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Mitochondrial diseases: past, present, and future

Abstract

Mitochondria are membrane-bound organelles found in almost all eukaryotic cells. Mitochondria are in charge of mastering and organizing cellular energy production in order to sustain life. Two genomic systems are responsible for mitochondrial biogenesis: nucli-genomes and another set of mitochondrial genes (mtDNA). MtDNA encodes 13 proteins that are required for respiratory chain function. Mitochondria play a role in a variety of cellular processes, including calcium signaling, cell cycle, differentiation, and cell death. Mitochondrial shape indicates good health, and their location in the cell is essential for their function. Mitochondrial dysfunction has been linked to Alzheimer's disease, metabolic disorders, ischemic brain, heart, and neurodegenerative diseases. In this section, we exemplify the clinical implications of mitochondrial diseases in terms of acquired defects.

Keywords: mitochondrial diseases, renal cytopathies, podocytopathies, myopathies

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Introduction

Primary Mitochondrial diseases are inherited metabolic genetic disorders caused by mutations in genes encoding structural mitochondrial proteins, nuclear DNA (nDNA), or proteins involved in mitochondrial function, and mitochondrial DNA (mtDNA). Defects in oxidative phosphorylation are the most prominent consequences of these disorders.[1] Secondary mitochondrial dysfunction is linked to a number of disorders, including Alzheimer's, muscular dystrophy, Lou Gehrig's disease, diabetes, and cancer.[2,3]

Mitochondrial biogenesis necessitates the coordination of nuclear and mitochondrial encoded gene expression in order to ensure the correct assembly and function of the mitochondrial respiratory chain's large set of proteins. Mitochondria create energy by passing electrons from donors with lower redox potential to acceptors with greater redox potential via different protein complexes. Protons are pushed from the matrix outward as part of this process, creating a potential difference across the inner membrane. As protons leak back toward the matrix, the associated potential energy is converted to ATP or lost as heat. Although the majority of electrons are finally transferred to molecular oxygen, some are lost during travel. This causes a one-electron reduction of oxygen to superoxide, which is then transformed to other radical species. Although the produced reactive oxygen species (ROS) are potentially harmful, they also induce mitochondrial uncoupling and cell signaling.[4,5]

Defects in mitochondrial DNA (mtDNA) are responsible for a number of disorders, including Leigh syndrome, MELAS (Mitochondrial Encephalomyopathy with Lactic Acidosis and Stroke-like episodes), MERF (Myoclonus Epilepsy with Ragged Red Fibres) and Leber's hereditary optic neuropathy.[6] All of these diseases caused by mtDNA mutations and are inherited through the maternal line, and their severity varies**.** A larger mutant load is associated with more severe clinical symptoms in the majority of these disorders.[7,8]

The three most prevalent neurodegenerative disorders, Parkinson's disease, Huntington's disease, and Alzheimer's disease, all have separate clinical aetiologies that include components linked to mitochondrial dysfunction. The loss of ATP, increased Ca2+ absorption, increased ROS generation, altered fission, and apoptosis can all disrupt neuronal function in terms of synaptic plasticity, energy metabolism, axonal transport, and neurotransmitter release, leading in behavioral disorders and neuronal death.[10,11]

Some mental illnesses may be related to rare aspects of mitochondrial dysfunction. Usually the prime pathological defect is characterized by genetic impairment of one or more of the biochemical aspects of mitochondrial metabolism resulting in psychiatric symptoms such as depression, psychosis, bipolar disorder (BD) and personality change.[12,13]

The number and size of mitochondria in drug-tolerant cancer cells has been found to rise, reflecting an increase in mitochondrial biogenesis.[14] The transfer of mitochondria from immune cells to cancer cells through nanotubes has been shown to metabolically boost cancer cells while depleting immune cells. The nanotube construction machinery was inhibited, which lowered mitochondrial transport and prevented immune cell depletion.[15] The outcome is negative when faulty mitochondria are found in high-energy-consumption cells like muscles, the cerebrum, or nerves.[16,17]

