Mitochondrial diseases are a heterogeneous group of progressive, genetically transmitted, multisystem disorders caused by impaired mitochondrial function. The disease course for individuals with mitochondrial myopathies varies greatly from patient to patient because disease progression largely depends on the type of disease and on the degree of involvement of various organs which makes the prognosis unpredictable both within the same family and among families with the same mutation. This is particularly, but not exclusively, true for mitochondrial disorders caused by mtDNA point mutations, which are maternally inherited and subject to the randomness of the heteroplasmy. For this reason, the prognosis cannot be given by single mitochondrial disease, but should be formulated by any single mitochondrial disease-related event or complication keeping in mind that early recognition and treatment of symptoms are crucial for the prognosis. The following approach can help prevent severe organ dysfunctions or at least allow early diagnosis and treatment of disease-related complications.

**Key words:** multisystem disorders, clinical heterogeneity, intrafamilial variability, dual genetic control

### Introduction

**Definition**

Mitochondrial diseases are a heterogeneous group of progressive multisystem disorders caused by impaired mitochondrial function. Mitochondria are subcellular organelles endowed with their own DNA (mitochondrial DNA or mtDNA) which is only maternally transmitted to all progeny. The most important mitochondrial role is the provision of energy in the form of adenosine triphosphate (ATP), which occurs through different metabolic pathways. One of these pathways, known as respiratory chain, depends on both nuclear DNA (nDNA) and mtDNA. This dual genetic control and the fact that mitochondrial diseases encompass defects in any of the multiple metabolic pathways that are contained within the mitochondrion account for the great heterogeneity, complexity and severity of clinical manifestations and disease classification.

**Brief molecular classification of mitochondrial disorders (1, 2)**

1. Disorders due to mutations in mtDNA (maternally inherited point mutations, sporadic large scale deletions).
2. Disorders due to mutations in nDNA (Mendelian/autosomal inheritance) that can affect five components of mitochondrial biology:
   a. genes encoding subunits of the respiratory chain;
   b. genes encoding mitochondrial assembly proteins;
   c. genes affecting mtDNA translation;
   d. genes controlling the phospholipid composition of the mitochondrial inner membrane (MIM);
   e. genes involved in mitochondrial dynamics.
3. Defects of mtDNA maintenance (Mendelian inheritance, but clinically similar to primary mtDNA defects).

**Demographics**

The prevalence of mitochondrial disorders in the general population is not known also because of the clear-cut separation into two main genetic groups: mtDNA point mutations and mtDNA deletions.

The prevalence is estimated around 1 in 5000 in patients tested for deletions and for common mutations of mtDNA which account for 5-40% of cases, depending on the study (3, 4).
In an investigation made in the North East of England from 1990 to 2004 to define the prevalence of mtDNA disease in adults with suspected mitochondrial diseases, 9.2 in 100,000 people were found to have clinically manifest mtDNA disease, making this one of the commonest inherited neuromuscular disorders. The m.3243A>G mutation was the most common pathogenic mtDNA mutation (40%), associated with extreme phenotypic variation. A further 34% of adults were affected with Leber’s hereditary optic neuropathy (LHON) caused by the m.11778G>A or m.3460G>A point mutations Single large-scale deletions of mtDNA represented 13%, and the m.8344A>G mutation a further 4%, of disease cases. The remaining 9% of affected adults harbored other mtDNA point mutations (5).

### Clinical features

It would be excessively reductive to confine the description of mitochondrial disorders to just one or two mitochondrial diseases because there is a quite consistent number of typical, genetically different, mitochondrial syndromes each of them characterized by a peculiar set of clinical signs and symptoms.

The following tables, courtesy of Prof. Di Mauro (1, 2) aim at providing a schematic and at the same time exhaustive description of the main clinical features of key mitochondrial disorders in compliance with their molecular and functional classification.

