# Treatment of Mitochondrial Cytopathies: Summary

loading...

Print This Email this

## Summary

Evaluating the efficacy of treatments for mitochondrial cytopathies is influenced by the relative rarity of these conditions and their variable and unpredictable natural course, as well as their extensive clinical and biochemical heterogeneity. The lack of conclusive evidence in favor of any one treatment, or combinations of treatments, makes it impossible to determine conclusively which metabolic therapies might be effective. It is important to note that there is no evidence suggesting therapy alters the ultimate course of these otherwise potentially progressive diseases. There is evidence to suggest some patients may have an improvement in symptoms and an improved quality of life. The majority of data available with regards to specific therapies is anecdotal, though more recently there has been an emphasis on controlled trials. Unfortunately, even in this setting, the patient population varies significantly and statistical constraints make it impossible to evaluate all potential responses.





Because mitochondrial diseases have so many potential symptoms, identifying which symptom or sign to evaluate as part of any study is problematic. If a study relies on one endpoint, improvements in other functions may be ignored and miss a potential benefit of a treatment. Attempting to measure every symptom and sign of the disease would be so burdensome that a study would be prohibitively expensive. As an example, relying on serum or CSF measurements of lactate alone may not fully demonstrate the full therapeutic benefit of a particular medication. It has also been demonstrated in many of the studies discussed that even with diminishment of lactate levels, there is not necessarily concurrent symptomatic improvement. Therefore, the use of other objective measures and

possibly many objective measurements (i.e., nuclear magnetic resonance spectroscopy of brain and/or muscle and bicycle ergometry) to evaluate the efficacy of these interventions remains crucial to proving or disproving their benefit. Determination of clinical improvements should also be included in an effort to prove a link between the biochemical and functional improvements.

Despite the lack of consistent data, providing supplements as part of an individual trial in which the patient serves as their own control seems to be a reasonable approach. The clinician and patient will need to use their best judgment as to the issues of efficacy and cost. The use of medications such as dichloroacetate is still under investigation and will likely remain reserved for those patients with life-threatening lactic acidosis that is not responsive to conventional treatment. Uridine remains under investigation with regards to its utility in the treatment of mitochondrial cytopathies.

« Previous Page Section 7 of 7 Table of Contents

Print This Email this

MORE ON THIS TOPIC

- Pediatric Attention Deficit Hyperactivity Disorder
- Generalized Anxiety Disorder
- Pediatric Generalized Anxiety Disorder
- Genomic Medicine News & Perspectives
- Anxiety Disorders News & Perspectives

**Reprint Address**
Address for correspondence and reprint requests: Dr. Bruce H. Cohen, Chief, Section of Pediatric Neurology, Cleveland Clinic Foundation, Desk S-80, 9500 Euclid Avenue, Cleveland, OH 44195.

Semin Neurol. 2001;21(3) 

**MOST EMAILED** **TOP RATED**

1. Principles of a New Treatment Algorithm in Multiple Sclerosis
2. Nine Smartphone Apps to Improve Your Practice
3. Treatment of Neuropathic Pain
4. Chronic Cerebral Spinal Venous Insufficiency in Multiple Sclerosis
5. Cell Phone Use Affects Brain Glucose Metabolism

**›› View More**

From Seminars in Neurology

# Treatment of Mitochondrial Cytopathies

**Deborah R. Gold**, MD and **Bruce H. Cohen, MD**, Section of Pediatric Neurology, Cleveland Clinic Foundation, Cleveland, Ohio.

Posted: 09/01/2001; Semin Neurol. 2001;21(3) 



## Abstract and Introduction

### Abstract

Mitochondrial cytopathies are clinically and biochemically heterogeneous disorders affecting energy production. Because of the diverse symptoms spanning organ systems, the large number of biochemical and genetic defects, and an unpredictable clinical course, there are limited data regarding proven effective therapies. In general, treatments for mitochondrial cytopathies are intended to augment energy production as well as reduce the production of free radicals and other toxic metabolites that further limit the generation of cellular energy. Theoretically, treatment can be aimed at increasing respiratory chain activity by supplementing relative deficiencies of cofactors required for proper functioning. Possible strategies to consider may include dietary management, supplemental vitamins and cofactors, and/or specific medications aimed at a particular symptom.

**Objectives**. On completion of this article the reader will be able to summarize the current treatment options for patients with mitochondrial disorders.

**Accreditation**. The Indiana University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

**Credit**. The Indiana University School of Medicine designates this educational activity for a maximum of 1.0 hours in category one credit toward the AMA Physicians Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

**Disclosure**. Statements have been obtained regarding the authors' relationships with financial supporters of this activity. There is no apparent conflict of interest related to the context of participation of the authors of this article.

## Introduction

Understanding therapy for those with mitochondrial disease requires knowledge of the underlying pathogenesis. The term mitochondrial cytopathies refer to the human illnesses resulting from primary and secondary mitochondrial dysfunction. The mitochondria are responsible for energy production, which is generated in the form of adenosine triphosphate (ATP). A series of well-orchestrated chemical reactions culminate in the phosphorylation of adenosine diphosphate (ADP) by the process of oxidative phosphorylation (OXPHOS), which occurs in the five enzyme complexes imbedded in the inner mitochondrial membrane that comprise the electron transport chain (ETC). In addition to energy generation, the mitochondria also play pivotal roles in both the generation of free radicals and the process of apoptosis, or "programmed" cell death. Although therapy primarily focuses on improving energy production, the other functions of the mitochondria may be important in future consideration of treatment options.

Physicians caring for those with mitochondrial cytopathies are faced with a new challenge. The current practice of specialized medical care stratifies physicians and their patients by diseases of organs and organ systems. Although dysfunction of one organ can affect another adjacent organ, such as congestive heart failure causing pulmonary edema, it is usually observed that successful treatment of the primary disease will result in improvement of other organ dysfunction. Mitochondrial cytopathies are not diseases of particular organs, but a disease or disease state of an organelle. The consequences of faulty ATP production are more severe in those tissues with a high-energy requirement, which may impact on the function of only a few selected organs or cause widespread damage affecting most organ systems. Successful management of an ill person with a mitochondrial cytopathy requires the orchestrated efforts of a primary care physician, medical specialists, and a physician comfortable with the intricacies of mitochondrial disorders. Because of the diverse nature of affected organ systems, evaluation of any given therapy can be quite a challenge.

In spite of the multiplicity of clinical presentations and underlying pathophysiology, there are several well-described phenotypes that have been instrumental in the evolution of our knowledge of mitochondrial diseases. Kearns-Sayre syndrome (KSS), typically seen in conjunction with a defect in metabolism of coenzyme $Q_{10}$, usually presents with ophthalmoplegia, retinopathy, cardiac conduction defects, ataxia, and short stature. Episodic vomiting, lactic acidosis, myopathy, seizures, strokelike events, and short stature tend to characterize mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes (MELAS). Myoclonic epilepsy with ragged-red fibers (MERRF) is distinguished by the presence of severe myoclonus, epilepsy, ataxia, and myopathy with ragged-red fibers. Leber hereditary optic neuropathy (LHON) is characterized primarily by blindness in men. Respiratory irregularities, myopathy/weakness, and visual and auditory impairments comprise Leigh's syndrome. Despite these well-defined syndromes, their clinical expression often overlaps.

