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**UNITED
MITOCHONDRIAL
DISEASE
FOUNDATION®**

**MitoFIRST Handbook
An Introductory Guide**

**Focus on Information,
Resources, Support, and Treatments**

ABOUT UMDF

The United Mitochondrial Disease Foundation is redefining hope for families affected by mitochondrial diseases - hereditary disorders, now considered as common as childhood cancers, that affect the cell's ability to produce life sustaining energy. The UMDF offers support to all sufferers of mitochondrial disorders regardless of diagnosis, suspected or confirmed.

We invite you to contact the UMDF at 1-888-317-UMDF (8633) or visit our website at www.umdff.org to learn more about mitochondrial diseases or to find out how to become a member.

When you call, you will find that the UMDF will enable you to:

- Talk to caring, professional staff who can answer non-medical questions
- Locate mitochondrial specialists closest to your vicinity
- Connect with a local chapter or support group
- Request a professional packet of literature to be sent to your local physician(s)

UMDF Membership Benefits:

- Receive a quarterly newsletter
- Link with others who have similar experiences through our Mitoconnect Networking Program
- Learn ways to increase awareness of mitochondrial diseases in your community
- Attend a national symposium for researchers, physicians, and affected families (some scholarships available to members)
- Vitamin/supplement discounts
- Online access to video-taped symposium seminars
- Ask a "mito doc" question online
- Receive a resource guide

For membership information, call 1-888-317-UMDF (8633) or visit www.umdff.org

INTRODUCTION

Dear Friend,

The fact that you are reading this ***MitoFIRST Handbook*** means that you have likely been impacted by a mitochondrial disease in some way. Whether you, your child, a family member or a friend has been diagnosed with a mitochondrial disease, our goal is to provide you with the knowledge and understanding, the resources, and the support you will need as you grapple with a diagnosis that is often under-recognized and misunderstood.

Living with mitochondrial disease presents many twists and turns and a maze of questions. It is our hope that this introductory guide will give you some answers. To gain the most from this guide, we suggest that you read each section in context and, if possible, consult any suggested online links for the complete articles.

While it was once thought that mitochondrial disorders were limited to children, it is now understood that onset of symptoms can begin in adulthood. Therefore, most of the information in this guide is applicable both to children and adults.

Please understand that this introductory guide is merely to be used as a tool. It is not meant to be a substitute for professional advice and services rendered by qualified doctors, allied medical personnel, and other professional and legal services. The responsibility for any use of this information, or for proper medical treatment, rests with you and your physician.

Yours toward a cure,



Charles A. Mohan, Jr.
CEO/Executive Director

UMDF MISSION

To promote research and education for the diagnosis, treatment and cure of mitochondrial disorders and to provide support to affected individuals and families.

WHAT IS MITOCHONDRIAL DISEASE?



Mitochondrial diseases are not one disease, but a group of metabolic diseases. These diseases result from failures of the mitochondria, specialized organelles present in almost every cell of the body. Mitochondria are responsible for providing more than 90% of the energy

needed by the body to sustain life and support growth. Food is converted into ATP (stored energy) by means of enzymes in the electron transport chain (or respiratory chain) inside the mitochondria. The process itself is called oxidative phosphorylation. Defects in either the mitochondrial DNA or the DNA of the nucleus can impair this process and cause mitochondrial failure.

When mitochondria fail, less and less energy is generated within the cell. When this happens, cell injury and even cell death follow. If this process is repeated on a large scale throughout the body, whole systems begin to fail.

The life of the affected person is compromised, changed or even ended.

Hallmarks of Mitochondrial Disease

1. A “common disease” has atypical features that set it apart from the pack.
2. More than one organ systems are involved
3. Recurrent setbacks or flare-ups in a chronic disease occur with infection

How many individuals are affected?

Every 15 minutes, a child is born who will develop a mitochondrial disease by the age of 10. We now know that this group of diseases is approaching the frequency of childhood cancers. The exact numbers of children and adults with a mitochondrial disease are hard to determine because many people who suffer from a mitochondrial disease are misdiagnosed. Some are misdiagnosed with such conditions as: atypical cerebral palsy, various seizure disorders, other childhood diseases and diseases of aging, chronic fatigue or fibromyalgia. Still others aren't diagnosed until after death.

WHAT ARE THE CAUSES?

Mitochondrial diseases can be due to inherited mutations or acquired mutations. There are primary (something inherently wrong with mitochondrial function) and secondary (the mitochondria are injured as a bystander to another process) disorders.