When speaking about mtDNA-related mitochondrial disorders it is worth reminding that there are thousands of copies of mtDNA instead of the two alleles of each nu-

### Table 1. Signs and symptoms of six key mitochondrial diseases due to mtDNA mutations.

<table>
<thead>
<tr>
<th>Tissue or factor</th>
<th>Sign or symptom</th>
<th>Δ-mtDNA-associated disease</th>
<th>tRNA-associated disease</th>
<th>ATPase 6-associated disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>KSS</td>
<td>Pearson</td>
<td>MERRF</td>
<td>MELAS</td>
</tr>
<tr>
<td>CNS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Seizures</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Ataxia</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Myoclonus</td>
<td>–</td>
<td>–</td>
<td>+/–</td>
</tr>
<tr>
<td></td>
<td>Psychomotor retardation</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Psychomotor regression</td>
<td>+</td>
<td>+/–</td>
<td>+/–</td>
</tr>
<tr>
<td></td>
<td>Hemiparesis/hemianopia</td>
<td>–</td>
<td>–</td>
<td>+/–</td>
</tr>
<tr>
<td></td>
<td>Cortical blindness</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Migraine-like headaches</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Dystonia</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>PNS</td>
<td>Peripheral neuropathy</td>
<td>+/–</td>
<td>+/–</td>
<td>+/–</td>
</tr>
<tr>
<td>Muscle</td>
<td>Weakness</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Ophthalmoplegia</td>
<td>+</td>
<td>–</td>
<td>+/–</td>
</tr>
<tr>
<td></td>
<td>Ptosis</td>
<td>+</td>
<td>+/–</td>
<td>+/–</td>
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<tr>
<td>Eye</td>
<td>Pigmentary retinopathy</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Optic atrophy</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Cataracts</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Blood</td>
<td>Sideroblastic anaemia</td>
<td>+/–</td>
<td>+/–</td>
<td>+/–</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Diabetes mellitus</td>
<td>+/–</td>
<td>+/–</td>
<td>+/–</td>
</tr>
<tr>
<td></td>
<td>Short stature</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Hypoparathyroidism</td>
<td>+/–</td>
<td>+/–</td>
<td>+/–</td>
</tr>
<tr>
<td>Heart</td>
<td>Conduction block</td>
<td>+/–</td>
<td>+/–</td>
<td>+/–</td>
</tr>
<tr>
<td></td>
<td>Cardiomyopathy</td>
<td>+/–</td>
<td>+/–</td>
<td>+/–</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Exocrine pancreatic dysfunction</td>
<td>+/–</td>
<td>+/–</td>
<td>+/–</td>
</tr>
<tr>
<td></td>
<td>Intestinal pseudo-obstruction</td>
<td>+/–</td>
<td>+/–</td>
<td>+/–</td>
</tr>
<tr>
<td>ENT</td>
<td>Sensorineural hearing loss</td>
<td>–/–</td>
<td>–/–</td>
<td>–/–</td>
</tr>
<tr>
<td>Kidney</td>
<td>Fanconi syndrome</td>
<td>+/–</td>
<td>+/–</td>
<td>+/–</td>
</tr>
<tr>
<td>Laboratory testing</td>
<td>Lactic acidosis</td>
<td>+/–</td>
<td>+/–</td>
<td>+/–</td>
</tr>
<tr>
<td></td>
<td>Muscle biopsy (Ragged-Red Fibers)</td>
<td>+/–</td>
<td>+/–</td>
<td>+/–</td>
</tr>
<tr>
<td>Inheritance</td>
<td>Maternal</td>
<td>–</td>
<td>+/–</td>
<td>+/–</td>
</tr>
<tr>
<td></td>
<td>Sporadic</td>
<td>+</td>
<td>–</td>
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</table>
clear autosome. For this reason, in most mtDNA-related diseases, mutated and wild-type mitochondrial genomes coexist, a situation known as heteroplasmcy. The degree of heteroplasmcy determines both the manifestation and the severity of the disease because a critical number of mutated mtDNAs is needed for clinical symptoms to manifest (threshold effect). This pathogenic threshold varies in different tissues according to their dependence on oxidative metabolism, explaining why brain and skeletal muscle are so often affected ("mitochondrial encephalomyopathies") even if every organ and tissue can virtually be affected (multisystem disorders). Also, because the number of mutated mtDNAs can distribute in different proportions in different tissues and organs as well as in the same tissues from one generation of cell to the next (mitotic segregation), both genotype and clinical phenotype of mtDNA-related disorders may vary in different individuals of the same generation and, in some tissues, in the same individual with time (1, 6, 7).

**Diagnosis**

Mitochondrial disorders should be suspected anytime an individual presents clinical involvement of more than one tissue and/or organ (multisystemic nature of these diseases) especially when both central and peripheral nervous system are affected ("mitochondrial encephalomyopathies"). Serum lactate increase helps reinforce the diagnosis and prompts further diagnostic procedures.

