, so the tissue tends to remain free of significant mitochondrial abnormalities.

However, in tissues that are postmitotic at birth, no selection process weeds out sick cells. In these tissues, mtDNA mutations accumulate and result in progressive dysfunction of individual cells and eventually of the organ itself. These phenomena are clinically relevant because a hallmark of most mitochondrial diseases is earlier onset of symptoms in persons with a heavier burden of genetic defects, and worsening disease with age.[4,10,11]

WHY DOES MITOCHONDRIAL DNA MUTATE?

Mitochondrial DNA acquires mutations at six to seven times the rate of nuclear DNA, presumably because the mitochondria lack protective histones and because the mtDNA is in close proximity to the electron transport chain, exposing it to high concentrations of free radicals, which can damage the nucleotides. In addition, the mitochondria lack DNA repair mechanisms, which results in mutant tRNA, rRNA, and protein transcripts.[3]

Mostly unknown at this time is how mutations in the nuclear DNA, which contains most of the mitochondrion's genes, may contribute to mitochondrial diseases, and how the mitochondria manage to replicate and carry out their functions with their DNA in two places.[3,6,10]

CLINICAL FEATURES

Muscles

Weakness due to myopathy is usually the first symptom in people in whom symptoms develop in adulthood. The weakness is often mild and can become more severe throughout the day, a pattern similar to that in myasthenia gravis. Involvement of the eyelid and extraocular muscles may be severe, which is also a common feature in myasthenia gravis. However, in myasthenia gravis, electromyographic studies usually show an electrodecremental response or the patient has antibodies to acetylcholine esterase, or both. Neither occurs in mitochondrial cytopathies.

Cramping of large and small muscles also may occur, which is a nonspecific finding of many muscle diseases.

Mitochondrial cytopathies vary greatly in presentation

Despite the subjective weakness, many patients have minimal objective findings, possibly because fatigability is difficult to quantify in a physician's office. Only in severe cases or late in the course of the illness are gross muscle bulk and strength reduced. However, a careful physical examination early on may reveal doughy muscle consistency, mild atrophy, and very mild weakness.

Some patients have mildly elevated levels of the creatine kinase MM fraction, although intermittent rhabdomyolysis can occur with illness or dehydration, causing myoglobulinuria and creatine kinase MM levels higher than 10,000 U/L.

Cardiac muscle (see below) and smooth muscles may also be affected. Poor motility of the esophagus, stomach, and intestines can cause considerable morbidity. Anorexia and weight loss can occur in the MELAS (mitochondrial encephalomyopathy, lactic acidosis and stroke-like) syndrome[12,13] and MNGIE (myoneurogenic gastrointestinal encephalopathy) syndrome[14,15] (TABLE 2) and may be mistaken for anorexia nervosa.

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TABLE 2

Described phenotypes of mitochondrial diseases

Leber hereditary optic neuropathy (LHON)
Key features: Visual loss beginning in young adulthood
Other features: Wolff-Parkinson-White syndrome, multiple sclerosis-type disease

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like syndrome (MELAS)
Key features: Varying degrees of cognitive impairment and dementia, lactic acidosis, strokes, and transient ischemic attacks
Other features: Hearing loss, dysmotility, weight loss

Myoclonic epilepsy and ragged-red fibers (MERRF)
Key features: Progressive myoclonic epilepsy, clumps of diseased mitochondria accumulate in the subsarcolemmal region of the muscle fiber and appear as "ragged-red fibers" when muscle is stained with modified Gomori trichrome stain
Other features: Short stature

Leigh syndrome subacute sclerosing encephalopathy
Key features: After normal development the disease usually begins late in the first year of life, but the onset may occur in adulthood; a rapid decline in function occurs and is marked by seizures, altered states of consciousness, dementia, ventilatory failure
Mutations associated with phenotype: 8993, 8994, pyruvate carboxylase deficiency, pyruvate dehydrogenase deficiency, cytochrome oxidase deficiency, SURF-1 mutation

Neuropathy, ataxia, retinitis pigmentosa, and ptosis (NARP)
Key features: Progressive symptoms as described in the acronym, along with dementia
Mutations associated with phenotype: 8993. The same mutation associated with the infantile form of Leigh syndrome, when heteroplasmy is between approximately 70% and 90%, will result in the NARP phenotype

Kearn-Sayre syndrome (KSS)
Key features: External ophthalmoplegia, cardiac conduction defects, and sensory-neural hearing loss

Myoneurogenic gastrointestinal encephalopathy (MNGIE)
Key features: Gastrointestinal pseudo-obstruction, neuropathy
Mutations associated with phenotype: Thymidine phosphorylase deficiency

Poor GI motility can lead to food avoidance resembling anorexia nervosa

The food avoidance that occurs with some mitochondrial illnesses is due to the extremely poor gastrointestinal motility and subsequent intermittent pseudo-obstruction. Conversely, the starvation that occurs in anorexia nervosa can eventually cause mitochondrial failure. Ipecac, which is often abused by persons with anorexia nervosa, is a specific mitochondrial poison.[16]

Brain

Migraine, dementia, seizures, and stroke-like episodes can occur at any stage of the disease, but like myopathy, brain involvement is not required for the diagnosis. Most adults undergoing initial evaluation for mitochondrial cytopathy are cognitively normal. Complex migraine is a common symptom. Other symptoms can include transient hemiparesis, hemisensory loss, aphasia, or altered mentation. Dementia may or may not occur, but is seen frequently in adult-onset mitochondrial diseases caused by mtDNA mutations, such as myoclonic epilepsy and ragged red fibers (MERRF) and MELAS (TABLE 2). Commonly, dementia presents with psychiatric symptoms, including atypical psychosis.

