

## Summary – Mitochondrial Toxicity Dr. Katherine Sims

**Introduction** Recognizing potentially toxic agents is important for everyone, but especially those with mitochondrial disease. Dr. Katherine Sims from Boston's Massachusetts General Hospital explains why identifying potential toxic agents from medications to environmental factors is an essential part of managing the disease. Dr. Sims has a special link to the mitochondrial disease community serving as the Chair of MitoAction's Medical Advisory Committee.

As both a pediatric neurologist and researcher, Dr. Sims notes that discussing any aspect of mitochondrial disease is a challenge because diseases associated with mitochondria were not discovered until the late 1980's and early 1990's. We are still learning about the mitochondria and how they relate to human disease. Today's discussion will focus on optimizing disease management from the patient's point of view. In addition, it is important for patients and doctors to register all observations in an organized way so that we can begin to understand how to treat symptoms while at the same time avoid aggravating the underlying mitochondrial disease

There are many reasons why certain substances may be toxic to the mitochondria. For instance, if the electron transport chain (ETC) is inhibited, patients with mitochondrial diseases may be severely affected because oxidative-phosphorylation is disrupted. Also, harmful free radicals can be formed from reactive oxygen species and disrupt mitochondrial functions. In primary mitochondrial disease we use a variety of drugs that may help with the numerous symptoms of the disease or may be needed to treat co-morbidities (other diseases or conditions that the patient may have which may or may not be related to the mitochondrial disease). Some of these drugs may actually be harmful to the mitochondria themselves so we need to always balance the medical need with potential harmful side effects to the mitochondria.

**Mechanisms of Toxicity** Anything can be toxic if it inhibits the electron transport chain. Oxidative-phosphorylation disease is affected by any disruption in the ETC. What appears to be a necessity, ie, oxygen, can in itself be damaging. There are many ways that free radicals can be formed and these free oxygen radicals can be toxins if not handled appropriately. Free radical damage can cause increased energy needs with a cascading effect of further damage. The key is to attempt to balance the treatment needs with the side effects of the treatment.

The pathobiology of mitochondrial toxicity is not well understood. Toxicity may be exacerbated by other problems and treatments, so always be watchful and observant of all symptoms. Mitochondrial function needs to be supported, not impeded. The types of toxic agents include: pharmaceutical products (medications), anesthesia, surgery, environmental agents, diet, stress related endogenous agents, and mitochondrial

cofactors. A table of the various agents discussed here will be included as an attachment to this summary.

**Pharmaceutical products** Establishing mitochondrial toxicity is not an FDA requirement for drug approval, so there is no real way of knowing which agents are truly toxic. Nor is there an absolute contraindication against any particular agent, BUT there are those that we know should be avoided. Some agents have been shown (either through research studies or anecdotal evidence) to have direct toxicity to the mitochondria. These agents directly inhibit or disrupt the ETC, protein production, DNA transcription, etc. Agents that cause indirect toxicity are those that increase free radicals, decrease the production of endogenous antioxidants, or deplete nutrients that are needed.

Anticonvulsants Specifically, most anticonvulsants are well tolerated except valproate (Depakote). This drug can inhibit many mitochondrial functions. It is known to play an important role in carnitine utilization by the mitochondria and has been shown to particularly inhibit complex IV. It can also cause liver dysfunction. This does not mean it should never be used, but caution needs to be taken regarding liver function. If used, plasma carnitine levels need to be monitored and maintained carefully.?

Psychotropics Certain psychotropic drugs have been shown to be potentially toxic. Certain antidepressants such as Prozac, Elavil, and Cipramil can cause autonomic dysfunction. Other psychotropic drugs such as antipsychotics, barbituates, and anti-anxiety medications also inhibit various mitochondrial functions.

Cholesterol Medications Cholesterol lowering drugs (especially statins) have been shown to reduce endogenous CoEnzyme Q10 which is produced in the same metabolic pathway as cholesterol, so in this way these drugs can be said to be potentially toxic. Other cholesterol medications such as cholestyramine that bind to bile acids can disrupt the ETC

Analgesics and Anti-inflammatories Pain relievers such as acetaminophen (sp?), Indocin, naproxen, Aspirin and the NSAIDS (non-steroidal anti-inflammatory drugs), all increase oxidative stress, and therefore could potentially be toxic. Aspirin is contraindicated for children, but it can be harmful for patients with mitochondrial disease as well because of the potential for Reye Syndrome (acute liver failure). However, patients should keep in mind that it is important to avoid fevers in Mito patients. Therefore, the benefits of some of these medications as fever-reducers may outweigh their potential side-effects.

Antibiotics Antibiotics, (specifically tetracycline, minocycline, chloramphenicol, and aminoglycosides), can be harmful to the mitochondria because they inhibit mtDNA translation and protein synthesis. They can cause hearing loss as well as cardiac and renal toxicity.

