Mitochondrial Disorders: Clinical, Pathologic and Genetic Classification

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Mitochondrial disorders are a wide spectrum and heterogeneous disorders that are first described in the early 1960s. It can be said that mitochondrial disorders are the most common Neurometabolic diseases of childhood. Thesedisordersnot only present with nonspecific symptoms, but also there is not a reliable biomarker specific for the screening of them. However increased plasma level of lactate or pyruvate can be considered an important marker of mitochondrial disease. As a general rule, the involvement of 3 or more organ symptoms without a unifying diagnosis should raise suspicion of mitochondrial disease.

Mitochondria are the main source of energy for all human tissues and contain many metabolic pathways, including the pyruvate dehydrogenase complex [PDHC], the carnitine cycle, the β-oxidation system, and the Krebs cycle. Defects in any of these pathways cause mitochondrial disorders. The reducing agents produced in the Krebs cycle and in the β-oxidation systems are transferred along the electron transport chain that in turn consists of four multimeric enzyme complexes (I to IV) plus two small electron carriers, coenzyme Q and cytochrome c. The energy produced by these reactions is used to pump protons from the mitochondrial matrix into the space between the inner and outer mitochondrial membranes.This "proton pumping" generates an electrochemical proton gradient, which is utilized by the last enzyme complex (complex V or ATP synthase) to produce ATP in a process known as oxidation/phosphorylation coupling. Electron transport chain and oxidative phosphorylation together are called "respiratory chain", or oxidative phosphorylation (OXPHOS) system. This system is controlled by both nuclear and mitochondrial DNA (nDNA and mDNA) and is the only metabolic pathway under dual control of both nuclear and mitochondrial genomes. Indeed,complexes I, III, IV, and V contain some subunits encoded by mtDNA and all subunits of complex II, most subunits of the other four complexes, as well as CoQ10 and cytochrome c are encode by nDNA.

Theterm"primarymitochondrialdisease"or"mitochondrialencephalomyopathy" refers specifically to mitochondrial dysfunction caused by genetic mutations, directly impacting the composition and function of the electron transport chain. Other Metabolic disorders that are associated with lactic acidosis are include: amino acid disorders, organic acidemias, urea cycle defects, pyruvate metabolism defects, Krebs cycle defects, mitochondrial OXPHOS disorders, disorders of liver glycogen metabolism, disorders of liver gluconeogenesis and biotidinase deficiency. Therefore, when mitochondrial dysfunction is confirmed by sophisticated biochemical testing, it can be challenging to distinguish whether the cause for this dysfunction is a gene that directly impacts the electron-transport chain or is secondary to an unrelated genetic or environmental cause.

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Nowadays Primary mitochondrial disorders are genetically divided in two main categories: mitochondrial DNA disorders (mDNA) and nuclear DNA disorders (nDNA). Nuclear genes Mutations are being considered the main reason of pediatric mitochondrial disease. This finding is explained by the predominance of proteins expressed in the mitochondria that are synthesized by nDNA (about 850 genes) compared with mDNA (13 genes).Therefore, it can be said that Autosomal recessive inheritance of nuclear genes disorders is likely the most common cause of mitochondrial disorders in children. Primary abnormalities of mDNA are: point mutations, deletions, and duplications. Inheritance pattern of Point mutations are maternal, but Deletions and duplications in mDNA are commonly inherited by sporadic pattern. mDNA abnormalities cause different disorders based on clinical view and therefore are heterogeneous, but some disorders such as Leigh disease and or MELAS are seen commonly. Interestingly, with increasing the age of the patient, the genetic basis of mitochondrial disorders is more likely to be caused by mDNA rather than nDNA abnormalities, so we can conclude that Common primary mitochondrial diseases in older patients are included disorders that are caused by mDNA-deletion and point mutations (e.g., Kearns- Sayre syndrome, MELAS and Leber hereditary optic neuropathy).

A-Disorder related to MDNA defects: this group can be divided in two main subgroups: Disorders that are caused by deletions and duplications in mitochondrial DNA, and II) Disorders that are caused point mutations in mitochondrial DNA.

B-Disorders related to NDNA defects: Inheritance pattern of these disorders are Mendelian and are included: I) Mutations in genes encoding proteins of the respiratory chain, II) Defects of intergenomic signaling, and III) Mutations of genes indirectly involved in OXPHOS.

Table 1: Genetic Classification of Mitochondrial Disorders Based on MDNA and NDNA Abnormalities.

MDNA Disorders		**NDNA Disorders**	
I) Deletions and duplications	Pearson syndrome	I)Mutations in genes encoding proteins of the respiratory chain	AR-inherited Leigh Syndrome
	Kearns-sayre syndrome		CoQ10 deficiency
	Sporadic PEO		Cytochrome c oxidase deficiency
II)Point Mutations	MELAS	II)Defects of intergenomic signaling	AD and AR PEO
	MERRF		MNGIE (mitochondrial neurogastrointestinal encephalomyopathy)
	NARP and maternally inherited Leigh Syndrome		Alpers
			Barth syndrome
			MDS (Mitochondrial depletion syndrome)
	LHON		MLASA

The third group of disorders that are related to NDNA defect are including: Freidreich's ataxia, Hereditary spastic paraplegia (HSP) and X-linked ataxia and sideroblastic anemia.

Introduction of the modified Gomoritri chrome stain, revealed “ragged-red fibers” (RRF) in muscle biopsy of patients that suffer from mitochondrial and consideredthe pathological hallmark of human mitochondrialmyopathy.Based on this pathologic finding Mitochondrial syndromes can be divided in two large groups: I) those with positive RRF in muscle biopsy, I) those with negative RRF in muscle biopsy. The first group, are included following disorders: MERRF, PEO, MELAS and Pearson syndrome and the latter group are consisting of Leigh encephalopathy, NARP, MDS and LHON.

Keywords: Mitochondria; Mitochondrial encephalomyopathy; NDNA; MDNA