A number of factors make it difficult to assess whether a given treatment may be effective. These include:

1. Mitochondrial cytopathies represent literally hundreds of different disease states. They may be caused by genetic mutations that result in deficient quantity or function of an enzyme, assembly of multisubunit enzymes, disorders of mitochondrial membrane structure, defects in substrate transport, or vitamin and cofactor deficiencies. The mutations themselves may involve nuclear DNA (nDNA) or mitochondrial DNA (mtDNA); point mutations, deletions, or rearrangements. It is not reasonable to believe that any one treatment would have a similar effect on all mitochondrial diseases.
2. Mitochondrial diseases affect an unpredictable combination of a number of organs or organ systems. This is a result of the process known as segregative replication, in which the abnormal mitochondria may be "compartmentalized" within a given organ (i.e., muscle, brain) and not others. There may be a "threshold" effect in which a certain level of mutant mitochondrial genomes is required for disease to be evident clinically and/or biochemically.[1] Despite the existence of this critical threshold, the genetic burden or measured biochemical deficiency does not necessarily correlate with the severity or rapidity of progression of the disease. The variability of clinical features among affected family members is enormous, even if the underlying genetic or biochemical defect is the same. In addition, exacerbations and remissions are characteristic of these disorders, potentially clouding evaluation of the efficacy of a particular intervention.

3. Mitochondrial diseases can be classified on the basis of a genetic defect, biochemical defect, or pathologic finding. Based on this classification, there are no defined methods of defining severity of illness, nor is there any understanding or consistent ability to predict the natural history of any one patient's illness. Therefore, treatment trials that are not conducted over a sufficient time period could reject a potentially adequate treatment.
4. Given the potentially systemic nature of the mitochondrial cytopathies, developing a treatment trial looking at efficacy of a particular medication or supplement by evaluating the response of all possible affected organ systems would be quite cumbersome and expensive and would require an unacceptable number of patients. On the other hand, trials that look at the response of only one organ system to therapy may miss an existent benefit to other organ systems.
5. The commonly investigated biochemical parameters (i.e., serum or cerebrospinal fluid lactate, pyruvate, enzyme assays) in isolation may not be a full indicator of therapeutic efficacy for any given supplement or medication. Monitoring progress via neurophysiologic studies, magnetic resonance spectroscopy (MRS), and/or objective muscle strength testing will likely add to the overall assessment of patients maintained on specific treatment regimens.

For these reasons, it is very unlikely that there will be class 1 proof that any specific medication or supplement will be effective in the treatment of mitochondrial cytopathies. There is good reason for this skepticism. At this time mitochondrial cytopathies are still considered by most to be relatively rare disorders. There are limited patients with any one specific mutation, and the clinical variability of those with a specific mutation is tremendous. Even if mitochondrial disorders are ultimately shown to be common, the vast phenotypic variability in terms of distribution of organ dysfunction and severity even among family members with identical genotypic disorders makes it impossible to know the natural history of disease progression (and unexplained occasional temporary remissions). Trying to collect class 1 data in a group of diseases with varied molecular genetics and biochemical defects is not likely to be possible.

Although there may be one best treatment approach for one individual with mitochondrial disease, it is naïve to think that there can be a unified treatment strategy for groups of patients identified as having a mitochondrial cytopathy. As mitochondrial diseases are often considered to be degenerative in nature, familiarity with the underlying pathophysiology of these disease processes can aid the clinician in developing potentially effective treatment regimens that can result in an improved quality of life. Despite this knowledge, therapy/amelioration of these disorders continues to pose quite a challenge. In general, therapeutic approaches are principally based on the use of antioxidants, vitamins and supplements ( Table 1. ), replacement of respiratory chain cofactors, dietary management, and medications aimed at reduction of a particular symptom (i.e., seizures, neuropathic pain, cardiac dysfunction).

**Section 1 of 7** **Next: Consulting Management »**

Print This Email this

Semin Neurol. 2001;21(3) © 2001 Thieme Medical Publishers

# Treatment of Mitochondrial Cytopathies: Nonpharmacologic Treatments



## Nonpharmacologic Treatments

### Dietary

Nutritional management of patients with disorders of energy production must be individualized, depending mainly on the specific underlying defect. Dietary management is likely to impact on the underlying disease process by activation of alternative pathways of energy production as well as play a role in decreasing endogenous formation of toxic metabolites.[10] Some key points with regards to dietary therapy, though, are applicable to the majority of patients. Patients should avoid prolonged periods without a meal; this may require frequent, small meals in an attempt to maintain normoglycemia. There is a subset of patients who are unable to tolerate an overnight fast and may therefore require a prebedtime snack consisting of complex carbohydrates. A good source of complex carbohydrate is uncooked cornstarch; however, it is not very palatable. Patients with long-chain fatty acid oxidation disorders may need to avoid dietary fats and ingest fats in the form of medium chain triglycerides (MCT oil).





### Aerobic Exercise

The effects of aerobic training on exercise tolerance, fatigability, lactic acidosis, and muscle pain have been studied in patients with mitochondrial myopathies. Ten patients with primary manifesting symptoms of exercise intolerance and muscle weakness were

enrolled in a training program consisting of aerobic exercise on a motorized treadmill three to four times per week. Following the 8-week program, the mean estimated aerobic capacity was 30% higher than at baseline ($P < 0.01$). Aerobic training resulted in an increase of total exercise duration by approximately 30% ($P < 0.02$). Both resting lactate and that obtained following exercise were decreased following the 8-week training program. Finally, there was a demonstrable decrease in heart rate and in the half-time for ADP recovery after exercise as shown by phosphorous magnetic resonance spectroscopy. In this group of patients those with defined mitochondrial DNA mutations ($n = 7$) showed slightly less of a response when compared to those with nuclear DNA mutations. The results of this study lend support to the use of aerobic training as part of the treatment regimen for patients with mitochondrial myopathies. If this is to be undertaken, it must be carried out in a well-supervised and monitored setting, such that safety is not compromised.[11]

« Previous Page Section 3 of 7 Next: Pharmacologic Treatments »

Print This Email this

Semin Neurol. 2001;21(3) 

# Treatment of Mitochondrial Cytopathies: Pharmacologic Treatments



## Pharmacologic Treatments

### Symptomatic Treatment

#### Seizures

Management of seizures typically involves the use of common anticonvulsants including (but not limited to) phenobarbital, phenytoin, carbamazepine, gabapentin, lamotrigine, benzodiazepines, and zonisamide. Valproate has been identified as a potentially dangerous medication because of its hepatotoxic side effect in some patients with metabolic diseases. There is considerable debate as to whether this medication should ever be used, regardless of the situation, or whether, in metabolic disease, it can be considered in the setting of seizures that have been refractory to other medications. Valproate is known to inhibit cytochrome oxidase (COX) as well as cause mitochondrial ultrastructural changes, but it is not know if these are clinically relevant. Phenobarbital and the benzodiazepines do interfere with mitochondrial function in vitro but it is not clear if this is clinically relevant. There may be a theoretical advantage to using some of the newer neuroprotective drugs such as gabapentin or lamotrigine. The ketogenic diet has been used safely in many patients with oxidative phosphorylation disorders. It should be avoided in those with fatty acid oxidation disease and in those patients that either do not enter rapid ketosis (indicating a primary or functional defect in fatty acid oxidation) or those that become encephalopathic with the onset of

fasting or initiation of high-fat feeds. The use of levo-carnitine in all patients on the diet is controversial, but those with known metabolic disease should have carnitine monitoring every 6 months.