Drug side effects, infections, and other environmental variables can all cause mitochondrial malfunction. Oxalate is mitochondria hazardous, and it is known to cause mitochondrial malfunction when it enters cells.[18]

Mitochondrial DNA is replicated during mitochondrial fission, and heteroplasmy occurs when random mutations accumulate during divisions. Mitochondrial DNA mutations are more common than nuclear DNA mutations because not all Mitochondria have DNA repair mechanisms like nuclei. When the number of damaged mitochondria surpasses the threshold expression, mitochondrial illness becomes clinically evident.[19]

Nuclear DNA controls the bulk of mitochondrial activity and biogenesis. Human mitochondrial DNA codes for 13 respiratory chain proteins, but nuclear DNA codes for the majority of the estimated 1,500 proteins and components present in mitochondria. Anemia, dementia, hypertension, cancer, retinopathy, seizures, and neurodevelopmental problems have all been associated to mitochondrial gene defects in nuclear-encoded mitochondrial genes.[20] The significance of mitochondria in insulin resistance in type 2 diabetes offspring was investigated in a research.[21]

Epidemiology: Following the advancement of whole genome sequencing, the first harmful mutation in mitochondrial DNA was detected in 1988, and 250 pathogenic mtDNA mutations have been

discovered in the subsequent three decades. Pathogenic nuclear or mtDNA mutations affect one in every 4300 persons (23 per 100,000) who have disease or is at risk of getting disease in the future.[22]

Clinical presentations

Mitochondrial cytopathies can damage almost every organ and cause a variety of clinical symptom.[23] Exercise intolerance, hypotonia, and, in extreme cases, myopathy are all common symptoms of skeletal muscle damage. Exercise intolerance is a frequent problem that might be mistaken for psychogenic tiredness, chronic fatigue syndrome, or rheumatic fibromyalgia.[24]

Peripheral neurological illnesses such as sensory and/or motor polyneuropathy, neurogenic bladder, and sensorineural deafness are examples of mitochondrial cytopathies. Cardiac illnesses such as myocardiopathy, arrhythmias, and heart block are also common. Diabetes, hypoparathyroidism, hypothyroidism, hyporeninemic hypoaldosteronism, and growth hormone insufficiency are other endocrine problems. Gastrointestinal symptoms can be caused by liver failure, intestinal dysmotility (such as vomiting, diarrhea, and pseudoobstruction), or malabsorption. Sideroblastic anemia, neutropenia, and thrombocytopenia are hematological symptoms. Many individuals are affected by progressive external ophthalmoplegia, ophthalmoparesis, pigmentary retinal degeneration, ptosis, cataract, optic atrophy, and blindness. Finally, various skin and hair lesions have been described.[25–27]

Diagnosis and Management

It was demonstrated that the quantity of mitochondria in muscles is relatively larger than many other organs; muscle biopsy is commonly utilized to identify mitochondrial disorders. To confirm these disorders, several procedures are employed, including Southern blot to detect significant deletions or duplications, Polymerase chain reaction and Sequencing, and specific mutation testing.[28] Many therapy strategies have been tested, with mixed results; pyruvate has been suggested as one among them.[29] In a number of mitochondrial malfunctioning models, N-acetyl cysteine has been found to be beneficial.[30] Hippotherapy should be evaluated in addition to the established physical, speech, occupational, and respiratory treatments.[31]

Diet and lifestyle: Extreme malnutrition, such as starvation, anorexia, and illness-related cachexia, trigger secondary mitochondrial dysfunction.[32] It has been established that adjusting the amount and quality of calories ingested on a daily basis improves mitochondrial function.[33]

