Functional Medicine University’s Functional Diagnostic Medicine Training Program

Mod 4 * FDMT 532B

**Mitochondrial Dysfunction and Cytopathy**
*(Disorders of Energy Production)*

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Contents

Mitochondrial Cytopathies .................................................................................................................................................. 2
Hallmarks of Mitochondrial Disease ................................................................................................................................. 2
Mitochondrian ...................................................................................................................................................................... 3
Cardiolipin ............................................................................................................................................................................ 3
Mitochondrial DNA ............................................................................................................................................................. 4
Symptoms of Mitochondrial Disease ................................................................................................................................. 5
Causes of Mitochondrial Disease ........................................................................................................................................ 6
Acquired Conditions ............................................................................................................................................................. 7
Associated Disorders ............................................................................................................................................................. 7
Medication-induced ............................................................................................................................................................... 8
Hereditary............................................................................................................................................................................... 9
Diagnosing Mitochondrial Dysfunction and Cytopathy ..................................................................................................... 10
Treatment of Mitochondrial Dysfunction/Disease ............................................................................................................... 15
References ............................................................................................................................................................................. 17
Mitochondrial Cytopathies

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

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 setback or flare-ups in a chronic disease occur with infection

The primary role of the mitochondria is to generate energy in the form of ATP. The electron transport chain (respiratory chain) and oxidative phosphorylation are the pathways in which energy is produced. These reactions occur along the inner mitochondria. During the transfer of electrons from one complex to another, electrons can escape producing reactive oxygen species (ROS). A high level of ROS and a low level of antioxidants results in oxidative stress, which causes damage to the mitochondria and surrounding tissue.
Aside from energy production, the mitochondria also participate in initiating and executing both apoptosis and necrotic cell death as well as maintaining calcium and iron homeostasis. Apoptosis is a term for programmed cell death. Necrotic cell death is a form of traumatic cell death that results from acute cellular injury. Apoptosis differentiates from necrotic cell death as the processes associated with apoptosis in disposal of cellular debris do not damage the organism. Apoptosis is a genetically controlled and evolutional conserved form of cell death essential for normal embryonic development and for the maintenance of tissue homeostasis in the adult. Normal homeostasis requires getting rid of diseased cells for the benefit of the whole organism. The target of choice for apoptosis and necrotic cell death is the mitochondria, since is it the source of energy production.

**Cardiolipin**

A phospholipid found almost exclusively in the mitochondrial membranes of the respiratory chain called cardiolipin, has been found to be involved with execution of apoptosis. Cardiolipin appears to support (stabilize) the structural integrity of Complex III (cytochrome bc1), Complex IV (cytochrome c oxidase) and Complex V (ATP synthase). Cardiolipin consists of four polyunsaturated linoleic acid chains (omega 6) that are subject to peroxidation by reactive oxygen species (ROS). This leads to the release of cytochrome c from the inner mitochondrial membrane to the intermembrane space and eventually into the cytoplasm, where it is recognized to initiate apoptosis. Research suggests that oxidative stress can cause premature cell death by this mechanism.
Mitochondrial DNA

Unlike other organelles in the cell, the mitochondria contain DNA, which is inherited mainly from the mother. Damage to the mitochondrial DNA (mtDNA) can lead to loss of expression of mitochondrial polypeptides, subsequent decrease in electron transport and increased generation of reactive oxygen species, loss of mitochondrial membrane potential, and release of signals for cell death (apoptosis). mtDNA damage represents an important target for intervention and as a biomarker for many diseases. Mitochondrial DNA contains 37 genes, all of which are essential for normal mitochondrial function. Thirteen of these genes provide instructions for making enzymes involved in oxidative phosphorylation. The remaining genes provide instructions for making transfer RNA and ribosomal RNA for proteins synthesis. It is interesting to note that nuclear DNA (nDNA) wraps around histones, which help shield it from the damaging effect of free radicals, while mDNA lacks the structural protection of histones and is in close proximity to the electron transport chain making it susceptible to free radical damage. mtDNA is prone to non-inherited (somatic) mutations and inherited mutations. mtDNA damage by oxidative stress can lead to lethal injury through the loss of electron transport, mitochondrial membrane potential and ATP generation. Somatic mutations have been reported in some forms of cancer, including breast, colon, stomach, liver, and kidney, as well as leukemia and lymphoma. The major reason for mitochondrial disease appears to be reactive oxygen species (ROS).
Symptoms of Mitochondrial Disease

