

Environmental Modifiers of Mitochondrial Disorders

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Mitochondrial encephalomyopathies comprise a group of clinically and genetically heterogeneous disorders characterized by mitochondrial respiratory chain dysfunction in multiple organs [1]. With the estimated prevalence of 10 to 15 cases per 100,000 individuals [2], these disorders can manifest at any age as a result of mutation(s) in either nuclear or mitochondrial genome.

The influence of epigenetic environmental factors on the course of heritable mitochondrial disorders has long been known to the researchers in the field. For example, in a study of a large group of affected and unaffected carriers of the three primary mitochondrial DNA point mutations (m.3460G>A, m.11778G>A, and m.14484T>C) causing Leber's Hereditary Optic Neuropathy (LHON), Kirkman et al. [3] identified that tobacco use and heavy consumption of alcohol are not only strong risk factors for loss of vision in LHON but also are responsible for the marked incomplete penetrance observed in this primarily mitochondrial disease [3]. This finding is important as it has a direct disease preventive implication for the asymptomatic carriers of LHON mutation. LHON is predominantly a male disorder as about 80% of the affected patients are male and, in many affected pedigrees, disease penetrance is much higher (50%) in males harboring the mutation than that in female (10%) carriers [4]. Currently, the cause of this gender difference remains unknown. However, a recent study in a LHON cybrid cell model has provided strong evidence that estrogen might have a protective role against the damaging effects of LHON mutations, and that could explain the lower penetrance of the disease observed in female mutation carriers [5].

Exposure to methanol in the presence of vitamin deficiency can also produce lactic acidosis and loss of vision pathology reminiscent of LHON presentation. In this context, for example, it was found that methanol toxicity from the consumption of home-made rum in combination with folate deficiency was the cause of blindness epidemic that occurred in the early 1990s in Cuba and affected some 50,000 individuals [6]. Formic acid, a by-product of methanol metabolism, is a well-known mitochondrial toxic metabolite that inhibits cytochrome c oxidase, the terminal enzyme of mitochondrial respiratory chain [7]. In Cuban blindness epidemic, individuals with folate deficiency were more susceptible to the formate accumulation and toxicity. Further evidence for the link between folate deficiency and increased susceptibility to methanol toxicity in humans comes from a study of cases of methanol poisoning in alcoholics. In these patients, it was found that ethanol-induced folate deficiency can potentiate visual toxicity of methanol due to impairment of the folate-dependent pathway involved in formate detoxification [8]. Experimental studies have shown that primates, in contrast to rodents, are more susceptible to methanol toxicity because of the lower levels of tetrahydrofolate and activity of 10-formyltetrahydrofolate dehydrogenase, the enzyme principally responsible for formate metabolism [9].

Certain anticancer drugs such as anthracyclines are known

to cause cardiomyocyte toxicity through mitochondrial damage and dysfunction and, therefore, patients with pre-cardiological conditions are especially at risk to chemotherapy with this group of medications [10,11].

Because mitochondrial ribosomes have bacterial origin, certain antibiotics such as amino-glycosides have an adverse effect on mitochondrial DNA translation and can cause sensorineural deafness when administered in high doses [12]. A unique, and usually homoplasmic A>G transition mutation at position 1555 of mitochondrial DNA (m.1555A>G) was first reported in 1993 to be the underlying cause of both aminoglycoside-induced and non-syndromic deafness [13]. Individuals harboring this mutation, which is located in the 12S mitochondrial ribosomal RNA gene, are particularly sensitive to this drug and are highly likely to experience a profound and permanent hearing loss upon exposure to these translational inhibitors of mitochondria even when administered at the recommended therapeutic doses [13,14].

Unlike amino glycosides that have a direct deleterious effect on mitochondrial function, Metronidazole, a bactericidal nitroimidazole with specific activity against anaerobic bacteria, has an indirect but positive impact as its administration has been reported to improve clinical presentations of two genetic mitochondrial disorders: ethylmalonic encephalopathy [15] and methylmalonic academia [16]. In ethylmalonic encephalopathy, mutation of the causal *ETHE1* gene that encodes a mitochondrial matrix sulfur dioxygenase, leads to accumulation of sulfide and subsequent inhibition of cytochrome c oxidase and short chain acyl-CoA dehydrogenase [12,15]. Treatment with Metronidazole decreases gut content of anaerobes which are the major source of sulfide production in human intestine. In methylmalonic academia, loss of activity in methylmalonyl-CoA mutase, a mitochondrial matrix enzyme encoded by *MUT* gene leads to accumulation of propionic and methylmalonic acid in the body and subsequent reduction of cytochrome c activity in liver and kidney tissues [17]. In the most common form, infants are normal at birth but develop lethargy, vomiting, dehydration, hepatomegaly, hypotonia, and encephalopathy [18]. In two patients with methylmalonic academia, treatment by metronidazole led to a substantial fall in the levels of blood propionate and urinary excretion of methylmalonate accompanied by significant clinical improvement [16].

In conclusion, given the fact that, currently, there are no cures or effective treatments for mitochondrial disorders and the fact that treatment options are severely limited and primarily supportive, understanding the environmental modifiers that can negatively or positively impact the course of the disease is crucial for the management of these devastating disorders. In this context, elucidating the role of gut bacteria, this new class of emerging disease modifiers, which has until recently received little attention, can greatly improve our current treatment strategies.

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