Ketogenic diet: A ketogenic diet (KD) is a high-fat, low-carbohydrate diet that promotes -oxidation and ketone body synthesis. There are three types of KDs. In every meal, the standard KD adopts a fat-to-carbohydrate-to-protein-ratio (e.g. 4:1 or 3:1). MCT-KD is a kind of medium-chain triglyceride (MCT) that may be used to deliver fat. The ketogenic diet has been shown to enhance mitochondrial function. The ketogenic diet is the standard of care for pyruvate dehydrogenase deficiency, but it is contraindicated in patients with known fatty acid oxidation disorders and pyruvate carboxylase deficiency.[34,35]

Physical exercise: Patients with mitochondrial dysfunction have a poor maximum oxygen uptake, resulting in exercise intolerance even during normal activities.[36] Exercise tolerance and biochemical enzyme activity can be improved by gradually increasing the quantity of daily exercise.[37] According to the previous studies, regular muscular exercise has been shown to improve mitochondrial function and reduce the burden of mitochondrial dysfunction.[38]

Immunizations: Vaccination is suggested to guard against potentially deadly infectious infections, even if there is no relationship between immunization and a flare-up of mitochondrial disease symptoms.[39]

Pharmacologic approach

Coenzyme Q10: Coenzyme Q (CoQ) is an essential endogenously synthesized molecule that links different metabolic pathways to mitochondrial energy production thanks to its location in the mitochondrial inner membrane and its redox capacity, which also provide it with the capability to work as an antioxidant. Coenzyme Q (CoQ) levels in a 70-year-old are half of those found in a 20-year-old young human. The use of CoQ has been shown to be effective in the treatment of mitochondrial dysfunction.[40]

Riboflavin

Riboflavin is a water-soluble B vitamin (B2) that serves as a flavoprotein precursor. It is a key building block in complex I and II and a cofactor in several other key enzymatic reactions involving fatty acid oxidation and the Krebs cycle. Riboflavin has been shown to alleviate symptoms and slow the progression of multiple acyl CoA dehydrogenase deficiency (MADD), which is caused by mutations in the electron transport flavoprotein dehydrogenase (ETFDH) gene. Several non-randomized studies have shown riboflavin to be efficacious in treating mitochondrial diseases, specifically complex I and/or complex II disease.[41]

L- Creatine

Phosphocreatine is formed when creatine, a chemical found in cells, interacts with phosphate in the mitochondria. It provides a high-energy phosphate source that is released during anaerobic metabolism. It also serves as an ATP intracellular buffer and an energy shuttle for the transport of high-energy phosphates from mitochondrial synthesis sites to cytoplasmic consumption sites. Creatine is present in the greatest amounts in tissues with high energy needs, such as skeletal muscle and the brain. Direct testing has revealed a decrease in phosphocreatine in skeletal muscle in individuals with mitochondrial myopathies. Brain creatine levels may be reduced in patients with mitochondrial encephalomyopathie.[42,43]

L-Arginine

L-Arginine is a semi-essential amino acid that contributes to growth, urea detoxification, and creatine synthesis. L-arginine is known to produce nitric oxide, a neurotransmitter with vasodilatory properties. Intravenous (IV) infusion of L-arginine was proved to reduce the severity of stroke-like symptoms by improving microcirculation dynamics, as well as improveed tissue injury secondary to ischemia in encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) due to mitochondria dysfunction.[44,45]

L-Carnitine

L-Carnitine is essential for the β-oxidation of fatty acids in mitochondria and the esterification of free fatty acids that would otherwise be sequestered by CoA. As acylcarnitine esters, carnitine transports long-chain fatty acids through the mitochondrial inner membrane. These esters are oxidized to acetyl CoA, which enters the Krebs cycle and produces ATP in the process. Lower amounts of free carnitine in plasma are connected to respiratory chain abnormalities, resulting in a partial decrease in β-oxidation.[46] The administration of L-carnitine to individuals with mitochondrial dysfunction may minimize the buildup of hazardous acyl compounds.[47] It was reported

that L-carnitine treatment benefited a rare instance of podocytopathy linked with type 2 diabetes that suggested acquired mitochondrial cytopathy.[48]