Signs and symptoms are usually dependent upon what organ systems are involved and can vary from mild to severe. Onset of disease is at any age. The most effected tissues are post-mitotic (terminally differentiated) tissues. The brain, muscles, nerves, retinas and kidney are all post-mitotic tissues making then more susceptible to mitochondrial disease. Their susceptibility is based on the fact that they have a high demand for energy and their diseased cells cannot be replaced.
<table>
<thead>
<tr>
<th>ORGAN SYSTEM</th>
<th>POSSIBLE SIGNS, SYMPTOMS, AND DISEASE$^{1,2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscles</td>
<td>Hypotonia, weakness, cramping, muscle pain, ptosis,</td>
</tr>
<tr>
<td>Brain</td>
<td>Developmental delay, mental retardation, autism, dementia, seizures, neuropsychiatric disturbances, atypical cerebral palsy, atypical migraines, stroke, and stroke-like events</td>
</tr>
<tr>
<td>Nerves</td>
<td>Neuropathic pain and weakness (which may be intermittent), acute and chronic inflammatory demyelinating polyneuropathy, absent DTR’s, neuropathic gastrointestinal problems (GERD, constipation, bowel pseudo-obstruction, paresis), fainting, absent or excessive sweating, dysautonomia (aberrant temperature regulation)</td>
</tr>
<tr>
<td>Kidneys</td>
<td>Proximal renal tubular dysfunction (Fanconi syndrome), may result in loss of protein, magnesium, phosphorous, calcium, and other electrolytes</td>
</tr>
<tr>
<td>Heart</td>
<td>Cardiac conduction defects (heart blocks), cardiomyopathy</td>
</tr>
<tr>
<td>Liver</td>
<td>Hypoglycemia, gluconeogenic defects, non-alcoholic liver failure</td>
</tr>
<tr>
<td>Eyes</td>
<td>Optic neuropathy, ophthalmoplegia, acquired strabismus and retinitis pigmentosa</td>
</tr>
<tr>
<td>Ears</td>
<td>Sensory-neural hearing loss, aminoglycoside sensitivity</td>
</tr>
</tbody>
</table>
| Pancreas and other glands | Diabetes and exocrine pancreatic failure  
|                    | Parathyroid failure (low serum calcium)  
|                    | Hypothyroidism                                                                                               |
| Systemic           | Failure to gain weight, short stature, fatigue, respiratory problems including intermittent air hunger            |

**THINK MITOCHONDRIAL DISEASE WHEN THREE OR MORE ORGAN SYSTEMS ARE INVOLVED**

**Causes of Mitochondrial Disease**

1. Inherited (genetic) – nDNA, mtDNA or a combination  
2. Non-inherited (somatic)/Acquired – reactive oxygen species, certain medication, toxic substances and the aging process
Acquired Conditions in Which Mitochondrial Dysfunction Has Been Implicated\(^3,6\)

1. Diabetes
2. Alzheimer’s disease
3. Cancer, including hepatitis C virus-associated hepatocarcinogenesis
4. Parkinson’s disease
5. Bipolar disorder
6. Schizophrenia
7. Aging and senescence (biological aging)
8. Anxiety disorders
9. Nonalcoholic steatohepatitis
10. Cardiovascular disease including atherosclerosis
11. Sarcopenia
12. Exercise intolerance
13. Fatigue, including chronic fatigue, fibromyalgia, and myofascial pain
14. Multiple Sclerosis
15. Autism

Disorders Sometimes Associated with Mitochondrial Dysfunction\(^6\)

Environmental

1. Vitamin deficiencies
2. Carbon monoxide poisoning
3. Lead, cyanide, and mercury poisoning
4. AZT toxicity (HIV/AIDS medication)
5. Aminoglycoside (antibiotics) – ototoxicity and nephrotoxicity
6. Amytal (barbiturate) poisoning

Autoimmune

1. Multiple sclerosis
2. SLE
3. Rheumatoid Arthritis
4. Thyrotoxicosis
5. Primary biliary cirrhosis
6. Guillain-Barre syndrome
7. Procainamide (antiarrhythmic drug) has been implicated as etiological factor in lupus
### Medication-induced Mitochondrial Damage and Disease

