Treatment of Mitochondrial Cytopathies

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Mitochondrial cytopathies are clinically and biochemically heterogeneous disorders affecting energy production. Because of the heterogeneity of disorders, the large number of biochemical and genetic defects, and wide spectrum of clinical course, there are limited data about proven effective therapies. Overall, treatments for mitochondrial cytopathies are intended to augment energy production and reduce the production of free radicals and other toxic metabolites that further limit the generation of cellular energy. 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 specific medications aimed at a particular symptom.

The clinical benefits for cofactor and vitamin therapy can include improved strength and endurance, although patients report a variety of benefits. Coenzyme Q10 can be given at dosages ranging from 5 to15 mg/kg/d in two to three divided doses. Levocarnitine is advocated at dosages of 30 mg/kg/d in two to three divided doses. Riboflavin (vitamin B2) at dosages of 100 to 400 mg/d has been shown to be beneficial in some patients. The use of creatine has been shown to improve strength in patients with mitochondrial myopathies, although its long-term use should be consider with caution Because of the potential for renal toxicity. The use of antioxidants .(<-lipoic acid, vitamin E, vitamin C, ®-carotene, selenium, vitamin K and N-acetylcysteine) to lessen free radical damage to the mitochondrial membrane has a scientific rationale, but again proof of effectiveness does not exist.

The other B vitamins have been used, with reports of effectiveness in small numbers of patients, likely those with a rare but specific vitamin-responsive syndrome. Treatment with Dichloroacetate associate with some degree of improvement in several studies. Its primary site of action is the pyruvate dehydrogenase (PDH) complex, which it stimulates by altering its phosphorylation state and stability.

In critical situations, when lactic acid and ammonia levels are extremely elevated, the use of continuous infusion insulin (0.05-0.1 U/kg/h), using very frequent glucose monitoring, may help reverse catabolism, decrease circulating toxic free fatty acids, and lower lactic acid and ammonia levels. The use of sodium benzoate, phenylbutyrate, and sodium phenylacetate can bind conjugate ammonia in the case of severe hyperammonemia. Enteral use of lactulose also can help lower ammonia levels.

Dietary management for mitochondrial disorders remains largely trial and error. A low-carbohydrate, high fat diet is helpful for some patients with complex I deficiency but others do better on a high-carbohydrate, low-fat diet. Patients

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with PDH deficiency should be treated with a ketogenic diet.

The use of frequent, small-volume feedings is generally well tolerated. For children with primary and secondary gluconeogenetic defects, avoidance of fasting is recommended.

Keywords: Children; Mitochondrial cytopathies; treatment