[Frontiers in Bioscience E4, 1706-1716, January 1, 2012]

Mitochondrial DNA related cardiomyopathies

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1. ABSTRACT

Cardiomyopathies are a heterogeneous group of diseases characterized by impaired heart muscle function. Over the last few years, interest in mitochondrial cardiomyopathies has been galvanized by a number of significant molecular biology discoveries. There is overwhelming evidence that genetic factors play a pivotal role in the pathogenesis of primary cardiomyopathies. Mitochondrial cardiomyopathy is a cardiomyopathy in which the clinical and pathological phenotype result from mitochondrial diseases due to pathogenic mutation in both mitochondrial and/or nuclear genes causing defects in the oxidative phosphorylation system (OXPHOS) in cardiac muscle. We review and provide an update of the current concepts, molecular genetics, clinical features, pathology, diagnostic modalities, and latest therapeutic options in mitochondrial cardiomyopathies specifically caused by mutations in the mitochondrial DNA (mtDNA).

2. INTRODUCTION

Primary cardiomyopathies (CM) are a significant important cause of morbidity and mortality throughout the world. Hereditary cardiomyopathies are major causes of heart failure, and a major public health problem (1). It has been reported that 5 million individuals are affected by heart failure each year, and it is the underlying or the contributing cause of death of an estimated 300,000 individuals in the United states (2). Heart failure related to genetic causes may present in adults and children. About 50% of children with mitochondrial cardiomyopathies develop heart failure which has a poor prognosis with a mortality rate of around 70% before the age of 30 years (3).

Cardiomyopathies are myocardial diseases characterized by ill-defined etiologies, often with a combination of genetic and acquired factors; by the coexistence of distinctive pathologic traits but sometimes nonspecific features; and by overlapping natural histories and functional patterns (4).

Although the causes remain largely unknown, recent investigations have recognized a significant role for genetic factors, with dominant, recessive, and X-linked modes of inheritance being possible (5). Hypertrophic cardiomyopathy is often caused by mutations in cardiac myosin genes and dilated cardiomyopathy may be associated with abnormalities of the dystrophin gene in a subgroup of patients (5). Peters T.J. *et al.* where among the first to discuss the fact that mitochondrial defects can cause cardiomyopathies when they found defective mitochondrial function as a characteristic feature of congestive cardiomyopathy (6).

During the last decade mitochondrial disorders or disorders of the mitochondrial respiratory chain have been defined as a major clinical entity (3). Historically, mitochondrial cardiomyopathy was defined as a cardiomyopathy caused by mitochondrial DNA mutations (7), but the nuclear genome encodes most proteins required for mitochondrial synthesis and function, and the mutation of a nuclear gene encoding a mitochondrial protein can also indeed cause cardiomyopathy (8). Cardiac dysfunction might be the major presenting feature, with most cases presenting as hypertrophic cardiomyopathies. Multiple studies have reported that cardiomyopathy is found in 15-40% of pediatric patients clinically diagnosed with mitochondrial disorder (3,9,10). Genetically, most of the respiratory chain complex polypeptides are encoded by the nuclear DNA gene. However, mitochondria contain their own DNA, contributing to components of the five complexes of the respiratory chain (5).

The mitochondrial genome is exclusively maternally inherited. The mode of transmission of mtDNA and of mtDNA point mutations differs from Mendelian inheritance. A mother carrying an mtDNA point mutation will pass it to all her children (males and females), but only her daughters will transmit it to their progeny (11).

The respiratory chain, embedded within the inner mitochondrial membrane, is made up of five enzyme complexes and the energy generated is used to produce ATP via oxidative phosphorylation (OXPHOS)(3). Mitochondrial respiratory chain proteins are under the genetic control of both nuclear and mitochondrial genes. Mutations within these genes and in particular mutations in human mitochondrial deoxyribonucleic acid (mtDNA) cause a large variety of multi-system disorders whose main unifying feature is the altered energy hemostasis (i.e., reduced adenosine triphosphate {ATP} production) (12) due to defects in OXPHOS . Organs such as the brain, heart, liver and skeletal muscle are markedly energy dependent and particularly vulnerable to defects of energy metabolism (3). Point mutations and deletions in the mtDNA have been found in a number of multisystem disorders associated with cardiac abnormalities. These include adult-onset hypertrophy and childhood-onset DCM. Until now the mechanism by which the mtDNA mutations cause cardiomyopathy is not entirely clear and is under intense investigation. Studies have suggested that mtDNA mutations might directly cause DCM or increase susceptibility to myocardial damage or stress (13). Little is known about the role of abnormal mitochondrial function and defects in mitochondrial DNA (mtDNA) and in causing cardiomyopathies. In the current review we conducted a systematic study and analyzed articles published in scientific biomedical journals to evaluate mtDNA defects as a common cause of primary cardiomyopathies along with the clinical features and cardiac dysfunction associated with these defects and latest reviews on diagnosis and therapeutic modalities.