Mitochondrial disorders can be inherited in different ways. In fact, nearly every inheritance "model" known has been demonstrated to occur in mitochondrial disease. However, most mitochondrial disorders known to date are inherited in either an autosomal recessive (both parents are unaffected carriers) or maternal manner.



In many cases, the patient is the only family member affected with a mitochondrial disease. These cases are called "sporadic" and make answering the questions regarding inheritance more difficult.

The first question is whether the problem is due to genetics, environment, or some combination of the two. Not all mitochondrial disorders are primarily genetic. For example, certain medications can damage mitochondria and cause symptoms due to resultant energy failure. Removal of these drugs may reverse the process, and the symptoms may resolve. There are other environmental causes of mitochondrial disease and likely many that we do not know about.



It is the opinion of some experts that most mitochondrial diseases are probably both genetic and environmental in origin. Even in the case of drugs such as HIV medications, thousands of individuals have no problem on these drugs while only a handful do. Likely, there are genetic reasons for the high susceptibility

to these drugs in an unlucky few - a genetic predisposition to an "environmental" disease.

SIGNS AND SYMPTOMS



Patients' symptoms can range from extremely mild to severe, involve one or more body systems, and can emerge at any age. Most patients' symptoms fluctuate over the course of their illness -- at some times experiencing no or few symptoms while at other times experiencing many and/or severe symptoms. Even family members with the same disorder can experience vastly different symptoms.¹ Symptoms may present unexpectedly at any age, or they may be evident from birth or infancy. Diseases

of the mitochondria appear to cause the most damage to cells of organs and systems that require a great deal of energy: the brain, the heart, the skeletal muscles, the GI system, the kidneys, the liver and the endocrine and respiratory systems. As a result, children and adults who have these diseases experience a vast array of symptoms. Although a few may have only mild symptoms such as learning disabilities and susceptibility to fatigue, many others face numerous, severe problems and the potential for premature death. Mitochondrial diseases are extremely complex; due to this complexity, the severity of these diseases is unpredictable, and the range of symptoms is diverse.

***Mitochondrial diseases should be considered
in any patient with unexplained multi-system involvement
with a progressive course.***

Adult Symptoms

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 might be mild and may not resemble any 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.²



1. Reprinted from "Myths and Facts about Mitochondrial Disease," Sumit Parikh, MD and Bruce Cohen, MD, Cleveland Clinic Journal Of Medicine
2. Reprinted from "Mitochondrial Cytopathy in Adults", Bruce Cohen, MD and Deborah Gold, MD, Cleveland Clinic Journal of Medicine

POSSIBLE SYMPTOMS

Brain

- * Developmental delays
- * Mental retardation
- * Dementia
- * Seizures
- * Neuro-psychiatric disturbances
- * Migraines
- * Atypical Cerebral Palsy
- * Strokes
- * Autistic features

Nerves

- * Weakness (may be intermittent)
- * Absent reflexes
- * Fainting
- * Neuropathic pain (pins ,needles, burning)
- * Dysautonomia - temperature instability and other dysautonomic problems

Muscles

- * Weakness
- * Muscle pain
- * Pseudo-obstruction
- * Irritable Bowel Syndrome
- * Cramping
- * Diarrhea or Constipation
- * Dysmotility
- * Gastroesophageal reflux
- * Hypotonia
- * Gastrointestinal problems

Kidneys

- * Renal tubular acidosis or wasting

Heart

- * Cardiac conduction defects (heart blocks)
- * Cardiomyopathy

Liver

- * Hypoglycemia (low blood sugar)
- * Liver failure

Eyes & Ears

- * Visual loss/blindness
- * Ptosis (droopy eyelids)
- * Ophthalmoplegia
- * Optic Atrophy
- * Hearing Loss/deafness
- * Acquired strabismus
- * Retinitis pigmentosa

Endocrine

- * Diabetes and exocrine pancreatic failure (inability to make digestive enzymes)
- * Parathyroid failure (low calcium)
- * Hypothyroidism

Systemic

- * Failure to gain weight
- * Fatigue
- * Unexplained vomiting
- * Short stature
- * Respiratory problems

