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Cardiological manifestations of mitochondrial respiratory chain disorders

A. Berardo, O. Musumeci, A. Toscano*

Department of Neurosciences, Psychiatry and Anaesthesiology, University of Messina, Italy

Mitochondrial Respiratory Chain Disorders (MRCD) are a heterogeneous group of disorders that share the involvement of the cellular bioenergetic machinery due to molecular defects affecting the mitochondrial oxidative phosphorylation system (OXPHOS).

Clinically, they usually involve multiple tissues although they tend to mainly affect nervous system and skeletal muscle. Cardiological manifestations are frequent and include hypertrophic or dilated cardiomyopathies and heart conduction defects, being part of adult or infantile multisystemic mitochondrial disorders or, less frequently, presenting as isolated clinical condition.

The aim of this review is to update the cardiological manifestations in both adult and infantile mitochondrial disorders going briefly over mitochondrial genetics.

Cardiac involvement is a common feature associated with early and late onset forms of MRCD. In particular cases, these conditions should be considered into the diagnostic algorithm of idiopathic cardiomyopathies. Physicians strictly related with this disorders need to be aware of heart complications and therefore periodical cardiological examinations should be performed in such patients. Finally, therapeutic strategies are suggested to treat cardiac disorders in MRCD

Key words: Mitochondrial cardiomyopathies, molecular diagnosis, therapy

Introduction

The mitochondria are complex organelles responsible for many essential functions of the cellular machinery. They are primarily involved in the production of energy, assembling ATP molecules that are the final product of the respiratory chain (1). However, mitochondria also have an important role in apoptosis through the activation of the caspases cascade (2, 3), thus participating to neurodegenerative processes (4,5). Other mitochondrial functions include heat production (6) and the transmission of maternal genetic traits (7, 8).

The respiratory chain is composed of five enzymatic multimeric complexes (I, II, III, IV and V), embedded in the inner mitochondrial membrane. In addition, coenzyme Q (a lipoidal quinone) and cytochrome *c* are involved in mitochondrial respiration, serving as 'electron shuttles' between the complexes (9, 10). Most of the cellular energy is produced by mitochondria making them a target for the development of bioenergetic tissues deficits. Mitochondrial respiratory chain disorders (MRCD) are caused by sporadic or inherited mutations in mitochondrial DNA (mtDNA) or nuclear DNA (nDNA).

Mitochondria are the only cellular organelles that possess their own genetic material, but their functions are crucially dependent on a wide array of proteins encoded by nuclear genes. Therefore, mitochondrial physiology and pathology are determined by both genomes (11).

Mitochondrial genetics and cardiological disorders

The human mtDNA is a 16,569-bp, double-stranded, circular molecule containing 37 genes, 24 of which participate in the translation mechanism (2 rRNA's - 22 tRNA´s). The 13 remaining genes left are responsible for the synthesis of respiratory chain subunits. Hence, among the approximately 900 genes that participate in the function of the organelle, only a few are localized in the mtDNA, whereas the remainder are in the nDNA. This explains why about 50% of adults and 80-90% of children, suspected to have a mitochondrial disease on the basis of biochemical and/or morphological features, remain genetically undiagnosed. Indeed, it is reasonable to believe that most mitochondrial diseases are caused by undiscovered nuclear genes (12-14). On the other hand, mtDNA mutations, which were studied in greater details, obey to different genetic rules than those applied to "mendelian" disorders (15). First, mtDNA is maternally inherited as sperm mitochondria's are elimi-

Address for correspondence: Antonio Toscano, UOC di Neurologia e Malattie Neuromuscolari, AOU Policlinico "G. Martino", via Consolare Valeria 1, 98125 Messina, Italy. Email: atoscano@unime.it

nated early in embryogenesis. Hence, mtDNA will only be transmitted through the maternal line. Second, there are multiple copies of mtDNA in each cell: *homoplasmy* refers to the situation in which all mtDNA copies are identical. If two or more sequence variants exist in a cell or individual, that condition is referred to as *heteroplasmy*. If deleteriously mutant (i.e, pathogenic) and normal mtDNA coexist in the same cell, the respiratory chain function will not be impaired as long as there is sufficient normal mtDNA to overcome the effects of mutant DNA. If, however, the ratio of mutant to normal mtDNA exceeds a certain critical *threshold*, then the respiratory chain function will be impaired. The threshold at which symptoms will manifest depends on the tissue involved. Skeletal muscle (especially extraocular muscles) brain, heart, retina, renal tubular cells, and auditory cells of the organ of Corti are the most common tissues affected. Third, *mitotic segregation* of the multiple existing copies of mtDNA explains why the level of mutant mtDNA can change during life (16); this may depend on the stage of embryonic development in which the original mutation occurs.