3. OXIDATIVE PHOPHORYLATION (OXPHOS) AND mtDNA

Oxidative phosphorylation is a metabolic pathway that uses energy released by the oxidation of nutrients to produce adenosine triphosphate (ATP). During oxidative phosphorylation, electrons are transferred from electron donors to electron acceptors such as oxygen, in redox reactions. These redox reactions release energy, in the form of ATP. In eukaryotes, these redox reactions are carried out by a series of protein complexes (electron transport chain) within mitochondria. The energy released by electrons flowing through this electron transport chain (ETC) is used to transport protons across the inner mitochondrial membrane (chemiosmosis). This electron flow generates potential energy in the form of a pH gradient and an electrical potential across this membrane. Finally, a large enzyme called ATP synthase uses this energy to generate ATP from adenosine diphosphate (ADP) in a phosphorylation reaction (5,14). The ETC is composed of four respiratory chain complexes (CI, NADH:ubiquinone oxidoreductase), (CII, succinate:ubiquinone oxidoreductase), (CIII, ubiqunol:ferricytochrome c oxidoreductase) , (CIV, cytochrome C oxidoreductase) (15). From a genetics stand point, proteins of the ETC are predominantly coded by nuclear DNA genes. A minority of components of ETC are coded by mtDNA genes. Mammalian mtDNA is a 16.6 kb circular double strand, a heavy strand enriched with guanine and light strand is enriched with cytosine. Mt-DNA codes for 37 genes, including thirteen genes that

Table 1. Clinical and genetic data for three major studies with C3303T mutation

Study (ref)	# of patients	Age at presentation	gender	Clinical feature	died at age	C3303T mutation
Silvestri *et al* (21)	7					
		1 month	F	CMP, CHF, hypotonia	9 months	homoplasmy
		3 months	M	CHF, lactic acidosis (heart transplant)	6 months	homoplasmy
		10 weeks	M	cardiomegaly, SIDS	< 1 year	NA
		NA (MOTHER)	F	exercise intolerance, fatigue		
		50	M	mitochondrial myopahy, heart failure, stroke	54	NA
		17	M	Myocardial infarction, sudden death		NA
		30	M	Sudden death		NA
Bruno *et al* (22)	8					
	family I	6 months	M	infantile CMP (solitary heart involvement)	6 months	homoplasmic
	family II	3	M	mild HCM, no obstruction		97% in muscle
	family III	10	F	HCM, myopathy		homoplasmic
		25	F	CMP, myopathy		homoplasmic
		20	M	myopathy, exercise intolerance		homoplasmic
		27	F	myopathy, exercise intolerance		homoplasmic
	family IV					
		3 months	F	infantile HCM, myopathy, hepatomegaly	6 months	homoplasmy in heart
		NA	F	CMP, myopathy	7 months	NA
Ueki *et al* (23)	1			CMP	8 months	heteroplasmic

encode RC components and - 24 genes that encode RNA apparatus. The RNA includes 22 tRNA and 2 rRNA(16). In normal individuals, all mtDNA sequences are identical and this status is termed homoplasmy. In individuals with mitochondrial disorders, the cell contains the wild type and mutant mtDNA sequences; a status termed heteroplasmy is applied (17). The number of mitochondria, in a cell depends on the metabolic requirements of that cell type. The threshold of cells with high energy requirements may result in earlier and more rapid onset of disease than those cells with lower energy requirements (18).

4. GENETICALLY DEFINED mtDNA DEFECTS

4.1. Large scale rearrangements of mtDNA

Large-scale mtDNA rearrangements either as single deletions or rarely, duplications are always heteroplasmic. There are a variety of clinical presentations, which include the Kearns-Sayre syndrome (KSS), sporadic chronic progressive external ophthalmoplegia (CPEO), and other rare syndromes (5). KSS is probably the most characteristic syndrome with a clinical onset before the age of 20 years, external ophthalmoplagia, and pigmentary retinopathy. Single deletions in the mtDNA can be detected in the majority of the cases of KSS. Cardiomyopathy is rarely seen in this syndrome and if present, has a late onset (5).

4.2. Point mutations (PM) of mtDNA

4.2.1. PM in the $tRNA^{Leu(UUR)}$ gene

4.2.1.1. Mutation A3243G

This point mutation in the mitochondrial DNA results in the nucleotide substitution of Guanine for Adenine at nucleotide 3243 (A3243G) in the leucine tRNA gene, and is the most prevalent mtDNA mutation. The mutation is associated with 80% of patients affected with MELAS syndrome (**M**itochondrial **E**ncephalomyopathy, **L**actic **A**cidosis, and **S**troke) (19), even though at least 12 other pathogenic mtDNA gene mutations reported in the literature are associated with this syndrome (19). Clinically, MELAS syndrome is characterized by abnormal development, lactic acidosis, episodic vomiting, seizures and recurrent cerebral episodes resembling strokes and causing hemiparesis or cortical blindness (5). Between 20-38% patients with MELAS syndrome may exhibit cardiac involvement (5,19), usually presenting as hypertrophic cardiomyopathy.