**Blood:** Serum creatine kinase levels are mildly elevated in most mitochondrial disorders. Increased serum lactate and consequent lactic acidosis is a hallmark of mitochondrial disorders, especially in pediatric cases, but it is not invariably present and, also, not necessarily severe.

**CSF:** Increased CSF lactate is a pathognomonic marker in mitochondrial encephalopathies.

**Neurophysiology:** Myopathic and/or mainly axonal polyneuropathic patterns can be evidenced. Degree of severity is quite variable, depending on the underlying disease.

**Skeletal muscle biopsy:** This diagnostic procedure represents the gold standard for the diagnosis of mitochondrial disorders. Apart from the histological reaction for Gomori Trichrome, which shows proliferation of (pathologic) mitochondria in affected fibers (Ragged Red Fibers), valuable diagnostic clues are given by the histochemical reactions for COX (cytochrome c oxidase, complex IV of respiratory chain) and SDH (succinate dehydrogenase, complex II of the respiratory chain) used alone or in combination. COX is frequently lacking or reduced in skeletal muscle fibers from patients with both mtDNA-related and nDNA-dependent mitochondrial disorders whereas SDH, which is entirely encoded by nDNA, is unaffected by deleterious mutations affecting mtDNA and therefore stands as an excellent marker of mitochondrial proliferation ("ragged blue" fibers). Also, ultrastructural studies may show evidence of mitochondrial proliferation and alterations (enlarged mitochondria with abnormal cristae and paracrystalline inclusions).

**Biochemistry:** Measurement of the activities of respiratory chain complexes can provide important diagnostic clues depending on whether respiratory chain deficiency is confined to one, two or all complexes. Studies can be performed on both frozen muscle tissue or fibroblast cultures.

**Genetics:** Maternal inheritance or sporadic (mtDNA defects), autosomal dominant or recessive (nDNA defects). Defects are detected by PCR, Southern Blot, sequence analysis of mtDNA or candidate nuclear genes, whole-exome or mito-exome sequencing.

**Imaging:** Increased lactate detectable by brain 1H-MRS; strokes that do not conform to the distribution of major brain vessels and commonly affect the occipital or parietal lobe in MELAS (TC and MR).

**Prognosis**

Although once considered rare, accumulating evidence suggests that mitochondrial disorders are relatively common, primary disorders of the respiratory chain affecting up to 1 in 5000 people (3, 4).

The prognosis for patients with mitochondrial myopathies varies greatly from patient to patient because disease progression largely depends on the type of disease and the degree of involvement of various organs. Indeed, the prognosis of mitochondrial diseases relies on disease type, degree of heteroplasmcy (mtDNA point mutations), duration, possible complications, consequent outcomes, and prospects for recovery. These variables affect both quality of life and survival rate and are by their nature unpredictable.

Also, a distinction is due between pediatric and adult cases, the former being usually more dramatically affected and severe. In the last years many efforts have been done to find more effective treatments if not a real cure to improve both quality of life and survival rate in affected children, the purpose being to try to guarantee fairly normal lives at least in selected cases. Many children, however, still have to face major disabilities and a poor prognosis, survival rate ranging between few months and teenage years.

Adult onset disorders are less aggressive, but can result in drastic changes from an active lifestyle to a debilitating illness in a short amount of time.

Genetic counseling for families with ascertained mitochondrial diseases is another important part of the prognostic puzzle and faces the same uncertainties and
Mitochondrial disease heterogeneity: a prognostic challenge

The following approach can help prevent severe organ dysfunctions or at least allow early diagnosis and treatment of disease-related complications.

**Cardiac assessment:** Cardiac arrhythmias are quite common and require routine electrocardiography monitoring because progression to high-grade atrio-ventricular block is often unpredictable, (i.e. KSS, MELAS, MILS). Supraventricular and ventricular tachyarrhythmias have been reported in patients with mtDNA disease, particularly in children. Also, echocardiography and/or cardiac MRI should be performed periodically even in asymptomatic subjects because hypertrophic cardiomyopathy, most commonly associated with mtDNA gene mutations, can become clinically evident only at an advanced stage and evolve to dilated cardiomyopathy if not treated. Cardiopathy is also a feature of nDNA defects especially mutations in respiratory chain ancillary proteins, often in association with Leigh disease (Table 2) (13). In addition, as demonstrated by a clinical study of a large population of pediatric patients with mitochondrial disorders (14) cardiac function in mitochondrial patients deteriorates rapidly regardless of the associated RC defect. Early and aggressive supportive treatment might increase the chances of survival even if mortality in subjects with cardiac complications remains higher than in individuals with predominant neuromuscular manifestations. In detail, pediatric patients with cardiomyopathy had an 18% survival rate at 16 years of age whereas patients without cardiomyopathy had a 95% survival at the same age.

