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Mitochondrial Diseases in Childhood what we need to know?

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Mitochondria are critical energy-producing organelles that synthesize adenine triphosphate via an oxidative phosphorylation mechanism (ATP). Typically, each nucleated cell includes hundreds of mitochondria, with cells that require more energy having a higher number to satisfy their energy requirements [1].

Additionally, mitochondria are involved in a variety of other cellular processes, including calcium homeostasis, steroid and heme production, and cell cycle regulation via retrograde signaling. Mitochondria constantly fuse and fission, forming a dynamic intracellular network in conjunction with organelle division. These processes occur continuously regardless of whether the cell is actively dividing or is post-mitotic, such as neurons and muscle. While much of the genetic maintenance of mitochondrial structure and function is understood, the products of many of the N1500 genes remain unknown [2].

The phrase "mitochondrial disease" refers to a collection of conditions caused by mitochondrial malfunction, mitochondrial respiratory chain (MRC) abnormalities, and related aberrant oxidative phosphorylation [3].

Any organ can have mitochondrial malfunction; however, it is more common in energy-intensive systems as the brain, heart, liver, and skeletal muscle system [4]. At the genetic level, mitochondrial illness has a dual genesis, as it can occur because of mitochondrial or nuclear DNA abnormalities [5].

These factors contribute to the extreme genotypic and phenotypic diversity of mitochondrial illnesses, which results in the involvement of several organs, each to a varying degree and with varying severity of symptoms, as well as varying clinical outcomes [6].

Mutations in the genes encoding mitochondrial proteins in the mitochondrial DNA (mtDNA) or nuclear DNA (nDNA) cause primary mitochondrial diseases, resulting in faulty mitochondria. Mitochondrial malfunction manifests itself in a variety of cellular abnormalities. These include abnormal calcium homeostasis, increased generation of reactive oxygen species (ROS), and dysregulated apoptosis. Numerous organs, particularly those with a high energy requirement, such as the nervous system, skeletal and cardiac muscles, kidneys, liver, and endocrine system, are unable to function properly because the mitochondria are unable to generate adequate energy. As a result, mitochondrial illnesses are clinically diverse, frequently affecting many organs and manifesting in a variety of ways. Due to its high energy requirements, the neurological system is particularly vulnerable. Neurological symptoms of mitochondrial disorders include cognitive impairment, epilepsy, peripheral nephropathy, sensorineural hearing loss, optic atrophy, encephalopathy, dementia, migraine, stroke-like episodes, ataxia, spasticity, chorea, and dementia [7].

Due to the high energy requirements associated with efficient and sophisticated functioning, the brain is particularly susceptible to illness consequences. The intricate balance of excitation and inhibition communication between neurons and glia is required for both higher brain functions such as cognition, movement, vision, and hearing and lower brain functions such as heart rate and breathing. Because

mitochondrial illnesses are so tightly linked to brain and muscle function, the early idea of multisystem problems was dubbed "mitochondrial encephalomyopathy" [8] Seizures are a symptom of cognitive impairment. Patients with mitochondrial disease are at an increased risk of seizures, which typically begin in childhood and are intractable with medication [9].

Blood, urine, and spinal fluid biochemical tests

Specific mitochondrial biomarkers in the blood, urine, and spinal fluid are recommended by most diagnostic algorithms. Lactate and pyruvate measurements in plasma and cerebrospinal fluid (CSF), amino acid measurements in plasma, urine, and CSF, plasma acylcarnitines measurements, and urine organic acids measurements are among the most performed tests in this setting.

Lactate accumulation occurs when the flux through glycolysis exceeds the mitochondrial utilization of pyruvate. Its utility is frequently hampered by inaccuracies in sample collection and management. Venous plasma lactate levels can be spuriously elevated if a tourniquet is used during collection or if a child is struggling during sampling. Plasma lactate levels that are significantly increased (> 3 mmol/l) in a properly taken sample indicate the existence of mitochondrial dysfunction, which can be secondary to organic acidemias, other inborn metabolic abnormalities, toxins, tissue ischemia, or certain other disorders [10].

Cerebral folate insufficiency is associated with a wide variety of neurologic and metabolic problems, including mitochondrial illness, and is diagnosed by measuring 5-methyltetrahydrofolate levels in the cerebrospinal fluid. Cerebral folate insufficiency was first discovered in patients with Kearns–Sayre syndrome (KSS) who suffered from mitochondrial illness [11].

Other tissues may need to be tested first when diagnosing a patient with a suspected mitochondrial dysfunction. Due to the high mtDNA concentration in renal epithelial cells, urine is increasingly acknowledged as a good specimen for mtDNA genome research [12].

This finding is especially relevant to the MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like events) disease and its most prevalent mutation, m.3243 A > G in MTTL1. When accessible, skeletal muscle or liver are ideal tissue sources for mtDNA genome sequencing due to their high mtDNA concentration, dependency on mitochondrial respiration, and chance of harboring a tissue-specific mtDNA variant not seen in blood [13].

Current clinical trials and treatments for mitochondrial illnesses

Numerous agents aimed at enhancing mitochondrial function or treating the effects of mitochondrial dysfunction have been tested in a small number of clinical trials. Numerous medicines are being studied for the treatment of mitochondrial disorders at the moment.The treatment of mitochondrial diseases entails the use of agents that enhance electron transfer chain function (coenzyme Q10, idebenone, riboflavin, dichloroacetate, and thiamine), energy buffering agents (creatine), antioxidants (vitamin C, vitamin E, lipoic acid, cysteine donors, and EPI-743), amino acids that restore nitric oxide production (arginine and citrulline), and cardiolipin protectors (e While there are no solutions for mitochondrial illnesses at the moment, the rising number of clinical trials assessing drugs that target various elements of mitochondrial dysfunction is optimistic and is likely to result in the development of new treatments of additional therapeutic options for these diseases in the future [14].

Prognosis

10 years is the average age of death - 74% (mortality influenced by age and underlying genotype).

Sepsis and unexpected abrupt death are the leading causes of death in juvenile children with mitochondrial disease, emphasizing the critical nature of closely monitoring these children' medical status. Additionally, enhanced surveillance and intervention planning are required for kids younger than six years of age, who are at a higher risk of death due to their undeveloped and frequently impaired immune

systems. During follow-up, further monitoring and magnetic resonance imaging of the brain are recommended to identify patients with risk signs such as multiple organ involvement [15].

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