In a study conducted by Anan et *al.* (9) of 17 patients with mitochondrial disease and cardiac involvement, it was found that all five patients with MELAS syndrome had the A3243G point mutation, and two of them presented with left ventricular hypertrophy on echocardiogram. The A3243G mutation may present as a part of a multisystem involvement and rarely present with the sole clinical manifestation of sever cardiomyopathy (20). Other phenotypes as CPEO, maternally inherited diabetes mellitus, and deafness, have also been described (20).

4.2.1.2. Mutation A3260G

A large pedigree with a clinical phenotype including proximal muscle weakness, exercise intolerance, increased blood lactate, both at rest and during exercise, and reduced cardiac ejection fraction was first described by Zeviani *et al.* (14). Three of the probands were found to have hypertrophic cardiomyopathy by echocardiography. Affected individuals were heteroplasmic for an A3260G mutation. Zeviani *et al.* (14) categorized this syndrome under the category "Maternally Inherited Myopathy and Cardiomyopathies".

4.2.1.3. Mutation C3303T

Table (1) summarizes the clinical and genetic data of three major studies on this mutation (21-23). This mutation in the mitochondrial $tRNA^{Leu(UUR)}$ gene was first described by Silvestri *et al* (21). Bruno *et al.* (22) later reported the same mutation in eight patients from four different families. In all families, tissues from the affected individuals appeared to be homoplasmic or near-homoplasmic for the mutant mtDNA (only the mutant genome could be detected). Finally, Ueki *et al.* (23) studied 44 patients referred to their hospital with lactic acidosis. One patient had the clinical phenotype of isolated

cardiomyopathy and tested positive for the C3303T mutation. Interestingly, an A3302G mutation, adjacent to the C3303T mutation has also been reported. In a paper discussing two case reports with this mutation (24), one of the subjects died of cardiorespiratory failure. The fact that these two genes are adjacent raises the question of whether the A3302G mutation could also cause cardiomyopathy, with a higher level of mutant mtDNA in the heart leading to a more severe phenotype (24)

4.2.2. PM in the tRNA$^{Leu(CUN)}$ gene

4.2.2.1. Mutation T12297C

The mutation was first reported in 1999 by Tessa *et al.* (25). They studied 10 children of 8 unrelated Italian families with dilated cardiomyopathy. All cases were Dystrophin negative. They identified the novel T12297C mutation in two siblings of unrelated parents with DCM and endocardial fibroelastosis. The mutation was heteroplasmic and very abundant in both patients (25). The same mutation was also described in a 36-year-old male who presented with congestive heart failure. Echocardiography suggested dilated ventricles. The ultrastructural findings showed mitochondrial proliferation, with a wide range of changes in size and shapeand cristolysis. An interesting finding was some mitochondria with peripheral mitochondrial rings of mitochondrial membranes, devoid of internal cristae. The mutation was heteroplasmic, with 88% mutant in the heart DNA (26).

Recently, one author of our group reported a family with multiple members who harbored the T12297C mutation as well as T14487C mutation, which is found in Leigh syndrome. All individuals tested were nearly homoplasmic for the T12297C mutation but no subjects had dilated cardiomyopathy (27).

4.2.3. PM in the tRNA ^{Ile} gene

4.2.3.1. Mutation A4317

This mutation was initially reported in a one-year-old old boy, who presented with general weakness, and metabolic acidosis. The child developed hypertrophic cardiomyopathy and died of heart failure on the 7th day of his presentation (28). Tanaka *et al.* (28) postulated and subsequently Tomari *et al.* (29) had enough in-vitro evidence to suggest that the A4317G mutation caused structural rearrangement of the T-arm region of the mt t-RNA^{Ile}. CCA-addition at the 3' terminus of tRNA is one of the essential steps for tRNA maturation in mitochondria. In human mitochondrial DNA, the CCA sequence of tRNA is not encoded in the tRNA genes but is post-transcriptionally synthesized by ATP (CTP): tRNA nucleotidyltransferase (CCA-adding enzyme). Importantly, it was found by Nagaike *et al.* (30) that the human mt CCA-adding enzyme requires the T-arm region of mt tRNA for efficient CCA-addition and it was based on the evidence that the pathogenic point mutation A4317G was found at a similar position in the T-loop of mt tRNA^{Ile}. Tomari et *al.* hypothesized and proved that strong inhibition of CCA-addition to the mt tRNA^{Ile} A4317G mutant is caused by structural rearrangement of the T-arm region induced by the mutation. Immature tRNAs without complete CCA sequence cannot be aminoacylated, nor protected by elongation factors, resulting in their instability in the mitochondria, and hence might lead to mitochondrial dysfunction (29).

4.2.3.2. Mutation A4269G

The first patient with this mutation was an 18 year of age, who died of cardiac failure. He initially presented at the age of 4, with short stature, multiorgan dysfunction, epilepsy, and later developed dilated cardiomyopathy. The A4269G mutation was found in the index case, and no mutation found in the 30 controls (31). Subsequently, it was found that this point mutation completely inhibits protein synthesis in mitochondria, and therefore leads to reduction of their respiratory activity (32,33). Hino *et al.* investigated the molecular mechanism by which the A4269G point mutation affects the translational activity of the mutant tRNA^{Ile}. They interestingly found that this mutation destabilizes the T-stem of the tRNA and decreases the affinity of binding of the elongation factor EF-Tu, which also happens to bind to the same T-stem of the tRNA. It was found that he weak interaction with EF-Tu affects mitochondrial translation, and it does not protect the mutant tRNA^{Ile} from degradation (32).