<table>
<thead>
<tr>
<th>DRUG CLASS</th>
<th>DRUGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholism medication</td>
<td>Disulfiram</td>
</tr>
<tr>
<td>Analgesic/anti-inflammatory</td>
<td>Aspirin, acetaminophen, diclofenac, fenoprofen, indomethacin, naproxen</td>
</tr>
<tr>
<td>Anesthetics</td>
<td>Bupivacaine, lidocaine, propofol</td>
</tr>
<tr>
<td>Angina medications</td>
<td>Perhexiline, amiodarone, diethylaminoethoxyhexesterol</td>
</tr>
<tr>
<td>Anti-arrhythmic</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Tetracycline, antimycin A</td>
</tr>
<tr>
<td>Anti-depressants</td>
<td>Amitriptyline, amoxapine, citalopram, fluoxetine</td>
</tr>
<tr>
<td>Anti-psychotics</td>
<td>Chlorpromazine, fluphenazine, haloperidol, risperidone, quetiapine, clozapine, olanzapine</td>
</tr>
<tr>
<td>Anxiety medications</td>
<td>Alprazolam, diazepam</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Amobarbital, aprobarbital, butabarbital, butalbital, methylphenobarbital, pentobarbital, Phenobarbital, primidone, propofol, secobarbital, thiobarbital</td>
</tr>
<tr>
<td>Cholesterol medications</td>
<td>Statins, bileacid-cholestryramine</td>
</tr>
<tr>
<td>Chemotherapy medications</td>
<td>Mitomycin C, proflormycin, adriamycin</td>
</tr>
<tr>
<td>Dementia</td>
<td>Tacrine, galantamine</td>
</tr>
<tr>
<td>Diabetes medication</td>
<td>Metformin, troglitazone, rosiglitazone, buformin</td>
</tr>
<tr>
<td>HIV/AIDS medications</td>
<td>Atripla, combivir, emtriva, epivir, epzicom, hivid, retrovir, trizivir, truvada, videx, videx EC, viread, zerit, ziagen, racivir (note: these are brand names)</td>
</tr>
<tr>
<td>Epilepsy/seizure medications</td>
<td>Valproic acid</td>
</tr>
<tr>
<td>Mood stabilizers</td>
<td>Lithium</td>
</tr>
<tr>
<td>Parkinson's disease</td>
<td>Tolcapone</td>
</tr>
</tbody>
</table>
Hereditary (or possible hereditary) Types of Mitochondrial Diseases

- Alpers disease
- Barth syndrome
- Beta-oxidation Defects
- Carnitine-Acyl-Carnitine Deficiency
- Carnitine Deficiency
- Creatine Deficiency Syndromes
- Co-Enzyme Q10 Deficiency
- Complex I Deficiency
- Complex II Deficiency
- Complex III Deficiency
- Complex IV Deficiency
- COX Deficiency (cytochrome c oxidase)
- CPEO (chronic progressive external ophthalmoplegia syndrome)
- CPT I Deficiency (carnitine palmitoyl transferase)
- CPT II Deficiency
- KKS (Kearns-Sayre Syndrome)
- Lactic Acidosis
- Leigh Disease/Syndrome
- LHON (Leber Hereditary Optic Neuropathy)
- LIC (Lethal Infantile Cardiomyopathy)
- Luft Disease
- MAD (multiple acyl-CoA dehydrogenase deficiency)
- MACD (medium-chain acyl-CoA dehydrogenase deficiency)
- MELAS (mitochondrial encephalomyopathy lactic acid and stroke-like episodes)
- MERRF (myoclonic epilepsy and ragged-red fiber disease)
- MIRAS (mitochondrial recessive ataxia syndrome)
- Mitochondrial DNA Depletion
- Mitochondrial Encephalopathy
- Mitochondrial Myopathy
- MINGE (myoneurogastointestinal disorder and encephalopathy)
- NARP (neuropathy, ataxia, and retinitis pigmentosa)
- Pearson Syndrome
- Pyruvate Carboxylase Deficiency
Diagnosing Mitochondrial Dysfunction and Cytopathy

Typically, diagnosing mitochondrial dysfunction and mitochondrial cytopathy is difficult due to the considerable variation in clinical presentation. There are no pathognomonic signs or symptoms. Functional medicine practitioners are well suited to suspect and/or recognize mitochondrial dysfunction and disease based on their overall training and, in particular, of energy production and oxidative stress.

The key to suspecting mitochondrial dysfunction or disease has its basis in obtaining a comprehensive history, including nutritional and environmental, and comprehensive examination (including body composition analysis). (As you read earlier in this lesson, there are a considerable amount of medications that can induce mitochondrial damage. A comprehensive history should disclose all previous and present medications.)