**Neuropathic Pain**

Treatment of pain is beyond the scope of this manuscript. However, gabapentin and/or carbamazepine can be used to treat neuropathic pain in association with mitochondrial cytopathies. Effective dosages may be less than that needed for anticonvulsant activity.

**Cardiac Disease**

Cardiac disease is common, especially in adults with mitochondrial cytopathies. Cardiac rhythm should be monitored by routine ECG frequently, probably on a yearly basis. In the setting of cardiac conduction defects or advanced heart block, pacemaker insertion may be used to reestablish normal cardiac rhythm. Cardiac failure should be managed with medications by an experienced cardiologist.

**Sodium Dichloroacetate**

Dichloroacetate (DCA) is an investigational drug that stimulates the activity of the pyruvate dehydrogenase multienzyme (PDH) complex. PDH catalyzes the irreversible oxidation of pyruvate, the product of glycolysis, to acetyl coenzyme A and carbon dioxide. Reducing equivalents in the form of NADH, which enter complex I of the ETC, are also generated. Acetyl coenzyme A then is condensed with oxaloacetate to form citrate, the first step in the citric acid cycle. Regulation of the enzyme complex is mediated by phosphorylation of one of its subunits, whereby in the phosphorylated state the PDH complex is rendered inactive. DCA stimulates PDH complex activity by inhibiting the PDH complex kinases that are responsible for phosphorylation, thereby maintaining the PDH complex in its unphosphorylated, hence active, state. The result is improved oxidation of lactate and consequent increased supply of acetyl coenzyme A and NADH. This NADH is then utilized by complex I, but if there is a defect at or distal to complex I, it is not known if lowering lactate concentrations or improving the flux through PDH can improve energy production. One property of DCA is that it may inhibit its own metabolism. The major side effect of DCA is a reversible peripheral neuropathy that may have some relation to thiamine deficiency.[12]

A number of reports support the effectiveness of DCA in treating congenital and acquired lactic acidosis. DCA has been associated with a lowering of serum lactate in addition to clinical improvement. Stacpoole et al report on 53 patients with congenital lactic acidosis who were treated over a 1- to 5-year period with oral DCA.[13,14] Decreased serum lactate was demonstrated in 27 whereas decreased serum and cerebrospinal fluid (CSF) lactate was observed in 11 patients. Some clinical improvement (vital signs, muscle tone, exercise endurance, cognition, stabilization of neurologic decline) was observed for 15% of the 39 patients whose subsequent clinical course was known. For patients who respond to DCA, there should be a 20% decrease of serum lactate within 6 hours of the first dose. For patients who do not respond within 24 hours of oral or intravenous dosing, any response is not likely and therefore treatment is probably unnecessary.[13,14]

In a controlled clinical trial involving adult patients with varied etiologies of severe lactic acidosis, intravenous DCA was shown to significantly reduce ($P = 0.001$) serum lactate concentrations when compared with placebo. The changes in serum lactate concentrations were not associated with clinical improvement or survival.[15]

More recently, DCA has been evaluated in the setting of mitochondrial encephalomyopathies. Most reports are anecdotal and present conflicting clinical outcomes. Two siblings with MELAS having clinical deterioration were treated with a combination of DCA (50 mg per kg) and multiple other medications, including vitamin $B_1$. The plasma lactate diminished within 2 days in both patients. The frequency and severity of myoclonic seizures (patient 1) were decreased within 1 month. The drug was maintained in this patient for 25 months without apparent side effects. No additional strokelike episodes, headaches, or abdominal pain were observed in the second patient for the 22 months of observation.[16] A patient with MELAS was shown to improve after treatment with oral DCA on two separate occasions with regards to reduction in serum and CSF lactate levels. Additionally, this patient showed reduction of neurologic decline and cessation of auditory and visual hallucinations in conjunction with the normalization of the biochemical parameters.[17] Improvement of magnetic resonance imaging (MRI) abnormalities occurred in two patients with Leigh syndrome following treatment with DCA (30 or 50 mg per kg per day). The improvement was mild and transitory (21/2 months) in one patient (PDH complex deficiency) and more significant and sustained over the follow-up period of 9 months in the second patient (complex I deficiency). Both demonstrated reduction of serum and/or CSF lactate associated with initiation and continuation of therapy.[18]

Other than a lowering of serum lactate, Tulinius et al[19] did not find any significant difference clinically following treatment with DCA in a 6-month-old boy with myopathy and cardiomyopathy.

DCA (50 mg per kg per day following a load of 50 mg per kg every 12 hours for three doses) was used to treat a 1-year-old girl with Leigh's syndrome. She demonstrated gradual improvement in her clinical symptoms (respiratory status, physical activity, and muscle

strength) and biochemical profile (lactate diminished in blood and CSF). Despite this, 2 months after the start of therapy, MRI revealed continued cerebral atrophy. At the same time 1H magnetic resonance spectroscopy was indicative of reduced neuronal function. The investigators conclude that DCA may lead to some improvement of neurologic symptoms via reduction of serum lactate without truly affecting the underlying disease process.[20]

In a double-blind, placebo-controlled study of DCA in 11 patients with mitochondrial disease, DeStefano et al evaluated several measures of oxidative metabolism following 1 week of treatment. A significant decrease ($P < 0.05$) in serum lactate, pyruvate, and alanine occurred both at rest and after exercise. In addition, proton magnetic spectroscopy showed a decrease of brain lactate/creatine ratio by 42% ($P < 0.05$) in addition to other changes indicative of improvements of oxidative metabolism (NAA/creatine ratio increased by 8%, $P < 0.05$). Evaluation of the gastrocnemius muscle by phosphorous magnetic spectroscopy showed no significant change following treatment with DCA. No significant clinical improvement was noted following treatment despite the biochemical improvements, but may be due to the short treatment time of one week.[21]

In association with the administration of intravenous DCA at a dose of 50 mg per kg per day for 13 days followed by 25 mg per kg per day for 6 days, arterial lactate decreased as did seizure activity in a patient with MELAS. Serial proton magnetic resonance spectroscopy revealed improvement in terms of the magnitude of the lactate peak and NAA/Cr ratio in the region comparible with this patient's symptoms.[22]

Three children with mitochondrial encephalomyopathy were administered DCA at a dose of 30 mg per kg per day. These children demonstrated radiologic and clinical improvements following this oral treatment regimen. MRS findings revealed a marked reduction of lactic acid peaks in two of the patients. Both serum and CSF lactate levels diminished. Serial MRI scans demonstrated gradual decrease of white matter lesions in two patients, and the pontine and medullary lesions in the third. Developmental progress was observed following treatment in the two patients with Leigh's syndrome. These patients received oral DCA for 21 or more months without any significant side effects.[23]

In summary, DCA will lower serum lactate and improve other biochemical markers such as CSF lactate or serum alanine in some patients. For patients with a DCA-responsive PDH deficiency, the use of DCA can be helpful. It is not clear for those with electron transport defects whether or not lowering lactate is helpful. By increasing the flux of pyruvate through PDH, the kinetics of the reaction pyruvate + NADH Æ lactate + NAD+ lowers the lactate, but also increases the ratio of NADH/NAD+. The NADH produced cannot be utilized by the (impaired) ETC. Furthermore, the putative role of the increased concentration of NAD+, produced by the conversion of pyruvate to lactate, is to allow glycolysis to proceed and generate ATP under anaerobic conditions. A reduced amount of available NAD+ results in reduced production of anerobically generated ATP.