4.2.3.3. Mutation A4295G

This mutation was detected in a 7-month-old girl who had sudden onset of cyanotic spells and died as a result of complications of hypertrophic cardiomyopathy (5). Ultrastructural studies of tissues at autopsy showed massive proliferation of mitochondria in heart and liver but not in skeletal muscle fibers. The patient's brother was also found to have concentric left ventricular hypertrophic cardiomyopathy. The brother underwent heart transplantation due to sudden decline in cardiac function and was doing well 8 months post transplant.

4.2.3.4. Mutation A4300G

The mutation was described in a large Italian pedigree with maternally inherited cardiomyopathy (MICM). The proband and 10 other family members developed isolated hypertrophic cardiomyopathy. Unlike the other point mutations in the tRNA (Ile) gene, the heart appeared to be the only organ affected in this patient (5).

4.2.4. PM in the tRNA^{Lys} gene

4.2.4.1. Mutation A8344G

The A8344G mutation in the tRNA (Lys) gene has typically been associated with a syndrome labeled MERRF (**M**yoclonic **E**pilepsy with **R**agged **R**ed **F**ibers) that is a multisystem disorder characterized by myoclonus, which is often the first symptom, followed by generalized epilepsy, ataxia, weakness, and ragged red fibers in the muscle biopsy. Patients usually present in childhood or early adulthood. A recent review of 18 patients revealed that 22% of them developed cardiomyopathy (4/18) (34). Interestingly, this mutation is also found in other phenotypes, including Leigh's syndrome, myoclonus or myopathy with truncal lipomas, and proximal myopathy (35).

4.2.4.2. Mutation G8363A

This mutation was first reported in two unrelated families with maternally inherited hypertrophic

cardiomyopathy (36). The index case in the first family was a Hispanic boy who presented at the age of 8 years old with heart failure and cognitive regression. The patient died at 17 years old of cardiorespiratory arrest. The patient's sibling presented at the age of 4 years with weakness of pelvic girdle, mild developmental delay, and hypertrophic cardiomyopathy. The proband in the second family was a 44-year-old African American, who was healthy until the age of 35 years, when she developed progressive hearing loss. Later clinical features included slurred speech, gait difficulties, chest pain, and shortness of breath. Echocardiography was suggestive of cardiomyopathy. The proband's daughter had severe mental retardation and congenital hypertrophic cardiomyopathy (36). A comprehensive literature review by Virgilio *et al.*, studying the clinical and molecular data of G8363A mutation in six large studies, found that 4 of 41 patients with a varying level of mutational load from (4-95%) in the blood, were found to have cardiomyopathy (9.7%) (37).

4.2.5. PM in the 12S rRNA gene

4.2.5.1. Mutation in A1555G

The A1555G mutation in the 12S rRNA gene was found in a family with maternally inherited cardiomyopathy. Unlike other mtDNA mutations associated with cardiomyopathy, this mutation was associated with restrictive cardiomyopathy. The mutation was found to be heteroplasmic in several tissues from the proposita including the heart muscle (38).

4.2.6. PM in polypeptide-encoding mtDNA

4.2.6.1. Mutations encoding the ND5 subunit of the respiratory chain complex I and mutations in the mt-ATP6 gene

4.2.6.1.1 Leigh syndrome

Leigh syndrome is a progressive neurodegenerative disease, mainly affecting infants but also reported in adults. One of the main diagnostic criteria is the presence of bilaterally symmetrical hypodensities in the brainstem and/or basal ganglia (39). It constitutes one of the progressive neurodegenerative disorder associated with abnormalities of mitochondrial energy generation. 10%-20% of individuals with Leigh syndrome have either the T8993G or T8993C *mt-ATP6* mutation; and 10%-20% have mutations in other mitochondrial genes (40). Extra-neurologic manifestations might include cardiac involvement and particularly hypertrophic cardiomyopathy (41).

4.2.6.1.2. Mutation in the overlapping region of mitochondrial *ATPase* 6 AND *ATPase* 8 genes

Ware *et al.* (10), reported four unrelated infants presenting as infantile hypertrophic cardiomyopathy. Subsequently, all patients developed multisystem disease. Sequencing of the entire mitochondrial genome revealed the following novel mitochondrial mutation (T8528C). This mutation results in alteration of both ATPases 6 and 8. Position 8528 is located at the overlapping region encoding the ATPase 6 and ATPase 8 subunits. The nucleotide alteration results in the change of the initiation methionine to threonine in the ATPase 6 subunit, and as a result abrogating the start of translation. The authors concluded that the mutation results in cardiomyopathy when nearly homoplasmic (10).