Think mitochondrial disease:

1. When three or more organ systems are involved
2. The clinical presentation is atypical
3. Abnormal or slow response to treatment
4. Recurrent setbacks

Assessment for mitochondrial disease requires a combination of clinical observations and laboratory testing.

Diagnostic Testing

Allopathically speaking, there are no acceptable criteria for establishing a diagnosis of mitochondrial cytopathy. The Thor-Byrne-ier scale has been used since the 1990’s as a scoring method based on major and minor criteria indicators.
Metabolic Screening and primary evaluation of suspected mitochondrial disease⁹,¹⁰

- **CBC**: Anemia, thrombocytopenia, and neutropenia are seen in a variety of metabolic diseases. Primary and secondary disorders of folate and vitamin B₁₂ metabolism should be considered.

- **Hemoglobin A₁c**: is a result of the non-enzymatic attachment of a hexose molecule to the N-terminal amino acid of the hemoglobin molecule. The attachment occurs continually over the lifespan of the red blood cell and is dependent on blood glucose concentration and the duration of exposure. Hyperglycemia is a known cause of oxidative stress.

- **Pyruvate and lactate** (blood): Pyruvic acid is used to evaluate for possible disorders of mitochondrial metabolism. Pyruvic acid is of value when measured with lactate. The pyruvate to lactate ratio is elevated in several mitochondrial disorders.

  Reference range for pyruvate: 0.7 – 1.4 mg/dl (0.08 – 0.16 mmol/L)
  Reference range for lactate: 0.6 – 2.3 mmol/L (after age 2)

  Elevated L/P ratio (>20) can indicate respiratory chain disorders, Krebs cycle disorders and pyruvate carboxylase deficiency. Depressed L/P ratio (<10) with high levels of pyruvate can indicate inherited disorder of pyruvate metabolism. Defects of the PDC (pyruvate dehydrogenase complex) can also cause a low ratio.

- **Plasma ammonia**: 50 percent of patients with plasma ammonia values over 200 umol/L had inborn errors of metabolism.⁸ Plasma ammonia (NH₃) can be leveled in severe liver disease, Reye’s syndrome, renal failure and inherited defects in the urea cycle.

  Reference range: 12-70 umol/L (20-120mcg/dL)

- **Creatine Kinase**: The major source of CK is in the cytoplasm of skeletal muscles, myocardium and brain. Creatine is also located in the inner mitochondrial membrane. Elevation of CK and CK isoenzymes are seen in many diseases.

- **Quantitative urine organic acid test**: Abnormal amounts of lactate, pyruvate, citric acid cycle intermediates, or 3-methylglutaconic acid suggest mitochondrial dysfunction.

- **Plasma amino acids**: There are many genetic errors affecting amino acid metabolism. Defects of either transport or catalytic activity of enzymes involved in amino acid metabolism result in the accumulation or excessive loss of one or more amino acids in biological fluids.

- **Ketones** (Beta-Hydroxybutyrate) measured in blood or urine: Significant if absent during fasting, which is suggestive of inborn errors of metabolism. There are three sources of ketone bodies: beta-hydroxybutyrate (78%), acetoacetate (20%) and acetone (2%).

- **Plasma acylcarnitine**: Identify disorders of fatty acid beta-oxidation.

From a functional medicine perspective the most sensitive and specific test to assess for mitochondrial dysfunctions is the urinary organic acid test.
Other diagnostic tests will depend on the patient’s specific conditions and needs. Additional tests, if deemed necessary would include: genetic testing, muscle biopsy, MRI, ophthalmic exam, EKG, audiogram, and thyroid blood tests.

The following are three examples of functional medicine tests for mitochondrial dysfunction and oxidative stress. Recall that oxidative stress can lead to mitochondrial dysfunction and disease.
Antioxidant Insufficiency

Blood Serum Concentrations

- Vitamin A
- β-Carotene
- Vitamin E
- Coenzyme Q10

Cellular Oxidative Damage Markers

- Membrane Fatty Acid Damage
  - Lipid Peroxide
- DNA Damage
  - 80HdG
- Vitamin C Depletion Marker
  - p-Hydroxyphenylacetate

Mitochondrial Dysfunction

- Blocked by Fat-soluble Antioxidants
- Blocked by water-soluble antioxidants
  - Glutathione
  - Selenium
  - Vitamin C: Polyphenols

Immune Disorders

- Aging
- Osteoporosis
- Heart Disease

Oxidative Stress

- Oxygen Radicals
- Superoxide
- Hydroxyl radical
- Peroxy nitrate
- ADMA (Asymmetric dimethylarginine)