Strokes and stroke-like episodes are common in some syndromes. The strokes tend not to occur in vascular distributions but may appear in the occipital lobe and in areas of the brain that are metabolically active, such as the basal ganglia, thalamus, and cerebellum. The

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neurologic deficit may last minutes to months and in some cases is irreversible. Complicated migraines are often difficult to differentiate from mild stroke-like events.

Neuroimaging is an important component of evaluation and can show lesions in the basal ganglia, unusual leukodystrophies, and areas of infarction. Magnetic resonance spectroscopy can show regions of elevated lactic acid concentrations.

Nerves

Nerve cells and Schwann cells are extremely active metabolically: nerve cells require a tremendous amount of energy to maintain the electrochemical gradient necessary for nerve transmission.

Neuropathy can cause distal weakness, pain, or autonomic features such as temperature instability, inappropriate sweating (or lack of sweating), orthostatic hypotension, or bladder dysfunction. In addition, autonomic neuropathy can contribute to gastrointestinal dysmotility.

Loss of deep tendon reflexes and weakness are the typical neurologic signs of neuropathy. Disabling neuropathic pain is one of the more troubling symptoms. In some patients the lack of appropriate sweating can be disabling, rendering them susceptible to heat stroke at temperatures that should be only mildly uncomfortable.[17,18]

Heart

The sinoatrial and atrioventricular nodes are the most metabolically active tissues in the body, and the muscular activity of the heart never ceases. Therefore, cardiac conduction defects and cardiomyopathy are complications of mitochondrial dysfunction.

In some patients, cardiac disease is the first sign of mitochondrial cytopathy. Third-degree heart blocks may develop quickly in Kearn-Sayre syndrome,[19] and Wolff-Parkinson-White syndrome can develop in patients with Leber's hereditary optic neuropathy (LHON).[20] For this reason, all patients with mitochondrial cytopathy should undergo electrocardiography regularly. A pacemaker or other intervention should be considered before symptoms arise if the electrocardiographic findings worsen.

Liver

Maintenance of glucose homeostasis is the most vital moment-to-moment function of the liver. A number of primary disorders result in failure of normal gluconeogenesis, due to either cytoplasmic enzyme dysfunction (eg, glucose-6-phosphatase deficiency) or mitochondrial enzyme dysfunction (eg, pyruvate carboxylase deficiency), but these usually present in childhood. However, secondary gluconeogenic defects are seen in some patients with electron transport chain disorders, as well as disorders of fatty acid oxidation, such as long-chain acyl-CoA dehydrogenase deficiency and carnitine palmitoyltransferase II deficiency.

Prolonged fasting may result in biochemical disturbances and subsequent mental status changes. Abnormal laboratory values can include nonketotic hypoglycemia, lactic acidosis, and elevated blood ammonia levels.

Eyes

Both retinitis pigmentosa[21,22] and optic atrophy may occur in mitochondrial diseases. Not all patients with these conditions have a mitochondrial disease, but this should be considered if there is a family history or if there are other features suggestive of multiorgan involvement. Optic atrophy is a hallmark of LHON—sometimes the only feature.[23,24]

No symptom is pathognomic; no single organ system is always affected

Ears

Sensorineural hearing loss occurs in some patients with mitochondrial diseases. Starting with high-frequency hearing loss, it can progress to total deafness. A number of mtDNA point mutations are associated with an extreme otosensitivity to aminoglycoside antibiotics. However, hearing loss, with or without aminoglycoside exposure, is also seen in persons without those identified mutations.[25,26]

Kidneys

The proximal renal tubular cells require an abundant and steady energy supply. Mitochondrial cytopathies often cause a loss of amino acids and electrolytes in the urine, especially in affected infants. Aminoaciduria, renal tubular acidosis, and Fanconi syndrome are often seen in childhood-onset disorders,

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but are usually not symptomatic in adults.[27,28]

Pancreas

Diabetes is a common late feature of mitochondrial diseases.[29,30] The common MELAS mutation (G to A substitution at position 3243 of the mitochondrial DNA) often is associated with diabetes mellitus, and in some families the phenotype is diabetes mellitus with or without high-frequency hearing loss. Many members of these families do not have the typical features seen in MELAS, for which there is no obvious explanation. As many as 1% of patients with adult-onset diabetes mellitus may have the MELAS A3243G mutation.[31]

Systemic manifestations

A symptom described by many patients is the intermittent sensation of air hunger, which is not associated with anoxia, cardiac malfunction, or pulmonary dysfunction, but is probably a physiologic phenomenon resulting from the energy failure caused by the relative inability to reduce molecular oxygen to water (by complex IV of the electron transport chain). Likewise, fatigue following little activity is a common feature in many patients.

Short stature is a key feature in some genotypic mitochondrial disorders.[12]

Chronic fatigue syndrome. A few case reports described patients with chronic fatigue syndrome who ultimately were diagnosed with an energy metabolism disorder that includes electron transport chain disorders, fatty acid oxidation disorders, and carnitine deficiency.[32–34]

Neither chronic fatigue syndrome nor mitochondrial cytopathies are caused by single diseases. The symptoms of both overlap considerably, and there is no simple way to screen for a mitochondrial cytopathy. In all likelihood, only a small fraction of those with chronic fatigue syndrome have a mitochondrial cytopathy. Evaluating every person who has chronic fatigue syndrome for mitochondrial cytopathy would not be practical and probably should be reserved for patients who have had an exhaustive but uninformative investigation of their illness. Abnormal screening studies such as elevated creatine kinase, serum lactate, or reduced serum carnitine along with multisystem signs or symptoms would suggest the need for a diagnostic muscle biopsy. However, sometimes only muscle pathology can yield the diagnostic result.[34]

Before suspecting mitochondrial cytopathy, rule out other causes

METHODS OF DIAGNOSIS

To recognize mitochondrial illness, one must be familiar with the various symptoms, and because these symptoms are so diverse, it is often difficult to comprehend that they could be related to the same underlying process.