Point mutations vs large rearrangements

As a general rule, mtDNA can harbour two different types of genetic variants, point mutations or large-scale rearrangements, which can involve deletions, duplications, or both together. Point mutations are commonly maternally inherited and they may differ from non pathogenic polymorphisms since a single change of a nucleotide base (e.g. A to G in position 3243 commonly for MELAS) (17) produces subsequently modifications in the corresponding product leading to defects in protein conformation. Several mutations in tRNA's genes (*MTT*) have been described in patients with heart dysfunction as isolated condition or in association with other organs involvement, like 3243A > G, 3260A > G, 3303C > T in the tRNALeu $^{(UUR)}$ gene (*MTTL1*); 4269A > G, 4295A > G, 4300A > G, 4317A > G, 4320C > T in the tRNAIle gene (*MMTI*); 8348A > G in the tRNALys gene (*MTTK*), 9997T > C in the tRNAGly gene (*MTTG*), 12297T > C in the tRNA Leu$^{(CUN)}$(*MTTL2*) and 15923A > G in the tRNAThr gene (*MTTT*).

The acronimus MIMYCA (Maternally Inherited Myopathy Myopathy And Cardiomyopathy) has been used in some conditions with predominant involvement of skeletal and cardiac muscles usually associated to the mutations 3260 A > G or 3303C > T in the tRNALeu $^{(UUR)}$ gene (*MTTL1*).

Few pathogenic variants of *cytochrome b* gene (*MTCYB*) have been described as causing a cardiomyopathy (see www.mitomap.org).

Large-scale rearrangements also include partial deletions or duplications of mtDNA (18). They differ from point mutations because they span hundreds or thousands of nucleotide bases (i.e. 4977 base pair are abrogated in the most frequently found "common deletion"). These types of mutations are usually sporadic; neither inherited nor transmitted to the offspring and they may produce Chronic External Ophthalmoplegia (CPEO), Kearns-Sayre syndrome or Pearson syndrome.

They originate during maternal oogenesis or at early stages of embryo development (19). Cardiac involvement is a rare manifestation of large-scale rearrangements as a component of multisystemic syndromes rather than presenting as isolated condition.

Nuclear genes and their regulation

As we mentioned, mtDNA produces only 13 components of the respiratory chain, meaning that most of them are codified by nuclear genes, synthesized in the cytosol and transported into the organelles. Mutations of nuclear genes segregate following mendelian rules, so that mitochondrial diseases can be inherited as a dominant, recessive or X-linked traits. The nuclear genes are classified as: 1) genes involved in the maintenance of mtDNA (*POLG1*, *ANT1*, *PEO1, TK2*) (20-24) and producing multiple deletions or depletion of the mtDNA; 2) genes encoding for subunits of the respiratory chain complexes (*NDUFS2, NDUFV2*) (25,26); 3) genes regulating the complexes assembly (*SURF1*, *SCO1*, *SCO2*, *COX10, COX15*) (27,28). Mutations in some of these genes have been reported in cardiomyopathies, mainly in infants.

ANT1 may cause Sengers' syndrome (OMIM no. 103220) characterized by hypertrophic cardiomyopathy, congenital cataract and, more variably, lactic acidemia (29). Also, in mice, it produces exercise intolerance, myopathy with "Ragged Red Fibers" (RRF) and hypertrophic cardiomyopathy with an evolution to a congestive heart failure (30).

Mutations in *SCO2* may cause a neonatal cardioencephalo-myopathy with a severe cytochrome c oxidase deficiency.

TAZ G4.5 gene, which codifies for a putative acyltransferase, involved in phospholipid biosynthesis, causes Barth syndrome, characterized by dilated or hypertrophic cardiomyopathy, endocardial fibroelastosis or left ventricular noncompaction (LVNC) (31). Others genes like *FXN* gene (Frataxin) in Friedreich ataxia may be associated with cardiac involvement.

Cardiological considerations in MRCD

The heart is one of the most frequently affected organs in MRCD's (35, 36). Cardiac involvement of multisystem mitochondrial disorders either manifests as impulse generation or impulse conduction disturbances.

or as primary myocardial impairment (hypertrophic or dilated cardiomyopathy). Frequent electrocardiographic abnormalities are atrial fibrillation, atrioventricular (AV) block, Wolff-Parkinson-White (WPW) syndrome, bundle branch blocks, QT prolongation, or ST and T-wave anomalies (37).