**Ophthalmology assessment:** Ptosis, strabismus, ophthalmoplegia, retinal hyperpigmentation, optic atrophy, visual field defects and nystagmus are often part, alone or in combination, of the mitochondrial clinical picture. Strict periodic eye examination along with specific techniques like optical coherence tomography are necessary when the optic nerve is directly involved (i.e. LHON and optic atrophy-plus syndrome, OPA1) to monitor the subtle progression of this highly disabling degeneration (15, 16).

**EEG monitoring:** epilepsy is a frequent complication of many mitochondrial disorders (MERRF, MELAS, MILS, autosomal encephalopathies) and seizure control is a main goal to prevent progressive cortical brain damage and thus guarantee a satisfactory quality of life. Periodical EEG monitoring allows identification of any brain electrical abnormalities and their correction by appropriate therapeutic adjustments.

**Respiratory assessment:** periodical spirometry and nocturnal saturimetry allow early detection of any respiratory dysfunction and early adoption of measures to prevent hypoxia. This is extremely important to avoid hypoxia-related symptoms, namely headache, fatigue,
nausea, dyspnoea and, ultimately, seizures, all of them contributing to deteriorate quality of life.

**Physiotherapy assessment:** Abnormalities of tone, posture, power, and balance often complicate mitochondrial disease in patients of all ages. Life-improving solutions include, for example, the use of special seats to support hypotonic infants/children and enable them to keep an upright posture, develop axial tone and have a more comprehensive visual engagement with their environment. Also, management of spasticity and dystonia with splinting, botulinum toxin, and pharmacotherapy can advantage affected individuals at many disease stages and lower the risk of falls. It is very useful to perform functional assessment of the patients at home because this approach can reveal their main areas of difficulties and help plan personalized health care support such as mobility and hygiene aids. Management of respiratory problems, including prevention of aspiration pneumonia, is another important issue that the physiotherapist has to care for (9).

### Table 2. Disorders due to mutations in nDNA.

<table>
<thead>
<tr>
<th>Mutations in respiratory chain subunits</th>
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<tbody>
<tr>
<td>• Leigh syndrome</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Mutations in respiratory chain ancillary proteins</th>
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<tbody>
<tr>
<td>• Leigh syndrome with cytochrome c oxidase deficiency (<em>SURF1</em>)</td>
<td></td>
</tr>
<tr>
<td>• Leigh syndrome and cardiopathy (<em>SC02, COX10, COX14, COX15, COA5, FAM36A, TAC01</em>)</td>
<td></td>
</tr>
<tr>
<td>• Leigh syndrome and hepatopathy (<em>SCO1</em>)</td>
<td></td>
</tr>
<tr>
<td>• GRACILE syndrome</td>
<td></td>
</tr>
<tr>
<td>• Defects of mitochondrial protein importation: Mohr–Tranebjaerg deafness–dystonia syndrome (<em>TIMM8A</em>); spastic paraplegia-13 (<em>HSP60</em>)</td>
<td></td>
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</tbody>
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<table>
<thead>
<tr>
<th>Defects of mtRNA translation</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>• Fatal neonatal lactic acidosis (<em>MRPS16, MRPS22, RMND1</em>)</td>
<td></td>
</tr>
<tr>
<td>• Spastic paraplegia (<em>SPG7</em>); dominant hereditary ataxia (<em>AFG3L2</em>)</td>
<td></td>
</tr>
<tr>
<td>• Infantile hepatocerebral syndrome (<em>GFM1</em>); infantile encephalomyopathy (<em>TUFM</em>)</td>
<td></td>
</tr>
<tr>
<td>• Myopathy, lactic acidosis, sideroblastic anaemia (<em>PUS1</em>); reversible hepatopathy (<em>TRMU</em>)</td>
<td></td>
</tr>
<tr>
<td>• Leukoencephalopathy, brainstem and spinal cord involvement, lactic acidosis (<em>DARS2</em>)</td>
<td></td>
</tr>
<tr>
<td>• Late-onset Leigh syndrome with COX deficiency (<em>TAC01</em>)</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Defects of the MIM lipid milieu</th>
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<tbody>
<tr>
<td>• Barth syndrome (<em>TAZ</em>)</td>
<td></td>
</tr>
<tr>
<td>• Sengers syndrome (<em>AGK</em>)</td>
<td></td>
</tr>
<tr>
<td>• Megaconial encephalomyopathy (<em>CHKB</em>)</td>
<td></td>
</tr>
<tr>
<td>• MEGDEL (<em>SERAC1</em>)</td>
<td></td>
</tr>
<tr>
<td>• Childhood myoglobinuria (<em>LPINT</em>)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Defects of mitochondrial dynamics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• DOA; DOA-plus (<em>OPA1</em>)</td>
<td></td>
</tr>
<tr>
<td>• Charcot–Marie–Tooth type 2A (<em>MFN2</em>)</td>
<td></td>
</tr>
<tr>
<td>• Charcot–Marie–Tooth type 4A (<em>GDAP1</em>)</td>
<td></td>
</tr>
<tr>
<td>• Fatal infantile encephalomyopathy (<em>DRP1, MFF</em>)</td>
<td></td>
</tr>
</tbody>
</table>