Unfortunately, despite lowering of serum and/or CSF levels of lactate, DCA treatment does not universally lead to overall clinical improvement.

« Previous Page Section 4 of 7 Next: Vitamins and Supplements »

Print This Email this

Semin Neurol. 2001;21(3) © 2001 Thieme Medical Publishers

# Treatment of Mitochondrial Cytopathies: Vitamins and Supplements

Physician Rating: ( 2 Votes ) Rate This Article:

Print This Email this

## Vitamins and Supplements

### Coenzyme Q

10

Coenzyme $Q_{10}$ ($CoQ_{10}$), also known as ubiquinone, is a lipid soluble antioxidant that is synthesized from tyrosine and mevalonic acid by animal cells. Multiple vitamins and trace elements are required for its biosynthesis. Ubiquinones are components of all cell membranes, including mitochondrial membranes.

Normal $CoQ_{10}$ levels are maintained by endogenous synthesis and dietary sources, which include primarily animal products. This compound can also be administered as an exogenous supplement. Normal muscle mitochondria, blood, and fibroblast levels have been established at 1811 ± 99 ng/mg (n = 10), 637 ± 84 ng/mL (n = 8), and 48 ± 1.3 ng/mg (n = 5) respectively.[24] Ubiquinone also exists in a partially reduced form (ubisemiquinone) and a fully reduced form (ubiquinol).





The role of $CoQ_{10}$ in energy metabolism is well documented. Large amounts of $CoQ_{10}$ are found in the mitochondrial inner membrane where it acts as a mobile electron carrier. Specifically, $CoQ_{10}$ shuttles electrons from ETC complex I to complex III and from complex II to complex III. In addition, $CoQ_{10}$ absorbs free radicals, which are probably generated to the greatest extent at the level of complex

I, thereby acting as an antioxidant and preventing propagation of lipid peroxidation. $CoQ_{10}$ also assists in regenerating active vitamin E from the tocopheroxyl radical.

Deficient $CoQ_{10}$ occurs in a wide range of human diseases and may occur due to insufficient dietary intake, impaired biosynthesis either due to endogenous causes or exogenous toxins, disproportionate utilization, or any combination of these.

Given its hydrophobic nature and large particle size, oral administration results in inconsistent absorption, requiring oil-based liquid preparations or suspension in oil. Typical dosing begins at 4 mg per kg per day but may require dosages as high as 15 mg per kg per day to achieve clinical efficacy.

$CoQ_{10}$ is the most widely recognized supplement used in the treatment of mitochondrial cytopathies. Reported beneficial effects have included decrease in serum lactate, improved exercise tolerance, increased muscle strength, and magnetic resonance spectroscopy improvements. As a cellular antioxidant, its role is theoretically important, as free radical production is known to increase in mitochondrial disease.

A number of primarily anecdotal reports suggest a favorable effect of $CoQ_{10}$ in disorders of energy metabolism. A 17-year-old girl with MELAS had symptoms unresponsive to intravenous betamethasone, oral nicotinamide, oral $CoQ_{10}$ (150 mg per day), and intravenous cytochrome c. Following initiation of $CoQ_{10}$ at a dose of 300 mg per day she demonstrated improvement of her ophthalmologic symptoms, increased exercise tolerance, and decreased serum lactate (both before and after exercise).[25] A 19-year-old girl with Kearns-Sayre syndrome and low serum $CoQ_{10}$ was treated with 120 mg per day of $CoQ_{10}$. Serum $CoQ_{10}$ increased to normal with concomitant lowering of fasting and postexercise lactate and improved ocular movements.[26] Seven patients with mitochondrial cytopathy and lactic acidosis were treated with 120 mg per day of $CoQ_{10}$. Five of the seven patients had low serum $CoQ_{10}$. Serum lactate following exercise was significantly diminished ($P < 0.05$) in four of the patients. Monthly neurologic exams revealed improved muscle strength in all but one patient. No echocardiographic improvements were noted. There were no reported harmful side effects related to this treatment regimen.[27] Abe et al[28] reported on a patient with MELAS whose CSF lactate and pyruvate decreased, with noted improvement in seizures and myopathy following treatment with $CoQ_{10}$.

In a double-blinded placebo-controlled crossover trial of $CoQ_{10}$ at 160 mg per day for 1 month, improved muscle strength and reduced fatigability were observed for those patients whose $CoQ_{10}$ levels were lower than controls prior to initiation of treatment. Following 3 months of therapy, there was a statistically significant increase in overall muscle strength testing ($P < 0.05$) but strength of specific proximal and distal musculature did not demonstrate significant improvement. The mean serum $CoQ_{10}$ levels increased to above normal range within 2 months of treatment with no significant change thereafter. These investigators did not find any significant change in the metabolism of lactate while patients were on $CoQ_{10}$. The global MRC score was the only significant improvement observed in this study.[29]

Chan et al[30] sought to determine clinically valuable metabolic parameters of patients with mitochondrial encephalomyopathies treated with $CoQ_{10}$ (150 mg per day) under exercise conditions. Nine patients were evaluated with bicycle ergometry prior to, during (3 months), and following treatment for 6 months. At rest, only two patients demonstrated elevated serum lactate levels, whereas, following exercise, seven patients had elevations of the same. In addition, the lactate-to-pyruvate ratio was abnormal at rest in eight patients and in all patients following exercise. At 3 months following onset of therapy, no clear change was noted in these biochemical parameters. At 6 months, however, there was a decrease in the lactate-to-pyruvate ratio at rest and in association with exercise ($P < 0.05$ for male patients, $n = 4$) in six of the patients.

