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 caspasases 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-
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 (MT-TL1); 4269A > G, 4295A > G, 4300A > G, 4317A > G, 4320C > T in the tRNAile gene (MT-TI); 8348A > G in the tRNAlys gene (MT-TK), 9997T > C in the tRNAgly gene (MT-TG), 12297T > C in the tRNA Leu(UCN) (MTTL2) and 15923A > G in the tRNAThr gene (MT-TH).

The acronymus 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 (MT-CYB) 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, PE01, TK2) (20-24) and producing multiple deletions or deletion of the mtDNA; 2) genes encoding for subunits of the respiratory chain complexes (NDUFS2, NDUFS2) (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-cardiographic 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
A. Berardo et al.

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, OPAL)* |
| **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** | *Stoke-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*  
*Severe subacute psychomotor delay and necrotizing symmetrical lesions in the brainstem, thalamus, cerebellum, spinal cord and optic nerves*  
*Elevated lactate in blood and CFS* | | *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 **MTTL1 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 hypokinesia 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
Cardiological manifestations of mitochondrial respiratory chain disorders

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.
Acknowledgments

We would like to thank all the colleagues from the Neuromuscular Center of the Department of Neurosciences, Psychiatry and Anaesthesiology of the University of Messina for their permanent work. Dr. Berardo specially would like to thank prof. C. Rodolico for his invaluable teaching lessons.

Funding/Support

The work was supported by Telethon grant n. GUP09004.