To make matters more difficult for the physician, there are no accepted criteria for diagnosis. The tests used to screen for mitochondrial diseases are often complicated to interpret. Although the gold standard for diagnosis is a pathologic point mutation that can be identified in leukocytes, a mutation cannot be found in many patients, and therefore a diagnosis may require visual and biochemical examination of muscle tissue.

A diagnosis of a mitochondrial cytopathy can be established with a combination of molecular genetic, pathologic, or biochemical data in a patient who has clinical features consistent with the diagnosis. However, there is no agreed-upon standard method of evaluation nor any accepted guidelines to determine whether the diagnosis is correct.

Rigid criteria for diagnosis require a known pathologic mutation, severe biochemical deficiency, or well-defined pathologic findings in an affected person. However, some experts feel that looser diagnostic criteria are acceptable. One practical method, referred to as the Thor-Byrne-ier scale (TABLE 3), represents a balanced approach to diagnosis, but still leaves many patients out of the “definite” category.[35]

I cannot overemphasize how important it is to evaluate the patient for other conditions that may mimic or secondarily result in mitochondrial dysfunction. The most common diseases that can cause overlapping symptoms are the endocrinopathies (diabetes and thyroid, parathyroid, and adrenal disorders) and collagen vascular diseases. However, hyperthyroidism, for example, can cause features similar to a mitochondrial cytopathy, and thyroid hormone can uncouple the process of oxidative phosphorylation.

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TABLE 3

Thor-Byrne-ier criteria for diagnosis of mitochondrial cytopathy

Major criteria

A classic mitochondrial clinical phenotype (see TABLE 2), or unexplained death of a newborn or infant
> 2% ragged red fibers in a skeletal muscle biopsy
< 20% activity of age-adjusted mean on biochemical or polarographic assessment of any electron transport complex (ETC), or < 30% in cell culture, or 20% to 30% in two different tissues
Pathogenic mtDNA abnormality

Minor criteria

Incomplete mitochondrial clinical phenotype
Ragged red fibers (but < 2%), or other electron microscopic change
20% to 30% residual ETC in tissue as measured by polarography, or 30% to 40% in tissue culture, or 30-40% in two tissues, or ATP synthesis < 2 SD below the mean, or galactose-sensitive cell growth
mtDNA abnormality of unproven pathogenicity
Abnormal metabolic studies (lactate, ^{31}P magnetic resonance spectroscopy)

Scoring

Definite: 2 major criteria, or 1 major + 2 minor criteria
Probable: 1 major criterion + 1 minor, or 3 minor criteria
Possible: 1 major criterion, or clinical manifestations + 1 minor criterion

ADAPTED FROM WALKER UA, COLLIN S, BYRNE E. RESPIRATORY CHAIN ENCEPHALOMYOPATHIES: A DIAGNOSTIC CLASSIFICATION. EUR NEUROL 1996; 36:260–267

For example, a patient in our clinic who had myopathy and biopsy-proven ragged-red fiber disease was found to have intermittent bursts of thyroid hormone from a multinodular goiter. Although this man may have two distinct diseases, it is more likely that the hyperthyroidism is the primary illness and that the apparent mitochondrial disorder is secondary.

The overlap of symptoms is further complicated by numerous similar clinical features, as in the case of diabetes. Diabetes is a common feature of mitochondrial diseases, but the ravages of primary diabetes can cause features seen in mitochondrial diseases, such as neuropathy, retinopathy, and cardiomyopathy.

If a patient's symptoms and signs fit into a well-described clinical phenotype, it is reasonable to proceed directly with mutational analysis, which can often be performed on blood lymphocytes. Although any point on the mtDNA can be tested for a point mutation, most laboratories offer routine testing of only a few (usually 3 to 15) specific mutations, in addition to a Southern blot, which will detect large deletions or duplications. Some laboratories offer a panel of the dozen or so most commonly identified mutations. The entire mtDNA can also be screened, but this is quite expensive. For example, for an adult with the clinical syndrome of MELAS, it is reasonable to test for the most common mutations associated with MELAS and possibly even those associated with NARP (neuropathy, ataxia, retinitis pigmentosa, and ptosis) or MERRF, but testing for LHON mutations is generally a waste of resources if the patient does not have optic atrophy.

Diabetes and thyroid disease have symptoms that overlap those of mitochondrial cytopathy

It is critical to remember that most of the mitochondrial structure is encoded by nDNA, and aside from a few mutations associated with mitochondrial disease, the nDNA gene products that are relevant to mitochondrial function remain unmapped territory. Automated sequencers and DNA chips will make the analysis of the mtDNA simpler in the future, but it is likely that many mitochondrial disorders will be due to nDNA mutations or mutations involving both nDNA and mtDNA that alone would not be pathologic.