DIAGNOSTIC PROCEDURES



Mitochondrial diseases are difficult to diagnose, and unfortunately, there are few physicians who specialize in these diseases. Referral to an appropriate medical center is critical. If experienced physicians are involved, diagnoses can be made through a combination of clinical observations, laboratory evaluation, cerebral imaging, and muscle biopsies. Despite these

advances, many cases do not receive a specific diagnosis. A single normal blood or urine lab test does not rule out mitochondrial disease. This is true for organic acids, lactic acid, carnitine analysis and amino acid analysis. Even muscle biopsies are not 100% accurate. Not all metabolic disorders primarily affect energy metabolism, but the clinical features may overlap. **There is no substitute for good clinical judgment.**

Laboratory Evaluation for Disorders of Energy Metabolism

Laboratory testing is the usual method by which physicians evaluate patients for disorders of energy metabolism (which include mitochondrial disorders, disorders of oxidative phosphorylation and beta-oxidation disorders). Most hospitals do not have a metabolic laboratory and therefore can run only the most basic tests. However, these hospitals can send specimens to any laboratory in the country. Not all laboratory tests are required for all patients, and your physician may decide that some tests are not necessary.

An initial laboratory evaluation is generally used as a non-invasive screening for inborn errors of energy metabolism. If the results of this evaluation are suggestive of a specific disorder, a direct test for the disease in question may be able to be performed. If the results of the initial evaluation are normal and there is a strong suspicion of a mitochondrial disease, a more intensive evaluation is performed. Secondary tests are more invasive (and may include a spinal tap), and because some of the tests may require urine specimens collected over time, a bladder catheter may be required in young children. Many of these tests require the specimens to be sent to a special laboratory.

Abnormalities found on the secondary tests will guide the physician as to the direction of further testing. However, as with the initial testing, normal results do not eliminate the possibility of a mitochondrial disease but make it less likely.

Tertiary tests are invasive and/or expensive, and may carry with them some risks, such as metabolic decompensation during a fast. However, if the physician strongly suspects a metabolic disease, such tests may be diagnostic. The muscle biopsy is a tertiary test, is the most complicated and invasive of all tests, and in children requires a general anesthesia. Although a muscle biopsy can be performed at any medical center, very few centers have the ability to do all of the testing necessary to make a diagnosis. Therefore, the physician must be very conscientious in planning where to send the biopsy before the test is performed.

Metabolic Screening (in all patients)

- Basic Chemistries
- Liver enzymes & Ammonia
- Complete Blood Count
- Creatine Kinase
- Blood Lactate & Pyruvate
- Quantitative Plasma Amino Acids
- Quantitative Urine Organic Acids
- Plasma Acylcarnitine Profile

Metabolic Screening In Spinal Fluid (for patients with neurological symptoms)

- Lactate & Pyruvate
- Quantitative Amino Acids
- Neurotransmitter studies
- Routine studies including Glucose, Protein, and Cell Count

Clinical Neurogenetic Evaluation (for those with developmental delays)

- Echocardiogram
- Electrocardiogram (EKG)
- Ophthalmic Exam
- Auditory Exam
- Brain MRI

Characterize Systemic Involvement

- Karyotype
- Fragile X Testing
- Neurology Consult
- Genetics Consult

Negative results have a high false negative rate; if mitochondrial disease is suspected, refer the patient to a mitochondrial disease center.

The lab tests above are from the Mitochondrial Medicine Society Website.

A list of tests and centers performing these tests can be found at:

www.mitosoc.org/blogs/diagnosis

TREATMENT

Even though mitochondrial disorders are long term and currently incurable, treatments are available. Early treatment of symptoms can reduce their impact and limit further disability. Avoiding various medications and stressful situations that worsen symptoms is also helpful. Certain medications and supplements may improve mitochondrial disease-related symptoms - just as they do for other incurable diseases such as diabetes and emphysema.

Purposes of Treatment

- alleviate symptoms
- slow down progression of the disease

Effectiveness of Treatment

- varies from patient to patient, depending on the exact disorder and the severity of the disorder.
- as a general rule, patients with mild disorders tend to respond to treatment better than those with severe disorders.
- in some circumstances, the treatment can be tailored specifically to the patient, and that treatment is effective; whereas in other circumstances, the treatment is “empiric,” meaning that the treatment makes sense, but that the benefit of treatment is not obvious or proven to be effective. It is not possible to predict the response to vitamins, supplements or diet changes before they are tried.