There are several additional reports of patients who either showed equivocal changes or did not seem to demonstrate improvements while receiving $CoQ_{10}$. In a multicenter trial, 44 patients with mitochondrial myopathy were treated for 6 months exclusively with $CoQ_{10}$ at a dose of 2 mg per kg per day. Sixteen of the 44 patients showed a 25% decrease of postexercise lactate levels. All patients demonstrated statistically significant increases in muscle strength. These 16 patients were subsequently studied an additional 3 months in a blinded study of $CoQ_{10}$ and placebo. Serum lactate levels were not further decreased in this time interval in those treated with $CoQ_{10}$, although those receiving placebo developed worsening of postexercise lactate. Muscle strength did not improve during the second treatment period. No change was noted in terms of cardiac conduction abnormalities or ophthalmologic findings during the study period of 6 months.[31]

Two patients with mitochondrial myopathies were treated for 1 year with either 100 mg or 50 mg daily of $CoQ_{10}$. Neither of these patients had abnormal (low) $CoQ_{10}$ levels. Following 1 year of treatment, neither patient demonstrated improvement of their ophthalmologic symptoms, quantitative isometric strength testing revealed no significant improvement, and $CoQ_{10}$ levels remained essentially unchanged. It must be noted that the dose of administered $CoQ_{10}$ in this study is less than is generally used to treat most

adults.[32]

Sixteen patients with varied mitochondrial cytopathies were treated with $CoQ_{10}$ in addition to vitamins $K_3$ and C, riboflavin, thiamine, and niacin. This open study, using 300 mg per day over a 2-month time period, did not show any benefit. The parameters evaluated included resting and postexercise serum lactate, phosphorous magnetic resonance spectroscopy, and regular follow-up of clinical symptoms.[33]

The reliance on clinical and biochemical parameters exclusively in the evaluation of patients with mitochondrial cytopathies who undergo an experimental treatment may not provide an entirely accurate sense of effectiveness of therapy. [31] P magnetic resonance spectroscopy can be utilized to evaluate energy parameters in the specific tissue of interest, providing a noninvasive, quantitative measure of brain and/or muscle metabolism. In the presence of disordered mitochondrial metabolism one might expect to see a low concentration of phosphocreatine, a high concentration of inorganic phosphate, and a high calculated ADP.[34] Muscle can be evaluated at rest, during exercise, and during immediate postexercise recovery. In disorders of mitochondrial respiration, a decrease in the phosphocreatine/inorganic phosphate (PCr/Pi) ratio can be observed at rest. There is delayed replenishment of phosphocreatine following exercise. In some patients with mitochondrial cytopathy there may be no abnormality on 31P MRS, likely indicating that skeletal muscle mitochondria are not involved.[35] Again, with utilization of this technique, conflicting reports exist as to the effectiveness of $CoQ_{10}$ therapy.

Eight patients and 18 healthy controls were treated with 150 mg of $CoQ_{10}$ per day for 6 months and evaluated by 31P MRS of the calf muscle at rest, during exercise, and during the postexercise recovery period. MRS was performed at the beginning of treatment and following 3 and 6 months of therapy. The mean PCr/Pi was significantly higher for controls prior to treatment and did not significantly change throughout the supplementation period. By 3 months of treatment, there was a nonsignificant repletion of phosphocreatine in the patient population. One patient had a dramatic improvement of the PCr/Pi at rest in addition to increased repletion of phosphocreatine postexercise following 3 months of treatment.[36]

Barbiroli et al[37] utilized in vivo phosphorous magnetic resonance spectroscopy to evaluate the effectiveness of $CoQ_{10}$ on improving brain and skeletal muscle mitochondrial respiration. Ten patients with mitochondrial cytopathies were evaluated by 31P MRS prior to and 6 months following treatment with 150 mg per day of $CoQ_{10}$. There were 36 age-matched, healthy controls. Prior to treatment all patients demonstrated low concentrations of phosphocreatine and high ADP, indicative of mitochondrial dysfunction. There was a significant increased ($P < 0.02$) brain concentration of phosphocreatine following treatment with $CoQ_{10}$, in addition to a significant decrease ($P < 0.01$) of brain concentration of inorganic phosphorous. With regards to the skeletal muscle evaluation, the 31P MRS spectra were not significantly different at rest either prior to or following treatment when compared with controls. Despite this, all patients did demonstrate a faster recovery of phosphocreatine following treatment and some (those with CPEO) reported increased strength.

Two patients with mitochondrial encephalomyopathy were treated with 150 mg per day of $CoQ_{10}$ and evaluated by bicycle ergometry and 31P nuclear magnetic resonance (NMR) spectroscopy prior to and 10 months after initiation of treatment. In both patients before treatment there was a low PCr/Pi at rest, in addition to a high resting serum lactate. Acidosis occurred during the exercise phase, followed by a delay in recovery after exercise. Furthermore, the bicycle ergometer test revealed a lowering of the ventilatory threshold as well as reduction of the maximum oxygen uptake. Pretreatment 31P NMR spectroscopy demonstrated the following abnormalities: twofold decrease of ATP concentration and abnormally low PCr/Pi ratio. Following 10 months of treatment, there was significant improvement during the exercise test aloug with a decrease in resting lactate, increase in oxygen consumption, increase in maximal load, and ventilatory threshold reached normal range. 31P NMR spectroscopy (performed on flexor digitorum superficialis muscle) corroborated these findings in that there was a significant increase from the baseline PCr/Pi ratio at rest in addition to improved recovery of all measured parameters. The decreased ATP concentration was still present, thought to a lesser degree. The postexercise PCr/Pi ratio was essentially unchanged for one patient but demonstrated a fourfold increase for the second patient. These results lend support to the efficacy of high-dose administration of $CoQ_{10}$.[38]

The literature suggests significant controversy regarding the efficacy of $CoQ_{10}$ supplementation. Regardless, many patients report improved function, and the side effects associated with its use are rare. The majority of treating clinicians will administer a therapeutic trial in escalating doses (4 to 15 mg per kg per day) to determine its efficacy in an individual patient.

### Idebenone

Idebenone is an analog of $CoQ_{10}$ and acts both as a free radical scavenger as well as stimulating ATP formation by functioning as a mobile electron carrier. It is currently not available in the United States.

A patient with LHON and myopathy was treated with oral idebenone (45 mg three times per day with increase by 135 mg per day every 2 days) following the onset of marked spasticity and weakness. By the sixth day of treatment (135 mg three times per day), the patient was able to walk, run, and climb stairs. On neurologic examination, there was marked reduction of spasticity of the lower extremities in addition to improved strength. Following observation of this improvement, idebenone was continued at a maximum of 405 mg per day for an additional 3 months, during which the patient remained clinically stable. Following withdrawal of idebenone, the patient again demonstrated weakness of the lower extremities and spastic paraparesis. Idebenone was reinitiated and within 2 weeks clinical improvement was again observed. This patient was additionally evaluated by brain and muscle 31P MRS. Following approximately 3 months of treatment there was an inerease in phosphoereatine concentration and a decrease from baseline of inorganic phosphate toward reference values. When reimaged following withdrawal of idebenone, these parameters were markedly worsened and did not markedly improve following reinstitution of medication. In addition, 3 weeks following initiation of treatment, muscle studies showed an increased rate of recovery of phosphocreatine and inorganic phosphate. Though similar worsening of variables were observed following discontinuation of this medication, once resumed there was no return to the previously observed recovery levels.[39]

A 10-year-old boy with LHON due to homoplasmic 11778 mutation was treated with oral idebenone (90 mg per day) after presenting with early-onset symptoms. After 7 months of treatment, visual acuity was improved slightly (6/90 bilaterally to 6/6).[40] However, spontaneous improvement in visual acuity is frequently reported in LHON.