4.2.6.1. 4.2.7. Point mutation in the mitochondrial *ND1* gene4.2.7.1. Mutation in G3337A

Zifa et *al.*(42) recently reported a novel G3337A mutation in human mitochondrial NADH dehydrogenase-1 gene (*ND1*) in two unrelated patients. The first patient was a newborn female requiring resuscitation at birth. She was hypotonic and had respiratory dysfunction. Cardiac findings included narrowing of the pulmonary artery, and aneurysm of the intraauricular septum, and some features suggestive of cardiomyopathy. The second patient was a 65-year old female with diabetes mellitus, who presented with chest pain and dyspnea. Her echocardiogram showed left ventricular hypertrophy. The mutation was 100% homoplasmic in both patients' blood and in mother's and grandmother's blood of patient 1. Surprisingly, patient 1's mother only complained of mild muscle hypotonia, weakness and exercise intolerance. Her maternal grandmother was totally asymptomatic at the age of 65 as well as her father. This mutation was not detected in 150 control individuals (42).

4.3. mtDNA lesions transmitted in a Mendelian manner

This group of mitochondrial disorders is associated with mtDNA abnormalities resulting from nuclear DNA (nDNA) mutations and which are inherited as Mendelian genetic traits. The nDNA mutation secondarily affects mtDNA resulting in multiple mtDNA deletions or mtDNA depletion syndrome (5,43).

4.3.1. Multiple familial mtDNA deletions

Zeviani *et al.* described an Italian family with adult-onset mitochondrial encepahalomyopathy characterized by the presence of progressive external ophthalmoplegia (PEO) and inherited as an autosomal dominant (AD) trait (44). Southern blot analysis of proband's muscle mtDNA of the probands demonstrated mitochondria harboring different mtDNA deletions. Maternal inheritance was excluded as the disorder was inherited through both paternal and maternal lineages in the subsequent generations. Interestingly, Yuzaki *et al.*, reported multiple mtDNA deletions in muscle specimens from two siblings with PEO, optic atrophy, muscle weakness and peripheral neuropathy. The siblings were born to consanguineous healthy parents (40,43). Subsequently, an autosomal recessive syndrome associated with multiple mtDNA deletions in muscle was described in six patients from two unrelated families from eastern Saudi Arabia. The patients presented with childhood-onset, autosomal recessive PEO and severe cardiomyopathy requiring cardiac transplantation (45). It has been reported that cardiac abnormalities are found in 37% of patients with AD-PEO with multiple mtDNA deletions (43).

4.3.2. Mitochondrial DNA depletion syndrome

Mitochondrial DNA depletion syndrome (MDDS) is an autosomal recessive disorder, which has been reported in skeletal muscle myopathies and hepatic failure and characterized by decreased mitochondrial DNA copy number in affected tissues (46). Thus, mitochondrial

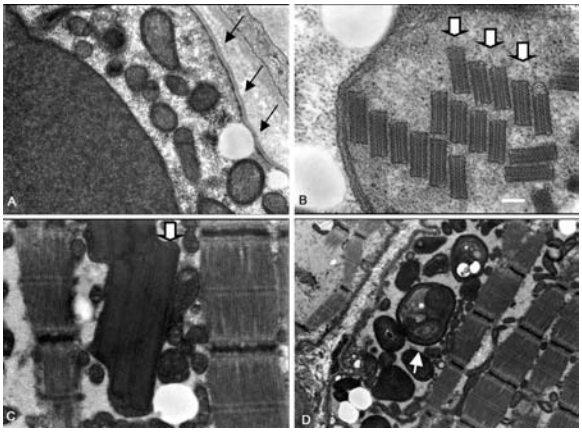

Figure 1. 1a-d: In mitochondrial myopathies the ultrastructural features may range from large, subsarcolemmal accumulations of mitochondria to myofibers containing disordered myofibrils, degenerating mitochondria and vacuoles (1a, arrows). One of the most frequent characteristic features of the abnormal mitochondria is the presence of very peculiar paracrystalline inclusions (1b-c, white thick arrows, white bar = 0.1 micrometer). The mitochondrial inclusions are sometimes described as having a "parking lot" appearance (1b). Another characteristic feature is the presence of lipid droplets together with these mitochondrial accumulations (1d). Membranous whorled mitochondria are also seen (white arrow). In the relaxed state the wide gap between two Z lines is about 2.2 micrometers and is the functional basic unit of muscle, which is also referred to as sarcomere. In isotonic, i.e. associated with a muscle shortening, contraction shortens the length of sarcomeres of a muscle fiber at the same time.

DNA depletion is tissue-specific occurring in either muscle or liver. The first case of depleted mtDNA with hypertrophic cardiomyopathy was a 5-month-old male with a history of progressive weakness, loss of muscle tone, and developmental delay from 3 months of age. Echocardiogram showed left ventricular hypertrophy without outflow obstruction. The patient died from respiratory distress and circulatory shock (46).