Representative implicated genes are indicated in parentheses. Abbreviations: DOA, dominant optic atrophy; GRACILE, growth retardation, aminoaciduria, cholestasis, iron overload, and early death; MEGDEL, 3-methylglutaconic aciduria with sensorineural deafness, encephalopathy, and Leigh-like syndrome.

### Specific treatments of mitochondrial diseases

Therapy for mitochondrial diseases is unfortunately scarcely adequate and sometimes palliative, but pharmacological treatments and surgical remedies are useful in prolonging and improving the lives of patients with mitochondrial diseases, which equals the concept of prognosis to that of chronic morbidity.

Specific pharmaceutical drugs have failed to show clear efficacy in treating mitochondrial diseases effectively, but improvement in fatigue and relief of myalgia have been reported with use of coenzyme Q10 and its analogue idebenone. Also, coenzyme Q10 replacement therapy at higher doses can benefit patients with coenzyme Q10 deficiency whereas Riboflavin can be effective in some patients with complex I deficiency. Some evidence has been reported of successful use of arginine for both acute treatment and prophylaxis of stroke-like episodes (2, 17, 18).
Treating symptoms of mitochondrial diseases

The difficulty in developing disease-modifying drugs to cure mitochondrial diseases has led to a focus on symptomatic treatments aiming at improving patient health which ultimately results in a better prognosis at least in terms of life quality if not, in some cases, of life span.

Lactic acidosis

It is one of the main symptoms especially in children. Acute episodes are corrected with sodium bicarbonate and dichloroacetate, but chronic use is not recommended because it is not effective and, also, it can cause peripheral neuropathy (17, 21).

Diabetes mellitus

Diabetes mellitus is a frequent complication of mitochondrial diseases, especially in patients with mitochondrial DNA mutations (22). Disease control relies on dietary advice, physical exercise, weight control and drug treatment in the same way as in non-mitochondrial diabetes. Metformin should be avoided in patients with mitochondrial disease because there is a risk of precipitating or exacerbating lactic acidosis.

Electrolyte disturbances

Hyponatraemia and hypokalaemia are not uncommon in children with mitochondrial diseases with renal involvement and both proximal and distal renal tubular acidosis have been identified (23). Their prompt investigation and treatment help avoid life-threatening adrenal crises.

Epilepsy

Seizures frequently complicate both pediatric and adult cases of mitochondrial disorders, the most common types being myoclonic and focal epilepsy. Common antiepileptic drugs are often effective and enable good seizure control. Levetiracetam, lamotrigine, carbamazepine, and clonazepam, alone or in combination, are most frequently used. It is recommended not to use sodium valproate and barbiturates which inhibit the respiratory chain and have occasionally been shown to precipitate hepatic failure in affected children (24, 25).

Table 3. Defects of mtDNA maintenance.