A patient with MELAS was treated with $CoQ_{10}$ augmented by the addition of idebenone. Following 8 months of treatment with 210 mg per day of $CoQ_{10}$, the patient demonstrated some improvement in terms of amelioration of sensory disturbance, alaxia, and muscle weakness. Serum lactate decreased slightly. Electroencephalogram (EEG) and Wechsler Adult Intelligence Scale (WAIS) testing remained unchanged when compared to prior to treatment. Motor and sensory conduction velocities normalized. Following the addition of 90 mg of idebenone, muscle strength improved further. Her EEG revealed marked improvement from baseline and from during treatment with $CoQ_{10}$ alone. Her WAIS scores increased by 14 points. CSF protein decreased from 64 mg/dL to 45 mg/dL. The idebenone dose was then increased to 180 mg per day for an additional 11 months. CSF lactate decreased. The improvements were maintained for a follow-up time of 20 months.[41]

The experience with idebenone may be too limited to draw any definitive conclusions. Further investigations may elucidate a role for this agent in a subset of patients with mitochondrial disease.

### Levo-Carnitine

Endogenous levo-carnitine (beta-hydroxy-gamma-trimethylammonium butyrate), found in many human tissues, is an amino acid derivative. It is synthesized in the liver and kidney from protein-bound lysine (supplemental oral lysine cannot improve carnitine synthesis) and methionine. It is a water-soluble compound that exhibits biologic activity only when in the levo isoform. Several enzymes and cofactors (iron, ascorbic acid, niacin, and pyridoxine) are involved in its biosynthesis, and only one matrix mitochondrial enzyme is involved in the pathway. Of note, skeletal and heart muscle are unable to synthesize carnitine, and these tissues are therefore dependent on uptake of carnitine from blood.

Normal plasma and tissue levels are maintained by both de novo synthesis and exogenous dietary sources. Meat and milk products contain the highest concentrations of dietary carnitine whereas plant products are poor sources. Normal plasma carnitine concentrations are about 25 umol/L in infants and 54 umol/L in adults.[42] The highest concentration of carnitine is found in skeletal muscle (98%), although distribution is shared with heart, kidney, liver, and brain.[43]

Carnitine is present in tissues and physiologic fluids as either free carnitine or as the acylcarnitine ester. In normal circumstances, approximately 85 to 90% is present in the free state. The majority of plasma acylcarnitine is represented by acetylcarnitine, which is often nonpathologically elevated in the fasting state. The ratio between aeylcarnitine to free carnitine varies with timing of the last meal, composition of that meal, nutritional status, exercise, and disease conditions and is quite sensitive to changes in mitochondrial metabolism. A ratio of 0.25 is considered to be normal, whereas greater than 0.4 is abnormal and is indicative of carnitine insufficieney or insufficient carnitine in light of the metabolic demands.[44]

Carnitine is necessary for transporting long-chain fatty acids across the inner mitochondrial membrane for the process of beta-oxidation. This occurs mainly in skeletal muscle, heart, and liver and is carried out by carnitine palmitoyltransferase I (CPT I), acylcarnitine translocase, and CPT II. A second major task of carnitine is to maintain intracellular homeostasis of acyl-CoA. Carnitine transesterifies the acyl-CoA esters that arise during beta-oxidation through the action of carnitine-acyltransferases. The acylcarnitine can then cross the mitochondrial membrane in exchange for free carnitine, thus allowing for restoration of free CoA within the

mitochondria. In addition to these major functions, carnitine may also play some role in altering the physiologic properties of cell membranes, such as membrane stabilization.[45] In the setting of inborn errors of metabolism, carnitine serves to detoxify the poisonous metabolic intermediates by forming a less toxic ester.

A number of pathologic conditions have been associated with abnormal metabolism of carnitine, the most frequent of which is carnitine deficiency. Carnitine deficiency can be defined as a state where the concentration is not adequate to meet the body's normal carnitine requirement. Systemic carnitine deficiency can be primary but may occur in many disease states, including disorders of oxidative phosphorylation, beta-oxidation, organic acidurias, malnutrition, valproate, and zidovudine use and in those receiving total parenteral nutrition without adequate carnitine replacement. Many metabolic disorders lead to elevated levels of acyl-CoA intermediates, which impair the function of adenine nucleotide translocase, the enzyme that exchanges ADP for ATP across the inner mitochondrial membrane. Carnitine forms an ester linkage with the acyl-CoA, forming the relatively nontoxic acylcarnitine, which is excreted in the urine. Elevated levels of acyl-CoA intermediates over time can lead to a secondary carnitine deficiency. Likewise, a carnitine deficiency itself can result in increased toxicity of the accumulated acyl-CoA compounds.

Clinical manifestations of a carnitine-deficient state are varied, including but not limited to cardiomyopathy, acute encephalopathy, myopathy, cognitive delay, central nervous system dysfunction, gastrointestinal dysmotility, and recurrent incidences of metabolic decompensation.

Treatment with levo-carnitine should be considered for any person with a primary or secondary carnitine deficiency. The role of carnitine therapy in mitochondrial disease is threefold. As already discussed, carnitine plays a role in reestablishing homeostasis of acyl groups, a process that is aberrant when mitochondrial dysfunction exists, leading to inhibition of respiratory enzymes. In addition, secondary carnitine deficiency exists in the setting of mitochondrial cytopathies; thus, carnitine replacement is essential. Finally, carnitine may provide improved integrity of the mitochondrial membrane, thus adding to membrane stabilization.[46]

The typical dose of levo-carnitine is 100 mg per kg per day for children and 2 to 4 grams per day for adults in three divided doses. In the nonacute setting, levo-carnitine is available as a liquid or tablet, but it is also available as an intravenous preparation. The intravenous dose is the same as the oral dose. Prior to initiation of carnitine therapy in any patient, plasma and urine carnitine and acylcarnitine profiles should be obtained. The primary adverse effects include diarrhea and nausea, though carnitine is usually well tolerated at typical doses. It should be noted that oral absorption is variable, and as little as 15% of the oral dose may actually be absorbed.

Of 48 patients studied by Campos et al,47 four had both total and free plasma carnitine deficiency (both defined as <30 mmol/L with normals in the low to mid 50s) with carnitine insufficiency (defined as ratio of esterified to free carnitine >0.25 with normal 0.13 ± 0.016), and 17 had isolated carnitine insufficiency. All 21 patients with carnitine deficiency or insufficiency were treated with 50 to 200 mg per kg per day of levo-carnitine. The following improvements were observed following initiation of treatment: 20 of 21 patients with muscle weakness demonstrated subjective improvement in muscle tone, four of eight patients with failure to thrive showed growth acceleration, and eight of eight patients with cardiomyopathy demonstrated improved echocardiographic findings and clinical improvement. The average treatment duration was 11 months (range 1 to 24 months). Plasma carnitine levels 10 days after initiation of treatment were normal or above normal. Many additional reports have demonstrated the beneficial effects of carnitine in the setting of cardiomyopathy due to underlying metabolic etiologies, including mitochondrial abnormalities.