5. DIAGNOSTIC MODALITIES AND CONSIDERATION

5.1. Clinical assessment and laboratory findings

Clinical manifestations of mitochondrial disease can vary widely and it is essential to have a multidisciplinary approach for investigation and diagnostic purposes. A mitochondrial disease may be suspected in a patient presenting with central nervous system (CNS) symptoms together neuropathy, diabetes mellitus, cardiomyopathy or deafness. A history of other affected family members and demonstration of likely maternal or Mendelian inheritance is very helpful. However, sporadic cases can occur. Routine blood tests are not always helpful. In some cases elevated lactate and lactate/pyruvate ratio may be observed (47). Serum creatine kinase (CK) is usually normal or only mildly elevated especially in infants or children with myopathy due to mtDNA depletion (11). Some patients may present with increased levels of AST, ALT, increased urine protein, and 3-methylglutamic acid in plasma. Other significant tests include decreased levels of free carnitine with a relative increase of acyl-carnitine species (11). Microcytic anemia might be found. EMG and nerve conduction studies are variable and are not always useful, because they can be normal. Neuroradiology is frequently abnormal in patients with CNS phenotypes and has been emphasized in the medical literature. Specific finding include stroke in the parieto-occipital lesions in MELAS patients with stroke and symmetrical lesions in the basal ganglia and brain stem in patients with Leigh syndrome (11,47).

5.2. Muscle biopsy: histochemistry, enzymology, electron microscopy and genetic analysis

Skeletal muscle biopsy remains a diagnostic keystone in the workup of mitochondrial disease. It is a safe straightforward procedure which provides invaluable morphological, biochemical and molecular information. As a general rule the skeletal muscle is biopsied rather than the cardiac muscle for purpose of diagnosis. One of the core stains used to illustrate the abnormal focal accumulation of mitochondria include the Gomori trichrome stain. Fibers with excessive numbers of mitochondria show irregular purplish patches in the subsarcolemmal region and between the myofibrils, hence the term -“ragged-red fibers, RRF”-. The same region stains blue with the histochemical reaction for the mitochondrial enzyme, succinate dehydrogenase (SDH). The finding of scattered cytochrome *c* oxidase (COX)-negative fibers suggests impaired mitochondrial protein synthesis, as seen in mtDNA deletions or in mutations of tRNA genes. Laboratories frequently perform a combined staining with COX and SDH together that may highlight COX-negative fibers containing proliferations of mitochondria. RRF may not be present in young children with mitochondrial disease and may be a normal finding in the muscle of healthy older individuals (>50 years). Ultrastructural findings of muscle fibers include an increased number of mitochondria (mitochondriosis), which are often abnormally shaped and may show concentric or parallel lamellar arrangement of cristae and/or crystalline inclusions (Figure 1). Intracytoplasmic lipid droplets have been occasionally described (4). The ultrastructural existence of myocytes is important not only for the mitochondrial myopathies, but also to exclude or diagnose other myopathies that can have a similar presentation (Figure 2). In general it is thought that muscle is a much better tissue than blood to search for pathogenic mtDNA mutations, in particular mtDNA deletions. It is possible to perform specific enzymatic assays of the individual respiratory chain enzymes, even if the muscle histochemistry is normal. Obviously, skeletal muscle is easily accessible and less invasive than cardiac muscle. The finding of multiple respiratory chain enzyme deficiencies most commonly indicate defects in mtDNA affecting protein synthesis (e.g., tRNA mutations or large-scale rearrangements), or MDDS (47). A single fiber can be dissected out of thick muscle sections and used to measure levels of that specific mutation by polymerase chain reaction (PCR) (11).

Table 2. Clinical and morphological features of patients with mitochondrial cardiomyopathies (3).

	Age of onset	Sex	Syndrome or defect	Patient stauts	Gross findings	Microscopic findings	EM
1	Birth	F	Sengers syndrome	Post mortem	Hypertrophy and dilated	Marked interstitial fibrosis Hypertrophic cardiomyocytes	Proliferation of mitochondria Densely packed cristae
2	10 years	M	Large scale mit.DNA del	EMB	NA	Hypertrophic cardiomyocytes Deficiency of cox in mosaic Pattern	NA
3	Birth	M	Partial COX deficiency	Post mortem	Hypertrophic heart (60g)	Hypertrophic cardiomyocytes	Collection of giant mitochondria
4	9 Weeks	M	Alpers syndrome	Post mortem	Hypertrophic heart (200g)	Marked interstitial fibrosis deficiency of COX in mosaic pattern	Proliferation of mitochondria densely packed cristae with tubular arrangements
5	6 Month	M	COX deficiency	Post mortem	Enlarged heart	NA	Huge collections of abnormal giant mitochondria

EMB: Endomyocardial biopsy, F: Female, M: Male, NA, not available.

4.4. Myocardial morphologic findings

Mitochondrial cardiomyopathy may manifest in a hypertrophic form, with diffuse concentric hypertrophy progressing toward a dilated pattern. Histologic findings generally include myocyte hypertrophy with perinuclear vacuolation. Myofiber disarray can be observed, but not to the extent seen in familial hypertrophic cardiomyopathy. Ragged red fibers are infrequently detected in the myocardium. Variable amount of interstitial fibrosis may be seen (4). In a recent comprehensive review by Holmegren *et al.* (3), of 101 pediatric patients with mitochondrial myopathy, 17 patients were considered to have cardiomyopathy. Morphologic examination of the myocardial tissue was performed in five cases. The findings are summarized in (Table 2). The findings varied from interstitial fibrosis, hypertrophic cardiomyocytes to the finding of COX deficiency with enzyme assays.