**Steroids** Steroids may reduce transmembrane mitochondrial potential. However, steroids used in local delivery (such as inhaled steroids that only target lungs or injected steroids that target specific locations) are generally recognized as safe. Other drugs which are used less by the Mito population but have potential toxicity include amiodarone which is used as an anti-arrhythmic (rapid heart rate), antivirals like interferon, antiretrovirals (used for HIV/AIDS), and cancer drugs. Metformin, used for diabetes, is also considered toxic to mitochondria. Beta blockers could have possible toxicity due to increased oxidative stress, and may also contribute to feelings of fatigue. Diuretics are usually not harmful to the mitochondria themselves, but they may cause fluid imbalances, which can be potentially difficult for Mito patients

In all cases of the drugs mentioned here, the objective is to balance the need for use of these drugs with the damage they may cause.

**Anesthesia** In mitochondrial disease, there seems to be an increased sensitivity to anesthesia, especially the volatile drugs (ie, those inhaled). For this reason, there should be very close management of any anesthesia used even when IV (for example, propofol). Often, a decreased dosage is adequate. The smallest dose over the shortest period of time should be the goal of all anesthesia for mitochondrial disease patients. Patients with mitochondrial diseases should make sure that their anesthesiologist is informed and knowledgeable about their condition so that they use the upmost caution and safety while using anesthetics.]

**Surgery** Surgery is a huge metabolic stressor for those with mitochondrial disease and must be managed very carefully. Acid-base balance status must be monitored closely because acidosis can be particularly harmful for those with mitochondrial disease. Fasting should be avoided as much as possible. For example, do not schedule surgery for the end of the day when the patient has been fasting since the night before. Instead, be sure the Mito patient's surgery is the first of the day. Also be sure a Dextrose IV with electrolytes (if indicated) is put in early before surgery to maintain adequate fluid and electrolyte balance and to deter catabolism.

**Environmental Agents** Tobacco smoke (primary or secondary inhalation) and alcohol are both potentially toxic for patients with mitochondrial diseases. Other environmental factors may not be as controllable, but patients should be aware of their toxicity. These include rotenone (chemical used in insecticides and pesticides) and fat-soluble chemicals with benzene rings such as hair dye and paint fumes.

**Diet** The Ketogenic diet (used sometimes for those with seizure disorders) can be a stressor for those with mitochondrial disease. This diet increases cellular utilization of the beta oxidation pathway. This diet can be helpful for those with a pyruvate dehydrogenase disorder. Avoid diet deficiencies of any kind. It is important for patients to have a balanced diet including pyridoxine (B6), ferredoxin, iron, copper, riboflavin (B2), zinc, and selenium as well as other vitamins and/or minerals. Avoid fasting! A state of hyperglycemia can also be toxic and lead to problems similar to those of diabetics. Hyperglycemia can cause increased superoxide production (oxygen free radical) in the endothelium, which can lead to a vascular endotheliopathy (vessel wall

dysfunction and metabolic derangement). Some foods like peas, beans, legumes, and almonds have substances in them that can be toxic to the mitochondria.

**Endogenous Stress Related Hormones** Stress hormones such as adrenalin, catecholamines, and testosterone can be harmful for Mito patients. Stress of any kind should be avoided as much as possible so as not to compromise mitochondrial function.

**Co Factors** CoEnzyme Q10 can become an oxygen radical and cause trouble if the dosage is too high. The most common dosage is 10 - 20 mg/kg/day. There is a small study that used 60 mg/kg/day for a short term and it was tolerated well. Usually, however, above 20mg (of ubiquinone) is NOT tolerated well; For Ubiquinol the dosage is usually under 10 mg/kg/day (range of 6-8mg/kg/day). In high doses riboflavin, L-carnitine and L-arginine can be harmful, so they also need careful monitoring.

**Conclusion** There are some substances which are clearly toxic to the mitochondria and we have some idea how they work; these should be avoided. There are many more that are only suspected of being toxic; of these we should take care in their use, monitor any effects carefully and make good observations and records of any effects. When using new treatments, we should add one new medication at a time in order to monitor the effect (both positive and negative). All of this information should be included in the developing registry.

In general, there are some things which we do know for both children and adults, and we can use this knowledge to guide our recommendations. Still, there is a lot more that we don't know. Many of our recommendations are based on anecdotal evidence or very small studies. For example, though there is a long list of psychotropic drugs which "may be toxic", many of them probably are not contraindicated but rather should be used with frequent observations and records about how they affect the patient, and changes should occur one drug at a time. Again, a key point to keep in mind is that the life-saving benefit of some of these drugs outweighs their possible side-effects. It is imperative to isolate the offending agent because we need to be able to use some medical treatments, and we have some control over which agent/drug we use.

It appears that some effects from a mitochondrial toxin are reversible. Deficiencies need to be identified and dealt with. The problem often is finding out just what the particular vulnerabilities are for each particular patient. Certain medications may trigger toxic reactions, but the challenge is to figure out whether these symptoms are from ongoing mitochondrial damage, natural history of the disease, or the use of new drugs.

When toxic agents can't be avoided, improving overall mitochondrial function is possible by including key elements such as CoenzymeQ10, L-carnitine, B Vitamins, antioxidants (Vitamin C, Vitamin E, Alpha-Lipoic Acid, selenium ), and others. Minimizing stress and illness is also important!