References

1. Smeitink J, van den Heuvel L, DiMauro S: The genetics and pathology of oxidative phosphorylation. Nat Rev Genet 2001; 2:342-52.
2. Niizuma K, Endo H, Chan PH. Oxidative stress and mitochondrial dysfunction as determinants of ischemic neuronal death and survival. J Neurochem 2009;109:133-8.
3. Colin J, Gaumer S, Guenal I, et al. Mitochondria, Bcl-2 family proteins and apoptosis: of worms, flies and men. Front Biosci 2009; 14:4127-37.
4. Wang X, Su B, Zheng L, et al. The role of abnormal mitochondrial dynamics in the pathogenesis of Alzheimer’s disease. J Neurochem 2009;109:153-9.
5. Pandolfo M, Pastore A. The pathogenesis of Friedreich ataxia and the structure and function of frataxin. J Neurol 2009; 256:9-17.
6. de Meis L, Arruda AP, da Costa RM, et al. Identification of a Ca2+-ATPase in brown adipose tissue mitochondria: regulation of thermogenesis by ATP and Ca2+. J Biol Chem 2006;281:16384-90.
7. Nakada K, Inoue K, Hayashi JI. Mito-mice: animal models for mitochondrial DNA-based diseases. 2001;12:459-65.
8. Birky CW Jr. The inheritance of genes in mitochondria and chloroplasts: laws, mechanisms, and models. Annu Rev Genet 2001;35:125-48.
9. Elston T, Wang H, Oster G. Energy transduction in ATP synthase. Nature 1998;391:510-3.
10. Noji H, Yoshida M. The rotary machine of the cell, ATP synthase. J Biol Chem 2001;276:1665-8.
11. DiMauro S, Schon E. Mechanisms of disease. Mitochondrial Respiratory-Chain Diseases. N Engl J Med 2003;348:2656-68.
12. Suomalainen A, Kaukonen J. Diseases caused by Nuclear Genes Associated with Mitochondrial Disorders. N Engl J Med 2006;355:254-62.
13. Filosto M, Mancuso M, Nishigaki Y, et al. Clinical and genetic heterogeneity in progressive external ophthalmoplegia due to mutations in polymerase Y. Arch Neurol 2003;60:1279-84.
14. Hudson G, Deschauer M, Taylor RW, et al. POLG1, C10ORF2, and ANT1 mutations are uncommon in sporadic progressive external ophthalmoplegia with multiple mitochondrial DNA deletions. Neurology 2006;66:1439-41.
15. Shoubridge EA. Nuclear gene defects in respiratory chain disorders. Semin Neurol 2001;21:261-7.
16. Shoubridge EA. Nuclear genetic defects of oxidative phosphorylation. Hum Mol Genet 2001;10:2277-84.
17. Zeviani M: The expanding spectrum of nuclear gene mutations in mitochondrial disorders. Semin Cell Dev Biol 2001;12: 407-16.
18. Scacco S, Petruzella V, Bertini E, et al. Mutations in structural genes of complex I associated with neurological diseases. Ital J Biochem. 2006;55:254-62.
19. Scacco S, Pettazzella V, Scacco S, et al. Pathogenetic mechanisms in hereditary disorders of complex I of the respiratory chain in neurological diseases. Biochim Biophys Acta 2009;1787:502-17.
20. Monnot S, Chabrol B, Cano A, et al. Cytochrome c oxidase-deficient Leigh syndrome with homozygous mutation in SURF1 gene. Arch Pediatr. 2005;12:568-71.
21. Scaglia F, Towbin JA, Craigen WJ, et al. Clinical spectrum, morbidity, and mortality in 113 pediatric patients with mitochondrial disease. Pediatr Neurol 2010;42:227-30.
22. Noji H, Yoshida M. The rotary machine of the cell, ATP synthase. J Biol Chem 2001;276:1665-8.
23. Scaglia F, Towbin JA, Craigen WJ, et al. Clinical spectrum, morbidity, and mortality in 113 pediatric patients with mitochondrial disease. Pediatr Neurol 2010;42:227-30.
24. Loefsen J, Elpeleg O, Smeitink J, et al. Mitochondrial DNA-based diseases. 2001;12:459-65.
25. Filosto M, Mancuso M, Nishigaki Y, et al. Clinical and genetic heterogeneity in progressive external ophthalmoplegia due to mutations in polymerase Y. Arch Neurol 2003;60:1279-84.
26. Hudson G, Deschauer M, Taylor RW, et al. POLG1, C10ORF2, and ANT1 mutations are uncommon in sporadic progressive external ophthalmoplegia with multiple mitochondrial DNA deletions. Neurology 2006;66:1439-41.
27. Shoubridge EA. Nuclear gene defects in respiratory chain disorders. Semin Neurol 2001;21:261-7.
28. Shoubridge EA. Nuclear genetic defects of oxidative phosphorylation. Hum Mol Genet 2001;10:2277-84.
29. Zeviani M: The expanding spectrum of nuclear gene mutations in mitochondrial disorders. Semin Cell Dev Biol 2001;12: 407-16.
30. Filosto M, Mancuso M, Nishigaki Y, et al. Clinical and genetic heterogeneity in progressive external ophthalmoplegia due to mutations in polymerase Y. Arch Neurol 2003;60:1279-84.
31. Shoubridge EA. Nuclear gene defects in respiratory chain disorders. Semin Neurol 2001;21:261-7.
32. Shoubridge EA. Nuclear genetic defects of oxidative phosphorylation. Hum Mol Genet 2001;10:2277-84.
33. Zeviani M: The expanding spectrum of nuclear gene mutations in mitochondrial disorders. Semin Cell Dev Biol 2001;12: 407-16.
34. Filosto M, Mancuso M, Nishigaki Y, et al. Clinical and genetic heterogeneity in progressive external ophthalmoplegia due to mutations in polymerase Y. Arch Neurol 2003;60:1279-84.
35. Hudson G, Deschauer M, Taylor RW, et al. POLG1, C10ORF2, and ANT1 mutations are uncommon in sporadic progressive external ophthalmoplegia with multiple mitochondrial DNA deletions. Neurology 2006;66:1439-41.
Chronic progressive external ophthalmoplegia and Kearns-Sayre syndrome: interdisciplinary diagnosis and therapy. Ophthalmology 2008;105:550-6.