<table>
<thead>
<tr>
<th>Mutated gene</th>
<th>mtDNA depletion</th>
<th>Multiple mtDNA deletions</th>
</tr>
</thead>
<tbody>
<tr>
<td>TK2</td>
<td>Infantile or adult myopathy</td>
<td>Adult autosomal recessive PEO</td>
</tr>
<tr>
<td>DGUOK</td>
<td>Infantile hepatocerebral syndrome</td>
<td>Adult myopathy ± PEO</td>
</tr>
<tr>
<td>PEO1</td>
<td>Hepato-cerebral syndrome Infantile-onset spinocerebellar ataxia</td>
<td>Adult autosomal dominant PEO-plus</td>
</tr>
<tr>
<td>SUCLA2</td>
<td>Infantile encephalomyopathy</td>
<td>—</td>
</tr>
<tr>
<td>SUCLG1</td>
<td>Infantile encephalomyopathy Methylmalonic aciduria</td>
<td>—</td>
</tr>
<tr>
<td>RRM2B</td>
<td>Infantile encephalomyopathy</td>
<td>Adult autosomal dominant or autosomal recessive PEO-plus</td>
</tr>
<tr>
<td>MPV17</td>
<td>Infantile hepatocerebral syndrome Navajo neurohepatopathy</td>
<td>Adult autosomal recessive PEO-plus</td>
</tr>
<tr>
<td>TYMP</td>
<td>Mitochondrial neurogastrointestinal encephalomyopathy</td>
<td>Mitochondrial neurogastrointestinal encephalomyopathy</td>
</tr>
<tr>
<td>POLG</td>
<td>Hepato-cerebral syndrome (Alpers syndrome)</td>
<td>Adult autosomal dominant or autosomal recessive PEO-plus; SANDO; MIRAS</td>
</tr>
<tr>
<td>POLG2</td>
<td>—</td>
<td>Adult autosomal dominant PEO</td>
</tr>
<tr>
<td>ANT1</td>
<td>—</td>
<td>Adult autosomal dominant PEO-plus</td>
</tr>
<tr>
<td>OPA1</td>
<td>—</td>
<td>DOA; PEO-plus</td>
</tr>
<tr>
<td>MFN2</td>
<td>—</td>
<td>DOA-plus</td>
</tr>
<tr>
<td>GFER</td>
<td>—</td>
<td>Congenital cataract, encephalomyopathy</td>
</tr>
<tr>
<td>MGME1</td>
<td>—</td>
<td>PEO, muscle wasting, proximal weakness, profound emaciation, respiratory failure</td>
</tr>
</tbody>
</table>

Abbreviations: DOA, dominant optic atrophy; MIRAS, mitochondrial recessive ataxia syndrome; mtDNA, mitochondrial DNA; PEO, progressive external ophthalmoplegia; SANDO, sensory ataxic neuropathy, dysarthria and ophthalmoparesis; SMA, spinal muscular atrophy. MGME1, mitochondrial genome maintenance exonuclease 1
Cardiomyopathy and arrhythmias

In patients with cardiomyopathy, early administration of β blockers and an angiotensin converting enzyme inhibitor (or angiotensin II receptor antagonist) is helpful in delaying disease progression, which explains why early diagnosis is fundamental. Rhythm disturbances include Wolff-Parkinson-White syndrome and various degrees of conduction block (from right bundle branch block to complete atrioventricular block) which can require radiofrequency ablation and/or implantation of pacing devices. Rhythm disturbances are easily identifiable on the electrocardiogram which, once again, stresses the importance of strict disease monitoring from the very early phases. Occasionally, cardiac involvement is the only, or earliest, manifestation of mitochondrial disease, leading to rapid cardiac deterioration and, when possible, cardiac transplantation before a diagnosis of mitochondrial disease is considered. After cardiac transplantation, survival depends both on the immune-mediated reaction to the new organ and on the degree of the disease-dependent multi-organ involvement (26-29).

Respiratory failure

Respiratory insufficiency can dominate the clinical picture especially in the late disease stages, the origin being either central or peripheral (weakness of diaphragm and/or respiratory muscles). In the latter cases, non-invasive positive pressure ventilation can help patients with their breathing and relieve them from hypoxia side effects (9).

Ocular disease

The most debilitating ocular problem in mitochondrial disorders is optic neuropathy which can be almost isolated, as in patients with LHON, or part of a multisystem involvement. In both cases, given the progressive nature of the neuropathy, this disabling disturbance is very difficult to treat. Visual aids should be used as much as possible to preserve residual visual activity.

Regarding eyelid ptosis, corrective ptosis surgery can dramatically improve both visual field and appearance, but the intervention is very delicate and subject to complications. For this reason, it should be performed only by dedicated ophthalmologists who are able to plan both timing and technique of surgery. Alternatively, surgically adjustable frontalis slings or less invasive ptosis props might be preferred to ptosis surgery (30).

Acknowledgements

The Authors wish to acknowledge the Italian Association of Myology (AIM) and the Associazione Amici del Centro Dino Ferrari.

References

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