Benefits of Treatment/Effectiveness of Therapies Vary

- treatment may be beneficial and noted immediately in some disorders
- benefit of treatment may take a few months to notice
- benefit of treatment may never be noticed, but the treatment may be effective in delaying or stopping the progression of the disease.
- some patients may not benefit from therapy

Key Points for Treatment

- dietary
- vitamins and supplements
- avoidance of stressful factors
- exercise

KEY TREATMENT POINTS

Although a “cure” for mitochondrial disorders may theoretically include a mitochondria “transplant” or genetic therapy to correct the underlying defect, these therapies are a long way off. In the meantime, it is important to minimize further mitochondrial damage and to improve function at the tissue and whole body level. Although none of the non-genetic therapeutic strategies mentioned are “curative”, it is important that mitochondrial and tissue structure and function are maintained until genetic therapies become a reality.¹

Another factor to consider in therapies for mitochondrial diseases is that single therapies targeting only one of the final common pathways of mitochondrial dysfunction are not likely to be beneficial. It is probable that the best therapy for mitochondrial disorders would be to target a number of negative consequences of mitochondrial dysfunction simultaneously. In general, this approach has been taken by many clinicians in that most patients are treated with a mitochondrial “cocktail” of supplements.

The decision to initiate therapy for mitochondrial disorders and the choice of the agents must be made on a case-by-case basis and with consultation from a physician with experience in the theory and practical issues related to mitochondrial therapies.¹

Treatment recommendations must be tailored by the patient's physician to meet that patient's needs. No treatment should be implemented or terminated without the direct supervision of a physician. In some cases, the treatment could be dangerous. It is not possible to predict the response to vitamins, supplements, diet, or exercise changes before they are tried.

VITAMINS/SUPPLEMENTS

Vitamins and co-factors are compounds that are required in order for chemical reactions, which make energy, to run efficiently. For most people, a regular diet contains all of the vitamins one could possibly need, and their bodies can make as much of any specific co-factor that they need. For those with mitochondrial disorders, added vitamins and co-factors can be useful. Most of these vitamins can be purchased from many sources, including the drugstore.

The use of supplemental vitamins and co-factors is controversial in that there are no proven benefits to some of these therapies. For specific information about the controversy, as it relates to you or your child's situation, ask your physician.

For disorders of OXPHOS, coenzyme Q10 is considered as a generally accepted effective therapy, although it may not ultimately be effective for an individual patient. Other treatments are proven therapies in specific disorders, but in other disorders those same therapies cannot be considered as "proven and effective" although they still may be helpful.

VITAMINS AND SUPPLEMENTS THAT MAY BE HELPFUL

Suggested To Most Patients

Supplement	Purpose	Your Dose
CoQ10	provide energy beyond enzyme defect site, antioxidant	
levo-carnitine (Carnitor®)	transports long-chain fatty acids, binds unused metabolic products	
Riboflavin (B2)	precursor of 2 cofactors involved in electron transport chain	

Second Tier Supplements

Supplement	Purpose	Your Dose
Acety-L-Carnitine	another form of carnitine, may have more neurological effect	
Thiamine (B1)	co-factor and activator of pyruvate dehydrogenase, reduce lactate levels	
Nicotinamide (B3)	may boost electron transport chain activity	
Vitamin E	antioxidant	
Vitamin C	antioxidant	
Lipoic Acid (a-lipoate)	antioxidant, co enzyme for pyruvate dehydrogenase & alpha ketogluta- rate dehydrogenase	
Selenium		
B-carotene	antioxidant	
Biotin	Involved in mitochondrial reactions outside the electron transport chain	
Folic Acid	for cerebral folate deficiency	

Medications, Minerals, Vitamins and Substrates that may be helpful (only to be used under a doctor's care)

Supplement	Purpose	Your Dose
Calcium	bone health; antioxidant	
Magnesium	bone health: antioxidant	
Phosphorous	bone health; antioxidant	
Vitamin K3	antioxidant	
Succinate	boost electron transport chain/ citric acid cycle	
Creatine	Energy booster/alternative energy source, weak antioxidant	
Uridine	Neuroprotection: DNA synthesis	
Citrates	boost citric acid cycle/Alkalinize	

MEDICATION PRECAUTIONS

Some medications should be taken with caution when you have a mitochondrial disorder. This is not an exhaustive list and does not pertain to every patient with a mitochondrial disorder. Review your individual disorder and medications with your personal physician.

Medications that should generally be avoided include valproic acid, statins, erythromycin, and propofol. There are no absolute contraindications and these medications can be given if an alternative drug is not available or appropriate. Antiretroviral drugs (anti-HIV drugs) are toxic to mitochondria and should be avoided if possible.