### Creatine

Creatine is an amino acid produced endogenously in the liver from arginine and glycine, and it is also found in meat products. Creatine phosphate is synthesized from creatine and ATP, and it is catalyzed by creatine kinase (CK). Unlike ATP, which the body is unable to store, creatine phosphate can be stored to a limited degree in tissues, allowing for a supply of the high-energy phosphate bond, which can be utilized when needed. The hydration of phosphocreatine to creatine and ATP thereby allows the ATP to be utilized by the tissue. Creatine is found in highest concentrations in skeletal muscle and to lesser degrees in cardiac muscle, smooth muscle, brain, sperm, and kidney.

Intramuscular phosphocreatine may be reduced in patients with mitochondrial cytopathies. Supplemental creatine seems to be most effective at increasing phosphocreatine and creatine in this setting. Harris et al demonstrated that administration of creatine to healthy subjects resulted in a greater effect for those patients whose initial total creatine concentration was low. There were no side effects from supplementation with doses ranging from 70 g to 330 g with maximum treatment time of 21 days.[48]

The rationale for using creatine is to increase the tissue concentrations and possibly increase the ability of muscle (or other organs) to

accumulate creatine phosphate. Tarnopolsky et al have shown that creatine monohydrate (at doses of 5 g twice per day for 2 weeks followed by 2 g twice per day for 1 week) improved strength for high-intensity anaerobic and aerobic activities and lean muscle mass in patients with neuromuscular diseases, including those with mitochondrial myopathy. Both trials were based on short-term results, and the long-term beneficial effects of creatine remain to be proven. Regardless, the use of creatine in critical situations seems to be reasonable.[49,50]

In one study of nine healthy men provided with either oral creatine (as creatine monohydrate, 20 g dose) or placebo demonstrated no effect on performance for maximum exercise or on phosphocreatine levels. However, the supplement was only administered over a 3-day period and was in a setting of likely normal muscle creatine levels; therefore, its relevancy to those with mitochondrial disease is not known.[51]

### Antioxidants

Numerous pharmacologic agents have been used in the treatment of mitochondrial cytopathies, including antioxidants. Antioxidants may improve enzyme function or slow the process of oxidative damage, although the benefit over time is not possible to measure. The more commonly employed antioxidants (and the typical daily dosages) for patients with mitochondrial disease include selenium (50 to 100 mcg), vitamin C (250 to 4000 mg in divided dosages), vitamin E (400 to 1200 IU in divided dosages), and lipoic acid (200 to 600 mg in divided dosages). Given the vast clinical presentation of the mitochondrial cytopathies and the fact that these agents have not systematically been studied in this setting, it is not possible to state that there are proven benefits. Despite this, they are routinely used in patients with these diseases.

### Riboflavin

Riboflavin (vitamin $B_2$) is a precursor to flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), which are cofactors of ETC complexes I and II, respectively. Riboflavin has been proposed to act therapeutically by one of several potential mechanisms including inhibition of the breakdown of complex I by providing more resistance to proteolysis or stabilizing the mitochondrial membrane. It has been used with some success in some patients with mitochondrial disease without any apparent side effects.

A 33-year-old patient with MELAS and complex I deficiency was administered a combination of riboflavin (100 mg three times per day) and nicotinamide (1 g four times per day) in a double-blinded, randomized fashion. In conjunction with this treatment, there was cessation of this patient's encephalopathic and myopathic symptoms. The spectroscopic findings were equivocal: resting PCr/Pi did not show any treatment effect, whereas high-energy phosphate recovery deteriorated upon withdrawal of nicotinamide (but not riboflavin). Sural nerve sensory testing revealed a drop in amplitude once therapy was withdrawn with recovery following the reinitiation of treatment ($P = 0.00007$ right, 0.017 left).[52]

A 10-month-old infant girl with a partial defect of complex I was treated with increasing doses of riboflavin (beginning at 3 mg per kg). It was observed that lactate levels normalized and muscle weakness improved at the maximal dose of 13 mg per kg.[53] Riboflavin was given to five patients with mitochondrial myopathy due to complex I deficiency in dosages ranging from 9 to 60 mg per day. Patients presented with either pure myopathic symptoms or encephalomyopathy. One patient had stabilization of the previously regressive disease and three showed clinical improvement, especially in the myopathic component. There was normalization of complex I activity in three of the patients in addition to improved lactate levels or muscle histopathology.[54] A 13-year-old girl with progressive exercise intolerance, severe lactic acidosis, and complex I deficiency was treated with 100 mg of oral riboflavin daily. There was remarkable and persistent clinical improvement with an increase in exercise tolerance. Exercise parameters (maximal work capacity, $O_2$ uptake, and base excess) also improved.[55] A 6-year-old boy with a defect of complex I and myopathy presenting as slowly progressive weakness was successfully treated with riboflavin and carnitine. Clinically, muscle strength and motor conduction velocities were improved. In addition, the complex I activity and carnitine levels normalized 7 months after the start of treatment.[56] More recently, Ogle et al[57] report on a 21/2-year-old patient with complex I deficiency, mitochondrial DNA mutation, and myopathy and who had persistent response to riboflavin therapy (20 to 25 mg twice daily) over a 3-year period. Despite persistent lactic acidosis, this patient demonstrated improvements in terms of overall muscle strength and endurance.

Riboflavin is not always effective, as demonstrated by the case of a 4-month-old infant with severe congenital lactic acidosis and complex I deficiency, who underwent a trial of riboflavin at a dose of 100 mg daily. The child's serum lactate and ratio to pyruvate remained significantly elevated, and the patient continued to demonstrate features of severe myopathy and cardiomyopathy until his death.[58] Four patients with MELAS in association with complex I deficiency treated with riboflavin, other supplements, and the ketogenic diet did not show improvement.[59] Another large trial of riboflavin in combination with other supplements found no significant therapeutic success.[33]

The results of treatment with riboflavin, with a large variation in doses and treatment duration in this diverse population, are not uniform but demonstrate that those with complex I deficiency and pure myopathy may benefit from supplemental riboflavin, with or without other supplements. Of course, the clinical course of these diseases remains variable such that any improvement observed may not be due to therapeutic interventions.

### Thiamine

The PDH complex catalyzes the thiamine-dependent decarboxylation of pyruvate. Thiamine pyrophosphate, the physiologically active form of thiamine, acts as a coenzyme for this decarboxylation. The use of thiamine has been established in the treatment of some forms of PDH deficiency, although its use in disorders involving more distal components of energy metabolism, such as electron transport chain disorders, is not established. There are no reported side effects with administration.