In addition, in 2007, we reported evidence of a cardiovascular autonomic impairment in a cohort of patients with different mitochondrial disorders (38).

On the other hand, when a mitochondrial condition affects selectively the heart, hypertrophic cardiomyopathy (HCM) or dilated mitochondrial cardiomyopathy may be clinically indistinguishable from other genetic determined cardiomyopathies and the onset usually begins in the neonatal period (39).

Cardiac abnormalities are often present in mitochondrial syndromes; different patterns of heart involvement are described herein and summarized in Table 1.

Classical mitochondrial syndromes

Kearns-Sayre syndrome (KSS)

This syndrome is characterized by the following triad 1) onset before the age of 20, 2) pigmentary retinopathy, and 3) ophthalmoparesis (40). Other features are usually present including cardiac conduction defects, cerebellar ataxia, dementia, elevated CSF proteins (> 100 mg/dl), deafness, and low stature. KSS is due to sporadic, single large-scale deletions of mtDNA, ranging from 1.3 to 8.8 kb (90% of the cases) in size, or, rarely, to mtDNA duplications (41). Calcifications at basal ganglia and thalamus or cortical or cerebellar atrophy can be seen by neuroimaging studies (42).

KSS is typically associated with cardiac conduction defects with abnormalities on electrocardiogram such as PR-interval prolongation, preceding 2nd or 3rd degree AV block, His-Ventricular (H-V) interval prolongation due to distal disease, dilated cardiomyopathy or Stokes-Adams syncope (43). Pacemaker implantation is usually indicated in these patients despite ventricular arrhythmias have been described such as "Torsade de pointes" (44), raising the question about which type of device is indicated. In addition, patients with KSS with ventricular conduction defects also have an accelerated and unpredictable rate of progression to complete AV block; sudden death occurs in 20% of the cases (45). For these reasons, no standard recommendations are available whether a preventive pacemaker implantation should be performed before any evidence of electro-cardiologic abnormalities. Some authors argue that implantation of defibrillators that simultaneously have pacing modes may be the most effective strategy in those patients. As a general rule, all patients with KSS should undergo extensive and periodical cardiologic examination to determine the presence of conduction abnormalities and the appropriate device to be implanted.

Chronic Progressive External Ophthalmoplegia (CPEO)

CPEO is characterized by a slowly progressive paresis of the extra ocular muscles, almost always associated with bilateral ptosis. There is often a severe proximal and oropharyngeal muscle weakness. Associations with low stature, deafness, diabetes mellitus and depression have also been variably described. Age at onset usually ranges in the third or fourth decade of life (46). When muscle weakness and exercise intolerance appear, they rarely are debilitating. Sporadic single deletion at 4977 bp (namely "common deletion") is the most common cause of sporadic CPEO (47), although *MTT's* and nuclear gene mutations have also been described, respectively in maternal and mendelian (adCPEO, arCPEO) variants (48). In CPEO cardiac manifestations are less severe and frequent than in KSS and manifested as partial conduction block or isolated ventricular extrasystolia. Periodic ECG should be performed in these patients (49).

Pearson syndrome

This infantile disorder is characterized by refractory sideroblastic anaemia and exocrine pancreatic dysfunction (50). These infants present refractory, transfusion-dependent, macrocytic anemia, neutropenia, and thrombocytopenia. Most of these patients die precociously and those who survive may develop, years later, a Kearns-Sayre syndrome. Pearson syndrome is usually due to heteroplasmic mtDNA deletions with a heteroplasmy rate of up to 90% in blood (51). Cardiac involvement is not frequently found although left ventricular dilatation and heart failure have sporadically been described (52).

Myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS)

The key features of this mitochondrial disorder are: 1) Stroke-like episodes before age 40 with cortical lesions, usually in the posterior regions, 2) Dementia and/or seizures, 3) Proximal muscle weakness with RRF on muscle biopsy (53). These symptoms can be variably combined with diabetes mellitus, low stature, deafness, cataracts and cardiomyopathy. Frequently, brain strokes can be preceded by migraine, fever or seizures and hemiparesis, hemianopsia or cortical blindness. Brain injuries can be seen as cortical lesions that do not conform to vascular territories, usually on parieto-occipital regions (54). Point mutations are frequently found, especially *MTTL1* 3243A > G mutation (80% of the cases) (55). Conversely, there are at least 12 other distinct pathogenic mtDNA gene mutations associated with the MELAS phenotype. These include mutations at position 3271 and 3291 in the

Table 1. Clinical features of the main mitochondrial syndromes.