41. Zeviani M, Moraes CT, DiMauro S, et al. Deletions of mitochondrial DNA in Kearns-Sayre syndrome. Neurology 1998;51:1525-33.

42. Sacher M, Fatterpekar GM, Edelstein S, et al. MRI findings in an atypical case of Kearns-Sayre syndrome: a case report. SKS Neuroradiology 2005;47:241-4.

43. Young TJ, Shah AK, Lee MH, Hayes DL. Kearns-Sayre syndrome: a case report and review of cardiovascular complications. Pacing Clin Electrophysiol 2005;28:454-7. Review.

44. Subbiah RN, Kuchar D, Baron D. Torsades de pointes in a patient with Kearns-Sayre syndrome: a fortunate finding. Pacing Clin Electrophysiol 2007;30:137-9.

45. Charles R, Holt S, Kay JM, Epstein EJ, Rees JR. Myocardial ultrastructure and the development of atrioventricular block in Kearns-Sayre Syndrome. Circulation 1981;63:214-9.

46. Berardo A, Coku J, Kurt B, et al. A novel mutation in the tRNAIle gene (MTTI) affecting the variable loop in a patient with chronic progressive external ophthalmoplegia (CPEO).Neurogenetics 2010;20:204-6.

47. López-Gallardo E, López-Pérez MJ, Montoya J, et al. CPEO and KSS differ in the percentage and location of the mtDNA deletion. Mitochondrion. 2009;9:314-7.

48. Van Goethem G, Martin JJ, Van Broeckhoven C. Progressive external ophthalmoplegia and multiple mitochondrial DNA deletions. Acta Neurol Belg 2002;102:39-42. Review

49. Jiménez-Caballero PE, Serviá M, Cabeza CI, Marsal-Alonso C, Alvarez-Tejerina A, et al. Rev Neurol 2006;43:724-8.

50. Finsterer J. Hematological manifestations of primary mitochondrial disorders. Acta Haematol 2007;118:88-98.

51. Knorr I, Metzler M, Niemeyer CM, et al. Hematologic features and clinical course of an infant with Pearson syndrome caused by a novel deletion of mitochondrial DNA. J Pediatr Hemat Oncol 2003;25:948-51.

52. Krauch G, Wilichowski E, Schmidt KG, et al. Pearson-marrow-neuropathy syndrome with worsening cardiac function caused by pleiotropic rearrangement of mitochondrial DNA. Am J Med Genet 2002;110:57-61.

53. Sproule DM, Kaufmann P. Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes: basic concepts, clinical phenotype, and therapeutic management of MELAS syndrome. Ann NY Acad Sci 2008;1142:133-58.

54. Kolb SJ, Costello F, Lee AG, et al. Distinguishing ischemic stroke from the stroke-like lesions of MELAS using apparent diffusion coefficient mapping. J.Neurol Sci 2003;216:11-5.

55. Goto Y, Nonaka I, Horiai S. A mutation in the tRNA Leu (UUR) gene associated with the MELAS subgroup of mitochondrial encephalomyopathies. Nature 1990;348:651-3.

56. Finsterer J, Genetic, pathogenetic, and phenotypic implications of the mitochondrial A3243G tRNA Leu (UUR) mutation. Acta Neurol Scand 2007;116:1-14. Review.

57. Hsu PC, Chu CS, Lin TH, et al. Adult-onset hypertrophic cardiomyopathy manifested as initial major presentation of mitochondrial disease with A-to-G 3243 tRNA Leu (UUR) point mutation. Int J Cardiol 2008;129:441-3.

58. Vilarinho L, Santorelli FM, Rosas MJ, et al. The mitochondrial A3243G mutation presenting as severe cardiomyopathy. J Med Genet 1997;34:607-9.