Doxorubicin, a chemotherapy medication, causes cardiomyopathy as a side effect, most likely through mitochondrial damage, and should be avoided.

Aminoglycoside antibiotics, such as gentamicin, streptomycin and tobramycin, can induce hearing loss by damaging mitochondria. These antibiotics should be avoided if the cause of the mitochondrial disorder is unknown. There are specific point mutations in the mtDNA that make one more susceptible to hearing damage.

Certain antipsychotic medications can increase the risk of diabetes and should be used with caution and frequent monitoring.

If IV fluids are necessary, Lactated Ringers solution should be avoided as it contains lactic acid.

Some individuals with mitochondrial diseases are more sensitive to volatile anesthetics and need a much lower dose to achieve a bispectral index of <60. Sevoflurane is tolerated better than isoflurane and halothane.

Medications can be essential to your health and well-being. Please review any concerns you have with your physician.

Many patients have already “self adjusted” their diet because they know what foods their bodies seem to tolerate. The following points below are not meant to be suggested therapies for all patients with OXPHOS disorders.

A dietitian experienced in metabolic disorders may be helpful with providing general dietary advice. Please do not make any of these dietary changes without consulting a physician.

GUIDELINES THAT CAN BE CONSIDERED

1. Avoiding fasting is perhaps the most important part of dietary treatment. This means avoiding prolonged periods without a meal (even an overnight “fast” from 8 pm to 8 am may be dangerous in some patients). This also means that some patients should not intentionally try to lose weight. Some patients with an acute illness causing vomiting or loss of appetite (like the flu) should be hospitalized to ensure continuous nutrition (intravenous glucose for example).
2. Small, frequent meals may be better than a typical three-meals-a-day routine for some patients.
3. A protein/complex carbohydrate snack before bedtime may be helpful to prevent low blood sugar overnight in some patients. This snack should not be mainly “sugar,” like a candy bar, flavored gelatin or sweetened cereal.
4. Ingesting excess iron is theoretically harmful to mitochondrial patients. There is no need to give supplemental iron in vitamins, or to purposely eat foods rich in iron unless there is significant iron deficiency. This does not mean that the person should not eat red meat. There is no reason to take vitamins with added iron. In addition, vitamin C should not be given around a meal rich in iron. This is important to remember because some experts feel that vitamin C is a good antioxidant and also may be helpful in some disorders of OXPHOS.

EXERCISE TREATMENT STRATEGIES

Essentially, there are two main forms of exercise: endurance exercise and resistance/strength. Endurance exercise in healthy individuals increases the number of mitochondria and oxygen consumption and reduces lactate production in any given exercise intensity. Resistance/strength exercise uses predominately anaerobic pathways and results in an increase in muscle size and strength.

Exercise Precautions

Many “mito” specialists strongly believe that exercise is necessary and can improve muscle strength, endurance, and general well being in patients with mitochondrial disease. The best advice is moderation: don't over do it or under do it. The patient should exercise up to his/her individual tolerance (which will vary from time to time) and stop once symptoms become significant. Exercise should be fairly frequent (perhaps at least twice a week), and the patient should push to the point of fatigue. Excessive exercise, however, especially in the presence of cramps or in hot weather, can precipitate a dangerous metabolic decompensation and should be avoided. The problem lies in determining “the point of fatigue”. Distinguishing true metabolic fatigue from simple laziness is not always easy. When the patient experiences significant pain or weakness, that is the time to stop. The amount of allowable activity varies substantially among patients, and from time to time, even in the same patient.

In some patients, rhabdomyolysis (muscle breakdown) can occur with exercise. Other potential triggers for rhabdomyolysis include illness, fever, fasting, alcohol and stress. Rhabdomyolysis should be suspected when the urine becomes “cola colored”. If present, medical attention should be immediately sought and hydration (by mouth or IV) given to avoid possible kidney damage.

Endurance Exercise - The rationale behind using endurance exercise in mitochondrial disease is to increase mitochondrial capacity, oxygen consumption and to decrease secondary deconditioning. If exercise is started at a low level and very gradually increased, this appears to be well tolerated.

Resistance exercise - Depending on the type of mitochondrial disorder, some patients have actual weakness instead of just decreased endurance. Consequently, strength exercise may be very important. Given that strength/resistance exercise does not require aerobic metabolism, many patients can perform several of these contractions. It is important for patients with mitochondrial disease to have a prolonged rest period between each exercise set to allow for ATP recovery.