	General Features	Cardiac involvement	Common mutations
Kearns-Sayre syndrome	*Ophthalmoplegia, Retinitis Pigmentosa, onset < 21 years *Cerebellar ataxia, dementia *Calcifications at basal ganglia and thalamus; cortical or cerebellar atrophy	*PR interval prolongation preceding 2nd or 3rd degree AV block *His-ventricular (H-V) interval prolongation due to distal disease *WPW syndrome *Dilated cardiomyopathy, Stokes-Adams syncope	*mtDNA deletions, rearrangements or exceptionally duplications *Common Deletion, 1.3 to 8.8 kb (90% of the cases)
CPEO	*Ophthalmoplegia, ptosis *Proximal muscle weakness and dysphagia	*PR interval prolongation preceding 2nd or 3rd degree AV block	*mtDNA deletions, rearrangements *mtDNA point mutations (MTTI, MTTL1) *Nuclear mutations in adCPEO and arCPEO (POLG, PEO1, ANT1,OPA1)
Pearson Syndrome	*Refractory sideroblastic, anemia and exocrine pancreatic dysfunction	*Left ventricular dilatation and heart failure	* mtDNA deletions with a heteroplasmy rate of up to 90% in blood
MELAS	*Stroke-like episodes before age 40 with cortical lesions usually in posterior regions *Dementia and/or seizures *Proximal muscle limb weakness with RRF	*Concentric, non-obstructive hypertrophic cardiomyopathy *Dilated cardiomyopathy *Sudden death *WPW syndrome in both childhood and adult patients	*MTTL1 3243A > G(80%), 3271, 3291 *MT-ND1 3308T > C, various MT-ND5 gene mutations, MT-COXIII 9957T > C *Large-scale deletions reported
MERRF	*Myoclonus, general seizures, ataxia, and RRF with symptoms usually beginning in childhood or in early adulthood	*High prevalence of left ventricular dysfunction and Wolff-Parkinson-White syndrome, an increased risk of cardiac death due to heart failure in patients with myocardial involvement	*MTTK 8344A > G, less frequent 8356T > C mutations
Leigh syndrome	*Severe subacute psychomotor delay and necrotizing symmetrical lesions in the brainstem, thalamus, cerebellum, spinal cord and optic nerves *Elevated lactate in blood and CFS	*Hypertrophic or dilated cardiomyopathy *Bradycardia	*MT-ATPase 6 8993T > G *Mutations have been described in all 14 genes coding for core subunits of: -Complex I (MT-ND1to6; NDUFS1,2,4,7,8; NDUFV1) -Complex II (SDHA, SDH) -Complex III (SURF1) -Others (CoQ10,PDH,SUCLA2)
NARP	*Sensory-motor axonal neuropathy, ataxia, seizures, pigmentary retinopathy and dementia	*Hypertrophic cardiomyopathy *Ventricular pre-exitation, peri-partum dilated cardiomyopathy	*MT-ATPase 6 8993T > G, 8993T > C *Mutations in Complex I subunits

MTTL1 gene, *MT-ND1* 3308T > C mutation, various *MT-ND5* gene mutations, *MT-COXIII* 9957T > C mutation, and large-scale deletions (56).

Cardiac involvement usually is part of the MELAS clinical spectrum (about 38% of patients), but isolated adult onset hypertrophic cardiomyopathy caused by *MT-TL1* 3243A > G mutation has been reported (57). Heart abnormalities include concentric, non-obstructive hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmias and sudden death (58, 59). Echocardiographic findings could suggest the diagnosis of mitochondrial cardiomyopathies because they may show a concentric, non-obstructive hypertrophic pattern, especially when associated with impaired left ventricle (LV) systolic function with a diffuse hypokinesis of wall motion, likely evolving to a dilated cardiomyopathy (60). On the other hand, sarcomeric genes-related cardiomyopathies might present with relative normal LV systolic function and asymmetric LV hypertrophy with increased thickness of the interventricular septum. Conduction disturbances, including

Wolff-Parkinson-White (WPW) syndrome, are present not only in infant population but also in adult MELAS patients (61). Therefore, the presence of cardiomyopathy in MELAS should be taken into account because it worsens the prognosis, especially in children, and greatly enhances the importance of a complete cardiological evaluation.