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TABLE 4

Primary evaluation of suspected mitochondrial diseases

TEST	COMMENTS
Blood glucose	
Hemoglobin A_{1c}	
Serum electrolytes	Calculate anion gap
Blood counts	Anemia, thrombocytopenia, and neutropenia are seen in a variety of metabolic diseases Primary and secondary disorders of folate and vitamin B_{12} metabolism should be considered
Blood lactate	Tourniquet must be released before blood is sampled
Urinalysis	High pH may suggest renal tubular acidosis
Plasma ammonia	Fasting sample most useful
Organic acids	Measured in urine, cerebrospinal fluid Samples must be kept refrigerated or frozen Urine collections may be random or timed, and may be collected after a fasting period or glucose load, depending on the clinical situation Abnormal amounts of lactate, pyruvate, citric acid cycle intermediates, or 3-methylglutaconic acid suggest mitochondrial dysfunction 3-methylglutaconic acid can be seen in women taking progesterone, or during extreme stress or glucocorticosteroid use
Ketones	Measured in blood or urine Significant if absent during fasting
Mitochondrial DNA (mtDNA) point mutations	Tested in blood or in muscle biopsy specimens If a patient fits into a specific, well-described mitochondrial phenotype, testing for specific, known point mutations may be helpful at this stage Some centers routinely screen for the 3 to 15 most commonly identified mtDNA mutations in all patients
Southern blot	If a patient fits into a specific, well-described mitochondrial phenotype such as CPEO, KSS, or MELAS, Southern blot testing may lead to a rapid diagnosis Muscle tissue is more sensitive than lymphocytes
Ophthalmology consult	Assess for retinitis pigmentosa or optic atrophy
Cardiac evaluation	Routine electrocardiogram and echocardiogram

A stepwise evaluation of mitochondrial cytopathy is sensible

In most instances, a stepwise evaluation is most sensible (TABLES 4–6). As a general suggestion, it is reasonable to evaluate patients with three or more distinct clinical symptoms involving at least two different organ systems.

Before starting an evaluation, especially if the patient has no central or peripheral nervous system involvement, he or she should be screened for common diseases that can produce the symptoms and signs the patient is experiencing. Thyroid disease, Cushing syndrome, rheumatic diseases, and inflammatory myopathies are obvious examples of illnesses that can cause seemingly unrelated systemic phenomena. Patients should also be advised that the evaluation is time-consuming and invasive and often will not yield diagnostic results.

Muscle biopsy

Muscle tissue can be tested for electron transport chain enzyme activity, carnitine disorders, fatty acid oxidation activity, and glycogen storage disease analysis. In addition, the mitochondria can be isolated from fresh mus-

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TABLE 5

Secondary laboratory evaluation of suspected mitochondrial diseases

TEST	COMMENTS
Blood lactate	Tourniquet must be released before blood is sampled
Serum pyruvate	Proper determination of pyruvate requires the specimen be instantly deproteinized Pyruvate not useful if lactate is normal Disregard results if not properly corrected
Lactate/pyruvate ratio	The ratio of lactate to pyruvate can be very helpful in determining if lactate acidosis is due to an oxidative phosphorylation disorder (L/P > 20)
Amino acids	Measured in blood, urine, or cerebral spinal fluid Urine collections may be random or timed and may be collected after a meal or after a fasting period, depending on the clinical situation "Generalized aminoaciduria" may indicate the presence of proximal renal tubular dysfunction due to mitochondrial cytopathy, as well as other medical conditions Alanine is the amino acid precursor to pyruvate, and therefore an elevated alanine can be helpful in diagnosis
Organic acids	Measured in urine or cerebral spinal fluid Samples must be kept refrigerated or frozen Different techniques, some more sensitive, are used by certain laboratories Urine collections may be random or timed, and may be collected after a fasting period or glucose load, depending on the clinical situation
Carnitine analysis	Measured in blood, urine, or muscle biopsy specimen Most laboratories determine the free carnitine and total carnitine Fractionation into specific acyl carnitines may be helpful in some situations Urine collections may be random or timed, and may be collected after a fasting period, depending on the clinical situation
Ketones	Measured in blood or urine Determining the ratio of ß-hydroxybutyrate and acetoacetate may be helpful. This test is most valuable if collected during an acute illness or after a fast
Urinary acylglycines	Useful in disorders of beta oxidation
Skin biopsy	Electron microscopy may reveal structural defects in mitochondrial structure A fibroblast culture can be established with the skin obtained from a biopsy Other testing of skin samples includes testing for electron transport chain activity, beta-oxidation disorders, and other specific diseases

Advise patients that evaluation is invasive, lengthy, and often unproductive

cle or liver tissue and tested with the previously mentioned studies and oxidative phosphorylation polarography. The mtDNA can be extracted from muscle tissue, which can be informative when the mutation is an acquired somatic mutation as opposed to an inherited germline mutation that would be also present in lymphocytes.

Because a muscle biopsy is invasive, the risks and costs of the procedure must be weighed against the chance the biopsy will yield positive results and the benefits gained by a diagnosis, such as treatment decisions and genetic counseling. If a genetic mutation can be determined by other means, there is no reason to proceed with muscle biopsy or other diagnostic tests.

Before a muscle biopsy is performed, a plan

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TABLE 6

Tertiary laboratory evaluation of suspected mitochondrial diseases

TEST	COMMENTS
Repeat testing	Repeating some of the above-listed tests, sometimes under different conditions (such as during an illness), may be helpful
Provocative testing	Under monitored conditions, usually in the hospital, repeating some of the above tests after a fast or after a specific meal or intravenous infusion may be helpful
mtDNA point mutations	If a patient fits into a specific, well-described mitochondrial phenotype, testing for specific, known point mutations may be helpful at this stage
mtDNA Southern blot	If a patient fits into a specific, well-described mitochondrial phenotype, Southern blot testing may be helpful at this stage Coenzyme Q_{10} blood test and muscle and mitochondrial levels are probably more important, but currently not available

needs to be arranged for how the sample is to be distributed. Reference laboratories should be contacted before the biopsy is done so that the muscle sample is prepared correctly.