Theoretically, resistance exercise may cause damage to the muscle and proliferate a satellite cell (a form of stem cell in muscle), which could lead to a reduction in the percentage of abnormal mitochondrial DNA (DNA shifting). This has been shown with direct damage to the muscle with various toxins and more recently with resistance exercise.

In patients with mitochondrial disorders, resistance exercise can improve strength; however, the concept of DNA shifting remains to be fully explored.

Again, it is very important to start at a low level and tailor the program to the base line strength of the individual and most importantly to allow for a very long recovery. (Normally the two minutes between each set should be extended to five to ten minutes between sets. A circuit set type program works best - 10 arm curls, followed by 10 sit ups, followed by 10 calf raises, followed by 10 knee extensions, and then back to the arm curls with at least a minute or two between each bout of activity.)

Additional Therapies

Other therapeutic interventions may be necessary for some mitochondrial disease patients. While they will not change the primary condition, they may be necessary to preserve and possibly improve current function, strength, and mobility.

Some additional therapies may include: speech therapy, physical therapy, occupational therapy, and respiratory therapy. Other therapies specific to the patient's needs may be beneficial as well.

THINGS TO AVOID

Physiological “Stress”

Stress, good or bad, can cause energy depletion, which may result in temporary, or sometimes permanent, worsening of the condition. It is impossible to avoid all physiologically stressful conditions. However, recognizing what may be stressful for a patient allows one to adjust the lifestyle.

Cold Stress avoidance is extremely important. Thermal regulation (temperature control) is not always normal in people with mitochondrial diseases and exposure to cold can result in severe heat loss and trigger an energy crisis. When going out into the cold, all exposed body parts should be covered, and exposure to extreme cold should be avoided for anything more than a short period. Over-bundling can be a problem, too (see below).

Heat Stress can be a problem in some people. This is especially true of those with an inability to sweat normally. Heat exhaustion and heat stroke may occur on hot days. An example of a typical scenario for this situation would be a child who seems to “wilt” in situations like hot classrooms, whereas other students function normally. Light clothing is important. Patients should avoid direct sunlight on hot days and stay indoors if it is too warm outside. An air conditioned environment may be needed.

Starvation or fasting - see nutrition/diet information

Lack of Sleep - may be harmful

Illness - especially with fever should be treated as soon as possible

Stressors specific to the individual patient.

Toxins

Alcohol has been known to hasten the progression of some conditions.

Cigarette smoke is known to hasten the progression of some conditions probably due to the carbon monoxide, which possibly inhibits complex IV of the OXPHOS chain. If there is already a dysfunction of OXPHOS, cigarette smoke will make it worse.

MSG (monosodium glutamate) has for years been known to cause migraine headaches in otherwise healthy individuals and may trigger these events in susceptible people with mitochondrial disease. **Read the label and avoid MSG.**

PROGNOSIS

It is not possible to chart the future of a person with a mitochondrial disorder. Those with a higher number of defective mitochondria do worse, on average, than those with a lesser number, but this is only valid for populations of patients and cannot be used to predict what will occur in any one patient.

Some of the information used in this introductory guide was taken from the following articles, which are also on our website at www.umdf.org:

Mitochondrial Cytopathies - A Primer

Bruce H. Cohen, MD
Cleveland Clinic Foundation

Myths and Facts about Mitochondrial Disease

Sumit Parikh, MD and Bruce Cohen, MD
Cleveland Clinic Foundation

Nutritional, Pharmacological and Exercise Treatment Strategies for Mitochondrial Disorders

Mark A. Tarnopolsky, MD, PhD, FRCP
McMaster University
Hamilton, Ontario

Mitochondrial and Metabolic Disorders - A Primary Care Physicians Guide

The Mitochondrial Medicine Society- www.mitosoc.org

SAMPLE EMERGENCY LETTER

To whom it may concern:

PATIENT:

DATE OF BIRTH:

DIAGNOSIS:

PLEASE NOTE

This sample letter is intended to serve only as a guide. Give this letter to your family physician to individualize for you or your child. UMD's intent on providing this sample is to provide guidance and should not be used without your physician's input.