Myoclonus epilepsy and ragged red fibers (MERRF)

This clinical entity is characterized by myoclonus, general seizures, ataxia, and RRF with symptoms usually beginning in childhood or in early adulthood (62). A majority of genetically tested MERRF patients carry the mitochondrial *MTTK* 8344 A > G mutation (63). Other symptoms may include deafness, cardiomyopathy, and lipomatosis. Onset in childhood is frequently described although there have also been late-onset cases.

Wahbi et al. (64) described in MERRF heart findings similar to the ones reported in MELAS, with a high prevalence of left ventricular dysfunction and/or WPW syndrome. An increased risk of cardiac death due to heart failure in patients with myocardial involvement has also been mentioned, especially in patients with an early onset of the disease. Interestingly hypertrophic cardiomyopathy was not so frequently found (64).

Neuropathy, ataxia and pigmentary retinopathy (NARP)

Point mutations at position 8993 (8993T > G and 8993T > C) of the *MT-ATP6* gene cause a neurodegenerative disorder, NARP syndrome (Neuropathy, Ataxia and Retinitis Pigmentosa) (65). The syndrome can be implemented by sensorineural hearing loss, seizures and cognitive impairment (66). The same ATPase 6 point mutations that cause NARP syndrome may also cause maternally inherited Leigh syndrome (MILS), a sub-acute necrotizing encephalopathy that could be a final common phenotype for a number of mutations associated with impaired bioenergetic production (67). Hypertrophic cardiomyopathy, leading to heart failure, is sometimes associated with this condition (68).

Leigh syndrome

In 1951, Denis Leigh described an infant with severe sub-acute psychomotor delay and necrotizing symmetrical lesions in the brainstem, thalamus, cerebellum, spinal cord and optic nerves (69). This condition is typically seen in infancy and childhood, but adult-onset cases have also been reported (70, 71). Clinical sub-acute syndromes that begins with ataxia and nystagmus, dystonic features, optic atrophy and epilepsy should prompt MRI studies with special care to symmetrical brain lesions. Usually, lactate levels are increased in blood and CSF. Deficits of the respiratory chain (particularly of complexes I, II, IV, or V) or of the pyruvate dehydrogenase complex, are responsible of Leigh syndrome. Although several mutations in mtDNA have now been described in association with this syndrome, maternally inherited point mutations in the MT-ATP6 gene (m.8993T > G/C and m.9176T > G/C) are the most common changes (72). Several reports described cardiac abnormalities (hypertrophic or dilated cardiomyopathy) in those patients, especially in complex I deficiency (68, 73, 74).

Therapy

Treatment of mitochondrial cardiomyopathies is related to the different types of heart dysfunction including medications, pacemakers, defibrillators or ventricular assist devices (LVADs) implantation or ablation (75).

Drugs such as angiotensin-converting enzyme (ACE) inhibitors and beta-blockers have been successfully used to treat heart dysfunctions in patients with mitochondrial hypertrophic cardiomyopathy (76).

Patients with an isolated heart failure, or with a predominant cardiac involvement, may benefit from cardiac transplantation (77).

Recently, Arakawa et al., using 11C-acetate-PET, demonstrated that in MELAS patients with a cardiomyopathy, there was a rescue of the impaired TCA-cycle metabolism using the L-Arginine, so improving the myocardial oxidative metabolism (78).

Several palliative therapeutic approaches are currently available for patients with mitochondrial cardiomyopathy i. e. the use of drugs preventing a severe mitochondrial damage (likely caused by oxidative stress) and supplements protecting or restoring the OXPHOS enzymes. The patients also have to avoid environmental agents (i.e. certain types of pesticides) that could inhibit mitochondrial function.

Conclusions

Both adult and infantile onset MRCD patients can have cardiac disturbances characterized by alterations of impulse generation, impulse conduction or myocardial impairment, manifesting either as hypertrophic or dilated cardiomyopathy. In adult patients, some phenotypes tend to affect predominantly cardiac muscle and often can be indistinguishable from other genetically determined cardiomyopathies. Among the MRCD syndromes, large deletions of mtDNA often tend to be associated with conduction disturbances. On the other hand, no correlation between the type of heart defects and the clinical presentations are observed in paediatric patients. Patients with OXPHOS defects who present with cardiac manifestations have a poor outcome; physicians should be aware of those complications and they must perform a complete heart evaluation in all cases and suggest an appropriate therapeutic approach.

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