Following treatment over a several week period with thiamine at 300 mg three times per day, three patients with Kearns-Sayre syndrome were found to have normalization of previously abnormal lactate and pyruvate levels. There was some change in overall level of fatigue, but clinical improvement in general was trivial.[60] Another patient, a 23-year-old with mitochondrial myopathy, cardiomyopathy, and lactic acidosis, was treated with thiamine (100 mg two times per day) in combination with prednisone (60 mg per day). Over a 3-week period, the patient demonstrated progressive improvement in overall strength. The previously life-threatening episodes of lactic acidosis also ceased, a finding that persisted over a 7-year follow-up period.[61]

One larger study of patients with mitochondrial cytopathies failed to demonstrate efficacy of treatment at doses of 100 mg per day for 2 months.[33]

### Vitamin K

3

In vitro studies show that in the presence of complex I inhibitors, vitamin $K_3$ (menadione) stimulates oxygen utilization in mitochondria, resulting in an increase of NADH oxidation.[62] One group of investigators utilized 31P nuclear magnetic resonance to assess the response to treatment with menadione (40 to 80 mg per day) and ascorbate (4 g per day) of a 19-year-old patient with mitochondrial myopathy associated with complex III deficiency. This treatment approach resulted in both clinical and metabolic improvement that persisted at 1-year follow-up. She was no longer wheelchair-bound though overall her weakness remained unchanged. The clinical improvements were supported by 31P NMR data, which revealed an increase in phosphocreatine concentration at rest and postexercise. A doubling of the initial dose of $K_3$ improved the phosphorous NMR spectra even further without apparent side effects. Symptoms deteriorated with withdrawal of treatment with recovery of function once reinstated.[63,64]

Toscano et al[65] treated a 16-year-old girl with ataxia, myoclonus, lactic acidosis, and complex III deficiency with vitamins $K_3$ (40 mg per day) and C (4 g per day). There was no significant change in lactic acidosis but there was mild improvement of her ataxia. After 5 months of therapy, the brain 31P-MRS indices were restored to normal. Skeletal muscle evaluation, though, revealed only slight improvement of mitochondrial bioenergetics.

One larger trial in which patients were treated with 60 mg per day of menadione and 2 g per day of vitamin C (in addition to multiple other supplements) did not substantiate the therapeutic benefit seen by these other investigators.[33]

$K_3$ is known to cause hemolytic anemia, hyperbilirubinemia, and kernicterus and is therefore contraindicated for neonates, pregnant females, or those being treated with coumadin. It is also difficult to find, and $K_1$, the common form of vitamin K, may have no benefit. As a practical alternative, $CoQ_{10}$ may provide the same benefit.

### Folate

A 23-year-old woman with Kearns-Sayre syndrome on phenytoin for a seizure disorder was found to have diminished CSF and plasma folate levels in addition to low free carnitine. She was treated with folate (40 mg per kg of body weight or 15 mg per day), D, levo-carnitine (10 g per day), and methionine (500 mg per day). Plasma folate increased to normal with supplementation but CSF folate remained unchanged. She also demonstrated clinical improvement to the point of being able to ambulate after having been bedridden.[66]

### Uridine

Uridine will soon be under investigation as a treatment for mitochondrial disorders. Uridine is a pyrimidine nucleotide, required for

synthesis of RNA and DNA. Normal cell and organ function rely on adequate synthesis, transport, and interconversions of pyrimidines. The synthetic pathway for uridine synthesis involves the mitochondrial dehydrogenation of dihydrooroate to oroate, which is intimately linked with $CoQ_{10}$ recycling and normal electron transport chain functioo. Any process that interferes with $CoQ_{10}$ recycling or electron transport chain function can impair oroate formation. The process of uridine synthesis concludes with condensing orotic acid with phosphoribosyl pyrophosphate (PRPP) to form uridine monophosphate. Disordered oxidative phosphorylation will impede the de novo synthesis of pyrimidines and further exacerbate cellular dysfunction. The theoretical argument for treating with exogenous uridine is to overcome the relative deficit due to impaired synthesis leading to improved cellular health.

Hereditary orotic aciduria produces a primary uridine deficiency and results in a syndrome of failure to thrive, megaloblastic anemia, orotic aciduria, congenital malformations, transient immunoglobulin deficiency, immune deficiency, and developmental delays. Lifelong supplemental uridine is required and may reverse some of the manifestations of this deficient state. Postulated beneficial effects of uridine are based primarily on animal research and include: appetite stimulation, anticonvulsant effects, prevention of lactic acid overproduction, antidepressant, cardioprotective, and prevention of cerebral edema, among others. Human trials are planned. Side effects have been reported and more commonly include a transient increase in seizure activity upon initiation of therapy, nausea, vomiting, and/or diarrhea (Robert Naviaux, personal communication, 2001).

« Previous Page Section 5 of 7 Next: Combination Therapy/Miscellaneous »

Print This Email this

Semin Neurol. 2001;21(3) © 2001 Thieme Medical Publishers

# Treatment of Mitochondrial Cytopathies: Combination Therapy/Miscellaneous



## Combination Therapy/Miscellaneous

1. Sixteen patients with mitochondrial myopathy, Kearns-Sayre syndrome, MELAS, or MERRF were treated with multiple supplements including vitamin $K_3$ (20 to 60 mg per day), vitamin C (1 g twice a day), a-tocopherol (200 IU twice a day), $CoQ_{10}$ (30 to 120 mg per day), and methylprednisolone (2 to 16 mg every other day). All patients underwent a baseline 31P-NMR spectroscopy, although only five were evaluated during treatment with this method. Ten patients were evaluated using near-infrared spectroscopy. Neither the 31P-NMR spectroscopy nor near-infrared spectroscopy demonstrated any acute changes in association with therapy. Follow-up range was 0.5 months to 15 years. Ten of the patients died. Despite the lack of objective data to demonstrate efficacy with this intervention, the authors felt there was a subset of patients who appeared to benefit from this treatment with prolonged survival, less functional disability, and/or fewer medical complications.[67]
2. Thirteen patients treated with daily doses of levo-carnitine (100 mg to 200 mg), ubiquinone (80 to 300 mg), tocopherol (50 to 100 mg per kg), riboflavin (50 to 100 mg), vitamin $K_3$ (80 to 160 mg), and vitamin C (2 g) underwent monitoring of serum carnitine, ubiquinone, and erythrocyte tocopherol levels. Total and free carnitine levels increased with treatment ($P < 0.05$,

total carnitine) but the acylcarnitine/free carnitine index demonstrated sustained elevation above that of controls (implying an increase of acylcarnitine generation). Serum ubiquinone and erythrocyte tocopherol levels were higher after treatment, though this did not reach statistical significance. Additionally, blood lactate levels were significantly decreased in four patients who clinically either stabilized or improved ($P < 0.05$).[68]

3. Lipoic acid functions as a coenzyme of the pyruvate dehydrogenase complex. In one study, treatment of a 33-year-old woman with CPEO with 600 mg per day of lipoic acid for 7 months was associated with a subjective improvement in symptoms and objective changes in 31P NMR spectroscopy of brain and muscle. At baseline this patient demonstrated reduced phosphocreatine concentration in conjunction with increased ADP concentration on brain MRS. Following treatment with lipoic acid there was an increased phosphocreatine content and decreased ADP, indicating that the brain was functioning under more stable conditions. Additionally, some improvements were seen with muscle 31P NMR spectroscopy though not as impressive (rate of phosphocreatine resynthesis postexercise did not improve after initiation of therapy).[69]

« Previous Page Section 6 of 7 Next: Summary »



Semin Neurol. 2001;21(3) © 2001 Thieme Medical Publishers