The following tests can be ordered on muscle samples taken during the biopsy:

- Routine light microscopy including immunohistochemistry. The modified Gomori trichrome stain is used to demonstrate ragged red fibers, and succinate dehydrogenase staining for ragged-blue fibers, which indicate clumps of diseased mitochondria. Cytochrome oxidase staining can demonstrate fibers absent in this enzyme, and some laboratories have the ability to stain for nuclear-encoded and mitochondrial-encoded subunits of cytochrome oxidase.
- Electron microscopy, looking for abnormally sized or shaped mitochondria, paracrystalline inclusions, and proliferation of mitochondria, usually beneath the subsarcolemmal membrane (FIGURE 2).
- Electron transport chain activity as determined by spectrophotometric assay. This is preferably performed on isolated mitochondria (obtained only from fresh muscle), but can be performed on fresh or flash-frozen muscle homogenate. This study determines the activity of the catalytic components of the various parts of the electron transport chain.
- Oxidative phosphorylation activity (polarography), which measures rates of oxygen utilization using different concentrations of ADP, tested by using a variety of substrates. This method can determine the functional activity of the five respiratory chain complexes and the integrity of the inner and outer mitochondrial membranes. In addition, the functional activity of pyruvate dehydrogenase, carnitine transport, and fatty acid oxidation can also be estimated. Polarography requires fresh mitochondria and therefore can only be performed within the first few hours after the tissue is removed from the body.
- Enzyme activity for beta oxidation disorders, including those of the enzymes of the beta oxidation spiral, carnitine transport, and carnitine palmitoyltransferase I and II activity.
- Determination of carnitine, acylcarnitine, and coenzyme Q_{10} levels.

Plan ahead on how to distribute muscle biopsy samples

TREATMENT

There are no cures for mitochondrial diseases. The focus of treatment should be to maximize normal organ function and alleviate symptoms, which includes standard medical therapies.

Are vitamin and cofactor supplements beneficial?

Most patients with mitochondrial cytopathies ask whether supplemental vitamin and cofactor therapies may be helpful (TABLE 7).

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Mitochondrial disease in muscle: Electron micrographic appearance

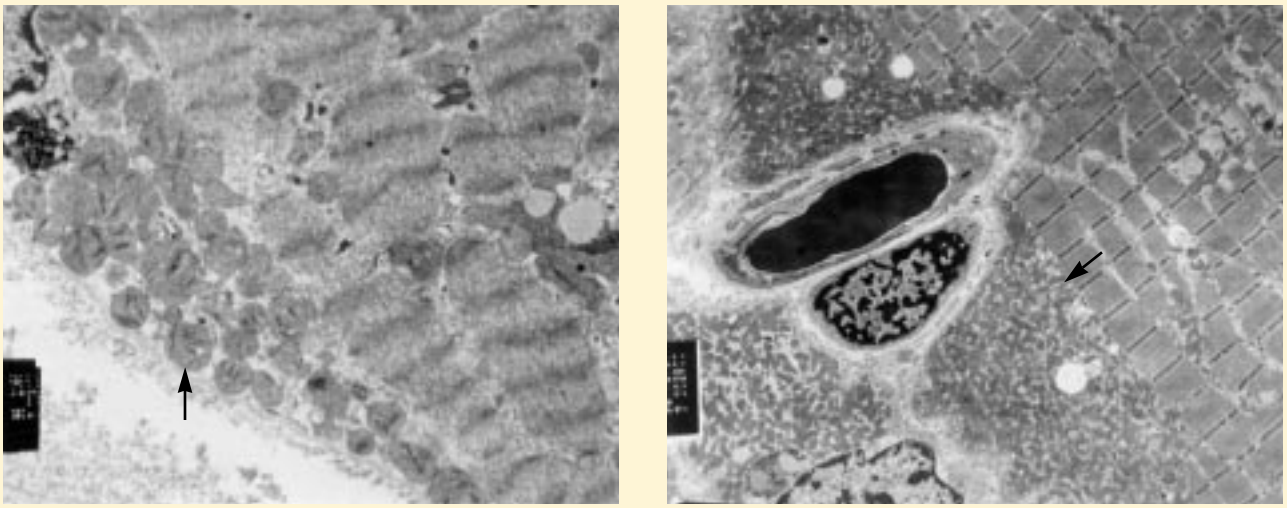

FIGURE 2. Electron photomicrographs of muscle biopsy samples from two patients with mitochondrial disease. **Left,** large mitochondria with needle-like paracrystalline inclusions (arrow) in a patient with dementia and intractable epilepsy. **Right,** pathologic accumulation of mitochondria (arrow) in the subsarcolemma of muscle tissue.

Aside from a handful of case reports in which an enzyme defect was due to cofactor deficiency or was very cofactor-responsive, there is no overwhelming evidence that the use of cofactors is helpful in most patients.

However, the value of cofactor therapy is difficult to measure. These diseases have a varied clinical course, and some patients have acute exacerbations followed by long periods of stability or partial recovery. In addition, there are literally hundreds of different defects that affect different organ systems in each person, making outcome measures almost impossible to determine. Even within one family sharing a common gene defect, the variability is so diverse it is not possible to determine a person's clinical course on the basis of the course of other family members. Furthermore, the treatment duration of many negative studies may not be long enough to determine improvement. Despite the lack of experimental data, most persons with mitochondrial cytopathies chose to take supplemental vitamins and cofactors. The cost of these supplements can be substantial, and therefore the physician and patient should use some degree of restraint deciding about cofactor therapy.