(name) has a disorder of mitochondrial metabolism. The clinical manifestations in this patient include (EXAMPLES – write in primary symptoms): seizures, migraine, strokes, stroke-like events, myopathy, neuropathy, movement disorder, hearing loss, visual loss, cardiomyopathy, cardiac conduction defect, gastroparesis resulting in intestinal pseudo-obstruction, fasting intolerance, clinical deterioration during viral infections and dehydration, etc.

The diagnosis of mitochondrial disease is based on the following clinical and laboratory findings: (write method of diagnosis). Individuals with such a metabolic disease have a risk of deterioration, sometimes permanent, due to the common effects of a physiologic stress such as a viral or bacterial infection, fever, anorexia or dehydration. There is no evidence-based medicine review to support these recommendations, but they are based on a consensus opinion of several authorities in the field.

Because of the patient's diagnosis, I have instructed the patient to carry this letter on their person and present it to any physician or emergency department that will be performing a medical evaluation. In addition to the standard evaluation and treatment, I do recommend that strong consideration be made for intravenous fluids if there is any history or anorexia, vomiting or diarrhea. Oral rehydration therapy does not seem to be as effective as it is in otherwise healthy patients. Although there is no substitute for the standard history and examination, special attention should be paid for evaluation of electrolytes, glucose, liver enzymes, CK, CBC, and urine analysis (including pH, presence of ketones, and specific gravity). If blood lactate and ammonia are readily available, these can be obtained as well. In general, I recommend a bolus of normal saline if there is evidence of dehydration, followed by D5 (or D10) with $\frac{1}{4}$ to $\frac{1}{2}$ NS with KCl (if appropriate) to run in at about 1.5 times maintenance. If levocarnitine is available I would also recommend placing 1000 mg in 19

each liter bag of intravenous fluids, or bolus with 1000 mg if the need for IV fluids will be brief. In some circumstances, patients feel much better after the IV fluid bolus and a few hours of IV therapy, but in other situations, IV fluids should be continued for 1-3 days (an observation admission is generally acceptable). In this particular patient, the history of prior response suggests that fluids will likely be necessary for (your doctors recommendations) hours.

Any identified medical condition should be treated as you would any other patient. Some patients with mitochondrial disease are susceptible to the ototoxic effects of systemic aminoglycosides, so these are best avoided unless there is no other adequate antibiotic coverage. There is no absolute contraindication to aminoglycosides.

If there is a need for emergency surgery we do suggest avoiding Lactated Ringers solution unless the clinical situation suggests otherwise. During anesthesia and in the post-operative period, blood glucose and lactate levels should be monitored. Some individuals with mitochondrial disease are more sensitive to volatile anesthetics, and in some circumstances only 10% of the typical dose of a volatile anesthetic is necessary to obtain adequate anesthesia. If possible BIS monitoring (bispectral index) should be done during anesthesia as a much lower dose achieves a BIS<60. Short courses of propofol has been safely used in patients with this diagnosis (1-2 hours) but prolonged anesthesia should be avoided. Malignant hyperthermia is rare in patients with this diagnosis but there is a concern for rhabdomyolysis. For elective and non-urgent procedures, the patient should be at baseline health status without any dehydration or infection prior to the procedure. Serious attention with respiratory therapy measures (such as incentive spirometers) should be used in the post-operative period.

If there are any questions, please call me. My office number is (your doctors telephone number) and after hours my service can be reached at (your doctors telephone number). I would appreciate if you could give the patient a copy of all lab results and a discharge summary.

Sincerely,

(your doctors signature)

UMDF RESOURCES

For additional information on the topics covered in this booklet, as well as other topics, please explore the United Mitochondrial Disease Foundation website at www.umdf.org.

A few links that may be of particular interest include:

www.umdf.org/askthemitodoc: Questions and answers provided by a team of mitochondrial disease experts.

www.umdf.org/helpfulresources: For more in depth information on specific disorders and articles to share with your health care professionals.

www.umdf.org/map: Want to become involved? See what the UMDF offers in your state. You will find information on UMDF groups, activities, events, and local resources.

www.umdf.org/library: Interested in previous issues of Mitochondrial News, the quarterly UMDF newsletter, and/or other UMDF publications? Check out our online library.

www.umdf.org/symposium: Looking for an opportunity to learn more about mitochondrial disorders and to network with others facing similar challenges? The annual Mitochondrial Medicine Symposium is designed for you! On this link you will find all of the up-to-date details.

www.umdf.org/researchgrants: Learn how the UMDF spends its research dollars. This peer-review process selects best-of-the-best applications for funding.

NOTES



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