4.5. Genetics based diagnosis

In a patient with a suspected mitochondrial disorder, it is reasonable to perform the basic mtDNA point mutation analysis in blood, before acquiring the muscle biopsy. Some genetic tests for mtDNA are widely available e.g. A3243G, A8344G, and T8993C. Patients under the age of 20 years might also be considered for muscle or blood mtDNA deletion analysis (47). As has been stated in other comprehensive reviews (47) we realize that this limited list of mtDNA point mutations and deletions would have a low yield. However, we believe that by performing an initial screening analysis of the common mutations a genetic diagnosis of mitochondrial disease would be achieved without the need for further invasive investigations. It is important not to forget to look for mutations in the nuclear encoded genes as well (47). As mentioned above thorough and full mtDNA sequencing on mtDNA extracted from muscle should be considered in patients whom the muscle biopsy show a mosaic pattern of histoenzymatic changes and/or the respiratory chain biochemistry is abnormal.

6. TREATMENT

Currently, treatment of respiratory chain disorders is empiric. Patients with confirmed mitochondrial disease benefit from a multidisciplinary clinical setting. The main aspect of management is offering them symptomatic therapy tailored for individual patient. These include management of hearing loss, visual problems, seizures and movement disorder, diabetes mellitus, respiratory, and cardiac complications. Early detection of cardiac complication is essential in patients with proven mitochondrial disease. Patients suffering from cardiac conduction defects (e.g. KSS) may benefit from pacing or insertion of an implantable cardiac defibrillator, which can be life saving. As discussed earlier, patients with MELAS as well as MERRF syndromes may develop left ventricular hypertrophy (LVH) and left ventricular failure, a cause of both mortality and morbidity in these patients. LVH should be closely monitored and treated accordingly (47). Cardiac transplantation is mostly offered to patients with isolated cardiomyopathy (i.e. those without dementia and other organ failure). Other aspects of therapy include pharmacological approaches, the so called mitochondrial cocktail. One recent study by (47) recommended coenzyme $Q_{10\ to}$ all patients with mitochondrial disease. A number of other pharmacological agents have been tried in mitochondrial disease but with limited benefit. Removal of noxious metabolites is another possible therapeutic modality. A metabolic block in the respiratory chain will result in accumulation of pyruvate as well as lactate. Bicarbonate is of transient benefit (11). Other options include dichloroacetate (DCA), which enhances the activity of pyruvate dehydrogenase, and may benefit children with MELAS and COX deficiency (11). Patients with mitochondrial encephalomyopathies may benefit from enzyme or metabolite replacement, vitamins and cofactors. For example folic acid can benefit patients with KSS. Combining L-carnitine with CoQ_{10} has also been recommended (11). L-Infusion of L-Arginine significantly improved acute stroke-like symptoms in MELAS patients (48). Gene therapy for mitochondrial disease with a number of *in vitro* experimental approaches has recently been reported but remains experimental (47). Methods for the repair of damaged mitochondrial genes or nuclear genes that encode mitochondrial proteins are under investigation (49). Lastly, a large chocrane review by Chinnery *et al.* of six randomized controlled trials concluded that two trials studying co-enzyme Q10 and two studying creatine produced conflicting outcomes, one trial using dimethylglycine showed no positive effects and one studying dichloroacetate improved some outcomes (50).

7. CONCLUSION

The incidence of heart failure is increasing worldwide with massive incidence in the Western world. In