Coenzyme Q_{10} (CoQ_{10}) is the best known cofactor used in treating mitochondrial cytopathies. CoQ_{10} is synthesized in vivo and functions as the mobile electron carrier residing in the inner mitochondrial membrane, transferring electrons from complexes I and II to complex III. It also can function as a powerful antioxidant. Benefits may include reduction in lactic acid levels,[36–39] improvement in muscle magnetic resonance spectroscopy findings,[40–42] improved muscle strength,[38] and decreased muscle fatigability.[36] Central nervous system symptoms generally do not improve with this therapy. Although numerous studies found CoQ_{10} therapy to be beneficial, others did not.[43–45] There are no significant side effects.

Most patients elect to take vitamins and cofactors

Levocarnitine (L-carnitine, carnitine), is a cofactor required for the metabolism of fatty acids. Only the levo-isomer is active. Carnitine palmitoyltransferase I (CPT I) catalyzes the binding of acyl-CoA with carnitine to form acylcarnitine, which is shuttled across the inner mitochondrial membrane in exchange for free carnitine. Once acylcarnitine is inside the mitochondrial matrix, CPT II reverses the reaction, resulting in free carni-

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TABLE 7

Vitamins, supplements, and medications used in mitochondrial diseases

SUPPLEMENT	DAILY DOSE	COMMENTS
Coenzyme Q_{10}	5–15 mg/kg in divided doses	Variable gastrointestinal absorption dependent on formulation Maximal benefit may take months
L-carnitine	30–100 mg/kg in divided doses	Prescription brand Carnitor IV and oral preparations available
Thiamine (vitamin B_1)	100–800 mg	
Riboflavin (vitamin B_2)	400 mg	
Niacinamide (vitamin B_3)	100–500 mg	Avoid niacin form, as it can cause uncomfortable flushing
Folate	1–10 mg	
Vitamin E	400–1200 IU in divided doses	May interfere with CoQ_{10} absorption
Selenium	25–50 µg	
Lipoic acid	200–600 mg in divided doses	
Prednisone	5–60 mg	Symptomatic improvement noted on patients, but should be used sparingly as withdrawal of treatment may lead to recurrence of symptoms

Reserve creatine phosphate for acute crises

tine and acyl-CoA, which is metabolized via beta oxidation.

Many disorders of intermediary metabolism, including those affecting electron transport, can result in carnitine deficiency. Under normal circumstances, about 25% of the necessary carnitine is synthesized in vivo and 75% is consumed in the diet. Carnitine deficiency can cause clinical myopathy or cardiomyopathy and lead to rhabdomyolysis.[46]

Benefits of levocarnitine therapy are improved strength (which is sometimes observed in those who do not have a carnitine deficiency), reversal of cardiomyopathy, and improved gastrointestinal motility, which can be a major benefit to those with poor motility due to their disease.[47] Supplemental carnitine therapy is accepted for those with proven carnitine deficiency, but remains an unproven but widely used treatment for those with mitochondrial disorders.[46]

Intestinal cramping and pain are the major side effects, which are alleviated in most cases by reducing the dose. It is reasonable to consider a therapeutic trial of levocarnitine in those with mitochondrial cytopathies.

Creatine phosphate is synthesized from creatine and ATP in a reaction catalyzed by creatine kinase. Unlike ATP, creatine phosphate can accumulate in small amounts in the body, and since creatine phosphate can be hydrolyzed to ATP and creatine it thus allows for storage of a high-energy phosphate bond.

Creatine is found in muscle, brain, kidney, and other tissues. Muscular creatine may be depleted in mitochondrial cytopathy, and supplemental creatine phosphate has been shown to be helpful in some patients with weakness due to their disease. Because the benefits may be transient, it is recommended that this therapy be reserved for acute crises and discontinued as soon as possible.[48–50]

B vitamins are inexpensive essential nutrients necessary for the function of a wide array of enzymes associated with energy production. The need for supplemental B vitamin therapy is not proven, aside from well-documented but rare cases of thiamine (vitamin B_1)-responsive pyruvate dehydrogenase deficiency[51,52]; riboflavin (vitamin B_2)-responsive

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forms of electron transfer flavoprotein (ETF) and ETF-coenzyme Q_{10} reductase deficiency (glutaric aciduria type II)[53]; and biotin-responsive biotinidase deficiency.[54] Riboflavin is the best studied of the B vitamins and has also been proposed to be helpful in preventing migraine,[55–57] and for this reason a trial may be reasonable in patients with mitochondrial disease.

Antioxidants. Antioxidant use makes sense on theoretical grounds.[58] Free radicals, which damage lipid membranes such as the inner mitochondrial membrane, are overproduced in disorders of mitochondrial function and may be scavenged by antioxidants.[59,60] These agents have not been systematically tested in mitochondrial disorders, and any benefit may not be detectable in a brief trial. Despite the lack of proof, these are routinely used in patients with these diseases.