59. Finsterer J. MELAS in the heart. Int J Cardiol 2009;137: 65-6.

60. Anan R, Nakagawa M, Miyata M, et al. Cardiac involvement in mitochondrial diseases. A study on 17 patients with documented mitochondrial DNA defects. Circulation 1995; 91:955-61.

61. Sproule DM, Kaufmann P, Engelstad K, et al. Wolff-Parkinson-White syndrome in patients with MELAS. Arch Neurol 2007;64:1625-7.

62. Wiedemann FR, Bartels C, Kirches E, et al. Unusual presentations of patients with the mitochondrial MERRF mutation A8344G. Clin Neurol Neurosurg 2008;110:859-63.

63. Molnar MJ, Perenyi J, Siska E, et al. The typical MERRF (A8344G) mutation of the mitochondrial DNA associated with depressive mood disorders. J Neurol 2009;256:264-5.

64. Wahbi K, Larue S, Jardel C, et al. Cardiac involvement is frequent in patients with the m.8344A>G mutation of mitochondrial DNA. Neurology 2010;74:674-7.

65. López-Gallardo E, Solano A, Herrero-Martín MD, et al. NARP syndrome in a patient harbouring an insertion in the MT-ATP6 gene that results in a truncated protein. J Med Genet 2009;46:64-7.

66. Gelfand JM, Duncan JL, Racine CA, et al. Heterogeneous patterns of tissue injury in NARP syndrome. J Neurol 2010 Oct 16. [Epub ahead of print].

67. Rojo A, Campos Y, Sánchez JM, et al. NARP-MILS syndrome caused by 8993 T > G mitochondrial DNA mutation: a clinical, genetic and neuropathological study. Acta Neuropathol 2006;111:610-6.

68. Bugiani M, Invernizzi F, Alberio S, et al. Clinical and molecular findings in children with complex I deficiency. Biochim Biophys Acta 2004;1659:136-47.

69. Leigh D. Subacute necrotizing encephalomyelopathy in an infant. J Neurol Neurosurg Psychiatry 1951;14:216-21.

70. Nagashima T, Mori M, Katayama K, et al. Adult Leigh syndrome with mitochondrial DNA mutation at 8993. Acta Neuropathol 1999;97:416-22.

71. Piao YS, Tang GC, Yang H, et al. Clinico-neuropathological study of a Chinese case of familial adult Leigh syndrome. Neuropathol Appl Neurobiol 2006;26:218-21.

72. Carrozzo R, Tessa A, Vazquez-Memije ME. The T9176G mtDNA mutation severely affects ATP production and results in Leigh syndrome. Neurology 2001;56:687-90.

73. Wang J, Brautbar A, Chan AK, et al. Two mtDNA mutations 14487T>C (M63V, ND6) and 12297T>C (tRNA Leu) in a Leigh syndrome family. Mol Genet Metab 2009;96:59-65.

74. Levitas A, Muhammad E, Harel G, et al. Familial neonatal isolated cardiomyopathy caused by a mutation in the flavoprotein subunit of succinate dehydrogenase. Eur J Hum Genet 2010;18:1160-5.

75. Fosslien E. Mitochondrial medicine–cardiomyopathy caused by defective oxidative phosphorylation. Ann Clin Lab Sci 2003;33:371-95. Review.

76. Finsterer J, Stöllberger C, Gelpi E. Successful heart failure therapy in mitochondrial disorder with noncompaction cardiomyopathy. Int J Cardiovasc Imaging 2006;22:393-6.

77. Santorelli FM, Gagliardi MG, Dionisi-Vici C, et al. Hypertrophic cardiomyopathy and mtDNA depletion. Successful treatment with heart transplantation. Neuromusc Disord 2002;12:56-9.

78. Arakawa K, Kudo T, Ikawa M, et al. Abnormal myocardial energy-production state in mitochondrial cardiomyopathy and acute response to L-arginine infusion: C-11 acetate kinetics revealed by positron emission tomography. Circ J 2010;74:2702-11.