Nitric Oxide

Other diagnostic tests that are of value include:

1. Adrenal Stress Index
2. RBC nutrient and toxic element analysis
3. Comprehensive Stool Analysis
4. Amino Acid
5. RBC essential fatty acid
6. Genomic testing

**INDICATIONS FOR THEIR IMPLEMENTATION IS USUALLY BASED ON THE BIOCHEMICAL UNIQUENESS OF THE PATIENT AND PATIENT HISTORY**
Treatment of Mitochondrial Dysfunction/Disease

To date, there is no single treatment for mitochondrial disease. Given the fact that the major reason for mitochondrial dysfunctions is reactive oxygen species and the concomitant damage, it is reasonable to consider nutritional therapy, in particular antioxidants. You must always consider the biochemical uniqueness of the patient when prescribing therapy.

Key Treatment Strategies

- Eliminate sources of exogenous free radicals (e.g. cigarette smoke, alcohol, food additives and environmental toxins)
- Stress Reduction (e.g. Tai Chi, breathing exercise, Qi Gong, meditation and counseling)
- Diet therapy – avoid fasting and eat more often (e.g. five meals per day) Eat organic foods if possible.
- Avoid physiological stress (e.g. extreme weather conditions, fasting, stressful exercise)
- Evaluate for additional functional medicine disorders and treat as indicated. It is especially important to evaluate and treat hyperglycemia if present. Hyperglycemia increases ROS production.
- Prescribe appropriated vitamins, supplements, and cofactors as indicated by functional testing. Use the interpretive guide recommendation from the urinary organic acid test to customize nutritional treatment.

(Caution on iron supplementation: Iron can generate free radicals, which can increase oxidative stress. Always perform a blood test to assess for iron status prior to supplement on all patients regardless of dysfunction or disease.)

Review of the key nutrients for proper mitochondrial function

<table>
<thead>
<tr>
<th>Required for TCA cycle</th>
<th>Iron, sulfur, B1, B2, B3, B5, cysteine, magnesium, manganese and lipoic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Synthesis of L-carnitine requires vitamin C</td>
</tr>
<tr>
<td>Required for PDC</td>
<td>B1, B2, B3, B5, Lipoic acid</td>
</tr>
<tr>
<td>Required for ETC</td>
<td>CoQ10, B2, iron, sulfur, copper</td>
</tr>
</tbody>
</table>

Review of key enzymes and nutrients required for oxidative-phosphorylation

<table>
<thead>
<tr>
<th>Enzymes</th>
<th>Manganese superoxide dismutase, copper/zinc superoxide dismutase, glutathione peroxidase, peroxidiredoxin, thioredoxin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutrients</td>
<td>Manganese, superoxide dismutase, copper, zinc, glutathione, selenium</td>
</tr>
</tbody>
</table>
Vitamin and cofactors to consider for the treatment of mitochondrial disease\(^2,^6\)

- Coenzyme Q10 (ETC, free radical scavenger oxidative phosphorylation)
- Thiamine B1 (decarboxylation, transketolase)
- Riboflavin B2 (fatty acid oxidation, flavoproteins)
- Niacin B3 (ETC, ADP-ribosylation, cholesterol)
- Pantotenic acid B5 (CoA synthesis, lipid metabolism)
- Pyridoxine B6 (Amino acid metabolism, steroid metabolism)
- Folate (RNA/DNA, amino acids, the single carbon pool)
- Cobalamin B12 (methyl group transfer)
- Vitamin C (antioxidant, hydroxylation, synthesis of collagen, carnitine and neurotransmitters)
- Vitamin D (down-regulates cell proliferation and inflammation, up-regulates the immune system)
- Vitamin E (antioxidant, especially membrane and plasma lipoprotein protection)
- Carnitine (fatty acid transport across the mitochondrial membrane)
- Lipoic acid (Keto-acid dehydrogenase cofactor, glutathione recycling)
- Biotin (carboxylation, glucoseogenesis, fatty acid synthesis)
- Zinc picolinate (superoxide dismutase, tissue repair)
- Selenium (glutathione peroxidase, thioredoxin reductase)

**In Summary**

The atypical presentations of mitochondrial dysfunction/disease leads to a vast array of signs and symptoms that makes it difficult to establish a diagnosis. The main rule to keep in mind is: “When a common disease has features that set it apart from the pack, or involves three or more organ systems, think mitochondria”\(^6\).
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