REFERENCES

1. **Luft R, Ikkos D, Palmieri G, Ernster L, Afzelius B.** A case of severe hypermetabolism of nonthyroid origin with a defect in the maintenance of mitochondrial respiratory control: A correlated clinical, biochemical and morphological study. J Clin Invest 1962; 41:1776–1804.
2. **DiMauro S, Bonilla E.** Mitochondrial encephalomyopathies. In: Rosenberg RN, Prusiner SB, DiMauro S, Barchi RL, editors. The molecular and genetic basis of neurological disease. Boston: Butterworth-Heinemann, 1997:201–235.
3. **Shoffner JM, Wallace DC.** Oxidative phosphorylation diseases. In: Scriver CR, Beaudet AL, Sly WS, et al, editors. The metabolic and molecular bases of inherited disease. New York: McGraw-Hill, 1995:1535–1610.
4. **Wallace DC.** Mitochondrial diseases in man and mouse. Science 1999; 238:1482–1488.
5. **Giles RE, Blanc H, Cann HM, Wallace DC.** Maternal inheritance of human mitochondrial DNA. Proc Natl Acad Sci USA 1980; 77:6715–6719.
6. **Shoffner JM.** Mitochondrial myopathy diagnosis. Neurol Clin 2000; 18:105–123.
7. **Andreu AL, Hanna MG, Reichmann H, et al.** Exercise intolerance due to mutations in the cytochrome b gene of mitochondrial DNA. N Engl J Med 1999; 341:1037–1044.
8. **Fischel-Ghodsian N, Prezant TR, Chaltraw WE, et al.** Mitochondrial gene mutation is a significant predisposing factor in aminoglycoside ototoxicity. Am J Otolaryngol 1997; 18:173–178.
9. **Corral-Debrinski M, Shoffner JM, Lott MT, Wallace DC.** Association of mitochondrial DNA damage with aging and coronary atherosclerotic heart disease. Mutat Res 1992; 275:169–180.
10. **Wallace DC.** Mitochondrial DNA mutations and bioenergetic defects in aging and degenerative diseases. In: Rosenberg RN, Prusiner SB, DiMauro S, Barchi RL, editors. The molecular and genetic basis of neurologic disease. Boston, Butterworth-Heinemann, 1997:237–269.
11. **Melov S, Shoffner JM, Kaufman A, Wallace DC.** Marked increase in the number and variety of mitochondrial DNA rearrangements in aging human skeletal muscle. Nucleic Acids Res 1995; 23:4122–4126.
12. **Pavlakis SG, Phillips PC, DiMauro S, DeVivo DC, Rowland LP.** Mitochondrial myopathy, encephalomyopathy, lactic acidosis and stroke-like episodes: a distinctive clinical syndrome. Ann Neurol 1984; 16:481–488.
13. **Goto Y, Nonaka I, Horai S.** A mutation in the tRNALeu(URR) gene associated with the MELAS subgroup of mitochondrial encephalomyopathies. Nature 1990; 348:653.
14. **Bardosi A, Creutzfeldt W, DiMauro S, et al.** Myo-, neuro-, gastrointestinal encephalomyopathy (MNGIE syndrome) due to partial deficiency of cytochrome c oxidase: a new mitochondrial multisystem disorder. Acta Neuropathol (Berl) 1987; 74:248–158.
15. **Nishino I, Spinazzola A, Hirano M.** Thymidine phosphorylase gene mutations in MNGIE, a human mitochondrial disorder. Science 1999; 283:689–692.
16. **Lietman PS.** Mitochondrial protein synthesis: inhibition by emetine hydrochloride. Mol Pharmacol 1971; 7:122–128.
17. **Huang CC, Chu CC, Pang CY, Wei YH.** Tissue mosaicism in the skeletal muscle and sural nerve biopsies in the MELAS syndrome. Acta Neurol Scand 1999; 99:125–129.
18. **Peyronnard JM, Charron L, Bellavance A, Marchand L.** Neuropathy and mitochondrial myopathy. Ann Neurol 1980; 7:262–268.
19. **Kenny D, Wetherbee J.** Kearns-Sayre syndrome in the elderly: mitochondrial myopathy with advanced heart block. Am Heart J 1990; 120:440–443.
20. **Mashima Y, Kigasawa K, Hasegawa H, Tani M, Oguchi Y.** High incidence of pre-excitation syndrome in Japanese families with Leber's hereditary optic neuropathy. Clin Genet 1996; 50:535–537.
21. **Kerrison JB, Biousse V, Newman NJ.** Retinopathy of NARP syndrome. Arch Ophthalmol 2000; 118:298–299.
22. **Smith PR, Bain SC, Good PA, et al.** Pigmentary retinal dystrophy and the syndrome of maternally inherited diabetes and deafness cause by the mitochondrial DNA 3243 tRNA (Leu) A to G mutation. Ophthalmology 1999; 106:1101–1108.
23. **Wallace DC, Singh G, Lott MT, et al.** Mitochondrial DNA mutation associated with Leber's hereditary optic neuropathy. Science 1988; 242:1427–1430.
24. **Chalmers RM, Schapira AH.** Clinical, biochemical and molecular genetic features of Leber's hereditary optic neuropathy. Biochim Biophys Acta 1999; 1410:147–158.
25. **Fischel-Ghodsian N.** Mitochondrial genetics and hearing loss: the missing link between genotype and phenotype. Proc Soc Exp Biol Med 1998; 218:1–6.
26. **Jacobs HT.** Mitochondrial deafness. Ann Med 1997; 29:483–491.
27. **Niaudet P.** Mitochondrial disorders and the kidney. Arch Dis Child 1998; 78:387–390.
28. **Niaudet P, Rotig A.** The kidney in mitochondrial cytopathies. Kidney Int 1997; 51:1000–1007.
29. **Odawara M.** Involvement of mitochondrial gene abnormalities in the pathogenesis of diabetes mellitus. Ann NY Acad Sci 1996; 786:72–81.
30. **Gerbitz KD, van den Ouweland JM, Maassen JA, Jaksch M.** Mitochondrial diabetes mellitus: a review. Biochim Biophys Acta 1995; 1271:253–260.
31. **van den Ouweland JM, Lemkes HH, Trembath RC, et al.** Maternally inherited diabetes and deafness is a distinct subtype of diabetes and associates with a single point mutation in the mitochondrial tRNA (Leu(URR)) gene. Diabetes 1994; 43:746–751.
32. **Plioplys AV, Plioplys S.** Serum levels of carnitine in chronic fatigue syndrome: clinical correlates. Neuropsychobiology 1995; 32:132–138.
33. **Kuratsune H, Yamaguti K, Takahashi M, Tagawa S, Kitani T.** Acylcarnitine deficiency in chronic fatigue syndrome. Clin Infect Dis 1994; 18(suppl 1):62–67
34. **Griggs RC, Karpati G.** Muscle pain, fatigue, and mitochondriopathies. N Engl J Med 1999; 341:1077–1078.
35. **Walker UA, Collins S, Byrne E.** Respiratory chain encephalomyopathies: a diagnostic classification. Eur Neurol 1996; 36:260–267.
36. **Goda S, Hamada T, Ishimoto S, Kobayashi T, Goto I, Kuroiwa Y.** Clinical improvement after administration of coenzyme Q10 in a patient with mitochondrial encephalomyopathy. J Neurol 1987; 234:62–63.
37. **Ogasahara S, Yorifuji S, Nishikawa Y, et al.** Improvement of abnormal pyruvate metabolism and cardiac conduction defect with coenzyme Q10 in Kearns-Sayre syndrome. Neurology 1985; 35:372–377.
38. **Bresolin N, Bet L, Binda A, et al.** Clinical and biochemical correlations in mitochondrial myopathies treated with coenzyme Q10. Neurology 1988; 38:892–899.