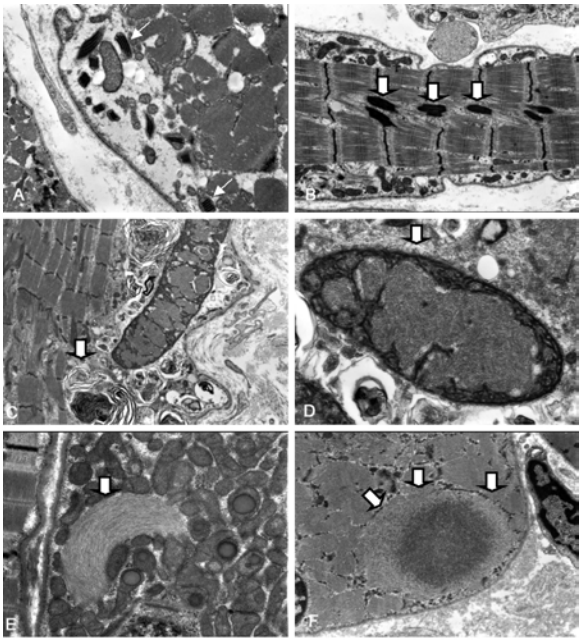

Figure 2. 2a-b: Nemalin inclusion myopathy is a congenital myopathy characterized by gross hypotonia in early infantile cases with cardiopulmonary insufficiency. The predominant feature is the presence of nemaline rods (white arrows and white thick arrows). Nemaline rods are identified within the cytoplasm and can also be demonstrated with a modified Gomori trichrome staining using histochemistry. Nemalin rods can be present as dense, irregular bodies in a random orientation just beneath the sarcolemma. On electron microscopy, they present as thickenings of the Z-lines within Type I fibers. The nemalin rods are derived from Z-band material and have also been characterized immunohistochemically with an antibody anti-alpha-actinin. At higher magnification, nemalin rods show variable rod length in the longitudinal section. Thin filaments extending from each end interdigitate with thicker filaments. 2c-e: Inclusion body myositis (IBM) contains a variety of inclusions ranging from abnormal filaments to myelin figures (membranous whorls) (2c, white thick arrow). Filaments can be identified within both the nucleus (2d) and cytoplasm (2e) of muscle fibers. 2f: In the cytoplasmic body myopathy there is a sharply-defined dense structure (white thick arrows), which characteristically shows radiation of thin filaments from the center.

particular, Canada and USA have heart failure that is also associated with obesity or excessive body-mass index. In Canada, it is estimated that there are 400,000 individuals living with congestive heart failure (CHF) (51). The average annual mortality rate for CHF is 10% per year with a 50% five-year survival rate (52). Hereditary CMP is one of the major causes of heart failure, and in recent years mitochondrial disorders have been recognized as a significant cause of cardiomyopathies. Mitochondrial defects can cause various syndromes and diseases as we have discussed, but they may also contribute to the pathogenesis of some degenerative diseases, to aging, and cancer. The complex constituents of the mitochondria are encoded by both nuclear and mitochondrial genes. A genetic defect could therefore be due to mutations in genes of either system. As the list of described mitochondrial and nuclear gene defects grows, comprehensive list in a mitochondrial gene database is invaluable for medical researchers and population geneticists. Among these comprehensive and excellent databases are the Human Mitochondrial Genome Database (mtDB) (http://www.genpat.uu.se/mtDB), which provides a complete human mitochondrial genome database (53), along with the MitoNuc, a database containing detailed information on sequenced nuclear genes coding for mitochondrial proteins in Metazoa (54).

As has been reported previously (5), we concur that mutations of mtDNA in patients with DCM are rare, and we note that most of the patients with mtDNA alterations would mostly present with hypertrophic cardiomyopathy. The frequency of mtDNA point mutation in "hot-spot" tRNA is very impressive, and up till now we can only speculate the pathogenic significance of this prevalence. The mechanisms leading to cardiac dysfunction in mitochondrial disorder remain unclear. A number of studies have attempted to explain how the dysfunctional mitochondria might cause cardiomyopathy. Some of the important regulatory functions of the mitochondria in the cells including the myocardial cells are I) calcium storage, particularly during induction of cell injury via anoxia or ischemia. Modulation of calcium storage mediates intracellular calcium, which is proven to be an important regulator of muscle contractility and of intramitochondrial dehydrogenase (e.g. NADH dehydrogenase complex, or succinic dehydrogenase complex) in heart. II) Mitochondria also serve as a potential modulator of cellular pH (55) and it has been suggested that defects in these functions directly or indirectly might impair heart muscle function. Experimental studies have been successful in developing a mouse model of abnormal mitochondrial function by knocking out the mouse gene for ANT-1. The phenotype is characterized by proliferation of mitochondria in skeletal and cardiac muscle. This results in defective OXPHOS and increased free radical production. The examination of the heart in these knockout mice reveals cardiac hypertrophy and mitochondrial proliferation (56). Even though mouse modeling is probably proving useful to understand mechanisms of mitochondrial cardiomyopathies, experimental studies on patient samples would be invaluable in helping us understanding in depth details of this disease. Developing sustainable cardiac specific cell lines and the trans-mitochondrial "*in vitro*" system (57) in order to perform researches on the biochemistry and molecular biology of mitochondrial cardiomyopathies certainly seems promising and would allow closer analysis of the mitochondrial function and a better understanding of the pathogenesis and probably address a more specific gene therapy. Understanding of mitochondrial function and regulation may have great potential to impact treatment of human inheritable and acquired diseases. Our University Research Group has been created to address the queries of different researchers at

national and international level engaged in discovering mitochondrial function abnormalities in many forms of disease. The backgrounds of our investigators and collaborators are wide-ranging and include many bio-medical and -engineering disciplines with active affiliations in different departments of the University.

8. ACKNOWLEDGEMENTS

S. Mohammed and W. Bahitham contributed equally to the preparation of this work and should be both considered as first authors. We are very grateful to Dr. L. Resch, neuropathologist, for reviewing the electron microscopy photographs. This work has been sponsored by the Saudi Cultural Bureau, Ottawa, ON, Canada. Wesam Bahitham is an MSc graduate student at the Department of Lab. Medicine and Pathology, University of Alberta, Edmonton, AB, Canada, and is sponsored by the Saudi Cultural Bureau.

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Key Words: Heart, Cardiomyopathy, mtDNA, Genetic defects, Review

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