Folinic acid

Folinic acid is a reduced version of folic acid, a water-soluble B vitamin (B9) that functions as a cofactor in a variety of metabolic processes. It's most typically found as leucovorin, which comes in two isomers: D (inactive) and L (active). According to a few case reports, mitochondrial illness can cause secondary cerebral folate insufficiency, which is characterised by low folate levels in the cerebrospinal fluid (CSF), notably in the C1 donor, 5-MTHF.[49]

Medication contraindications

Several medications, including aminoglycosides, erythromycin antibiotics, statins, and valproic acid, should be avoided in patients with mitochondrial dysfunction.[50]

Interventional procedures

Fever, dehydration, fasting, hunger, surgery, and anesthesia make patients with mitochondrial dysfunction more sensitive to physiologic stresses. As a result of a stressful incident, an abnormal metabolic intolerance may emerge. Maintaining appropriate hydration, giving patients with adequate anabolic substrate, and avoiding drugs that may induce mitochondrial toxicity are all general considerations to avoid the emergence of acute metabolic derangement in mitochondrial dysfunction.[51]

Anesthesia

Volatile anesthetics are more dangerous to patients with mitochondrial dysfunction, thus lower dosages should be used. Sevoflurane is better tolerated than isoflurane or halothane in individuals with mitochondrial dysfunction.[51] Propofol is harmful, and patients with mitochondrial dysfunction are at a higher risk of developing propofol infusion syndrome.[52]

Surgery: The risk of surgery is associated with preoperative and postoperative fasting, which can be avoided by ensuring adequate hydration with dextrose-containing IV fluids. Lactated Ringer's solution is not recommended. To avoid uncontrolled catabolism, intravenous fluids and nutrition are maintained until the patient is discharged.[53]

Organ transplantation: In certain situations, patients with electron transport chain deficit may benefit from a liver transplant. It was recorded that, there are favourable benefits with heart transplantation's in cardiomyopathy caused by mitochondrial dysfunction. Patients with hepatocerebral syndrome caused by deoxyguanosine kinase mutations are now being investigated for liver transplantation, which has resulted in long-term survival in some cases with little neurologic damage.[54]

Assistive devices: cochlear implants: Sensorineural hearing loss is a common symptom of mitochondrial dysfunction, which is exacerbated by specific mtDNA mutations. The A3243G mutation in MELAS and the mtDNA deletions seen in Kearns-Sayre syndrome are linked to spontaneous hearing loss. The effectiveness of therapy is determined by the severity of the hearing loss. The results range from simply detecting environmental sounds to understanding language in a quiet environment.[55] Cardiac conduction defects may be associated with mitochondrial dysfunction.[56] After their success in other cardiac conduction disorders, automatic internal cardiac defibrillators (AICDs) may be considered for those patients.[57]

Emerging therapies: Peroxisome proliferator-activated receptors (PPARs) signalling controls gene expression in a variety of metabolic pathways, including gluconeogenesis, fatty acid metabolism, and cell survival.[58] A PPAR pan-agonist (Bezafibrate), which is approved by the FDA for diabetes, was recently reported to improve myopathy in experimental models by improving mitochondrial biogenesis and tissue ATP levels.[59] Resveratrol has been studied for its potential role in the treatment of several diseases; it is thought to be beneficial in mitochondrial dysfunction, but data is still lacking and more research is needed to confirm its efficacy.[60]

Gene therapy prior to conception

Mitochondrial Replacement Therapy (MRT) is an in-vitro fertilization that involves transferring the nuclear DNA from the affected person to another person's healthy egg cell while leaving the defective mitochondrial DNA behind.[61] Many ethical concerns have been raised in such cases regarding biological motherhood, as the child receives genes and gene regulatory molecules from two different women. The use of genetic engineering in a trial to break the hereditary cycle of mitochondrial diseases by producing babies devoid of mitochondrial dysfunction is still being debated on ethical grounds.[62]

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Conflicts of interest

The authors declare having no conflict of interest.

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