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39. **Abe K, Fujimura H, Nishikawa Y, et al.** Marked reduction in CSF lactate and pyruvate levels after CoQ therapy in a patient with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS). Acta Neurol Scand 1991; 83:356–359.
40. **Gold R, Seibel P, Reinelt G, et al.** Phosphorous magnetic resonance spectroscopy in the evaluation of mitochondrial myopathies: Results of a 6-month therapy study with coenzyme Q. Eur Neurol 1996; 36:191–196.
41. **Barbiroli B, Iotti S, Lodi R.** Improved brain and muscle mitochondrial respiration with CoQ. An in vivo study by 31P-MR spectroscopy in patients with mitochondrial cytopathies. BioFactors 1999; 9:253–260.
42. **Bendahan D, Desnuelle C, Vanuxem D, et al.** 31P NMR spectroscopy and ergometer exercise test as evidence for muscle oxidative performance improvement with coenzyme Q in mitochondrial myopathies. Neurology 1992; 42:1203–1209.
43. **Bresolin N, Doriguzzi C, Ponzetto C, et al.** Ubidecarenone in the treatment of mitochondrial myopathies: a multi-center double-blind trial. J Neurol Sci 1990; 100:70–78.
44. **Zierz S, von Wersebe O, Bleistein J, Jerusalem F.** Exogenous coenzyme Q (CoQ) fails to increase CoQ in skeletal muscle of two patients with mitochondrial myopathies. J Neurol Sci 1990; 95:283–290.
45. **Matthews PM, Ford B, Dandurand RJ, et al.** Coenzyme Q10 with multiple vitamins is generally ineffective in treatment of mitochondrial disease. Neurology 1993; 43:884–890.
46. **Pons R, DeVivo DC.** Primary and secondary carnitine deficiency syndrome. J Child Neurol 1995; 10(suppl 2):8–24.
47. **Campos Y, Huertas R, Lorenzo G, et al.** Plasma carnitine insufficiency and effectiveness of L-carnitine therapy in patients with mitochondrial myopathy. Muscle Nerve 1993; 16:150–153.
48. **Harris RC, Soderlund K, Hultman E.** Elevation of creatine in resting and exercised muscle of normal subjects by creatine supplementation. Clin Sci 1992; 83:367–374.
49. **Tarnopolsky MA, Roy BD, MacDonald JR.** A randomized, controlled trial of creatine monohydrate in patients with mitochondrial cytopathies. Muscle Nerve 1997; 20:1502–1509.
50. **Tarnopolsky MA, Martin J.** Creatine monohydrate increases strength in patients with neuromuscular disease. Neurology 1999; 52:854–857.
51. **Naito E, Ito M, Yokota I, et al.** Concomitant administration of sodium dichloroacetate and thiamine in West syndrome caused by thiamine-responsive pyruvate dehydrogenase complex deficiency. J Neurol Sci 1999; 171:56–59.
52. **DiRocco M, Lamba LD, Minniti G, Caruso U, Naito E.** Outcome of thiamine treatment in a child with Leigh disease due to thiamine-responsive pyruvate dehydrogenase deficiency. Eur J Paediatr Neurol 2000; 4:115–117.
53. **Gregersen N.** Riboflavin-responsive defects of beta-oxidation. J Inherit Metab Dis 1985; 8(suppl 1):65–69.
54. **Wolf B, Heard GS, Jefferson LG, Proud VK, Nance WE, Weissbecker KA.** Clinical findings in four children with biotinidase deficiency detected through a statewide neonatal screening program. N Engl J Med 1985; 313:16–19.
55. **Schoenen J, Jacquy J, Lenaerts M.** Effectiveness of high-dose riboflavin in migraine prophylaxis. A randomized controlled trial. Neurology 1998; 50:466–470.
56. **Yee AJ.** Effectiveness of high-dose riboflavin in migraine prophylaxis. Neurology 1999; 52:431–432.
57. **Mattimoe D, Newton W.** High-dose riboflavin for migraine prophylaxis. J Fam Pract 1998; 47:11.
58. **Sastre J, Pallardo FV, Garcia de la Asuncion J, Vina J.** Mitochondria, oxidative stress and aging. Free Radic Res 2000; 32:189–198.
59. **Mecocci P, MacGarvey U, Kaufman AE, et al.** Oxidative damage to mitochondrial DNA shows marked age-dependent increases in human brain. Ann Neurol 1993; 34:609–616.
60. **Beal MF.** Does impairment of energy metabolism result in excitotoxic neuronal death in neurodegenerative illness? Ann Neurol 1992; 31:119–130.

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