Mitochondrial diseases: what the cardiologist should know?

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Abstract

Mitochondrial diseases (MD) are a heterogeneous group of rare genetically determined disorders, characterized by mitochondrial respiratory chain defect and subsequent energy metabolism imbalance. Due to almost exclusive aerobic metabolism of the heart, cardiac involvement in MD is common and can be accompanied by other manifestations of the multi-organ involvement, but may be also the first or the sole clinical manifestation of MD. All tissues of the heart may be affected but the most frequently affected tissue is the myocardium. The most frequent cardiac manifestation found in MD are cardiomyopathies, but cardiac abnormalities may be varied and include arrhythmias, heart failure, pulmonary hypertension, aortic root dilation, and pericardial effusion. Given the progressive nature of cardiac involvement in MD, its association with poor prognosis and increased mortality, and the fact that it can remain asymptomatic until an advanced stage is reached, often due to limited patient mobility, cardiac screening should be a part of standard management of MD patients. All patients with cardiac involvement should be reviewed by a cardiologist with an expertise in the management of such patients.

Key words: mitochondrial disease, mitochondrial cardiomyopathy, cardiac involvement, conduction system disease

Introduction

Mitochondrial diseases (MD) are a heterogeneous group of rare genetic disorders, characterized by a mitochondrial respiratory chain defect and subsequent cell energy metabolism imbalance. Although their symptoms may involve nearly all organs, the most prone tissues are those characterized by a high energy requirement, such as the nervous and muscle tissue, and the myocardium [1]. No epidemiological studies are available to estimate the number of patients with MD in Poland, and similar data are hardly available elsewhere in the world. Cardiac complications including heart failure (HF), arrhythmias, conduction disturbances, and sudden cardiac death, remain a major cause of mortality in this patient group [1, 2]. According to the neurological and cardiac society guidelines, patients with neuromuscular disease, including MD, should receive both neurological and cardiac care [3]. Cardiologists will be increasingly involved in the multidisciplinary care of these patients and thus should be familiar with the pathophysiology of these diseases, their clinical characteristics, and the spectrum of cardiovascular symptoms and signs.

Etiopathogenesis

The mitochondrial respiratory chain is controlled by both mitochondrial DNA (mtDNA) and nuclear DNA (nDNA), and thus MD may result from defects of both mtDNA and nDNA [1, 4]. mtDNA defects are the cause of most cases (about 70%) of MD in adults [5, 6]. Due to this dual genomic control, MD may show a maternal, autosomal recessive, autosomal dominant, or X-linked inheritance pattern [4]. mtDNA mutations may also occur de novo [4]. Their incidence is more than 1/200 live births which makes them one of the most common pathogenic alleles in the general population [7]. Of note, the presence of a mutation does...
not necessarily lead to a disease, as most mtDNA are heteroplasmatic, with a variable amount of the mutated mtDNA in different cells, and the mitochondrial respiratory chain defect usually requires a threshold of 60–90% of mutated mtDNA in relation to the wild-type mtDNA [8]. It has been estimated that the prevalence of MD in adults due to both mtDNA and nDNA mutations is about 1/4300, and thus they are among the most common heritable neuromuscular diseases [9].

**Clinical presentation**

Due to the presence of mitochondria in all nucleated cells, the disease may affect various tissues and manifest with a wide spectrum of clinical presentations, from oligosymptomatic forms involving one organ (e.g., deafness or diabetes) to complex, polysymptomatic multisystem disorders (Figure 1). Symptoms may develop at any age, and the age at presentation usually correlates with the level of mutation and the severity of biochemical defect [8]. Tissues and organs with a high energy demand (i.e., brain, eye, heart, and skeletal muscle) are most susceptible to abnormal mitochondrial function [1]. Frequent symptoms common for MD include progressive external ophthalmoplegia, ptosis, proximal myopathy, weakness, exercise intolerance, and myalgia [4]. In many patients, multiple symptoms are present, often forming specific constellations of concomitant symptoms that define about 50 syndromes (Table 1) [8, 10, 11], but most patients present with nonspecific mitochondrial multiorgan disorder syndromes which are difficult to categorize and pose a diagnostic challenge for clinicians.

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**Figure 1. Clinical manifestations of mitochondrial diseases**
Cardiac involvement in mitochondrial myopathies

Mitochondria amount for about 35% of the myocardial cell volume, and mitochondrial oxidative phosphorylation is the main source of energy in the heart, responsible for nearly all (>95%) adenosine triphosphate (ATP) synthesis. Due to this almost exclusively aerobic metabolism of the heart, cardiac involvement in MD is common and can be accompanied by other manifestations of the multiorgan involvement, but may also be the major clinical manifestation of MD. In a metaanalysis of 825 patients, structural abnormalities were identified by standard transthoracic echocardiography (TTE) in 29% of patients, mostly with mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) or myoclonic epilepsy with ragged-red fibres (MERRF) and with mutations most commonly associated with these defects (m.3243A>G and m.8344A>G) [12]. All cardiac structures may be affected but the most common involvement is that of the myocardium [13]. The most frequent cardiac manifestation are cardiomyopathies [14] but cardiovascular abnormalities in patients with MD may be varied and also include arrhythmias and conduction disturbances, HF, pulmonary hypertension, aortic root dilation, and pericardial effusion [13].

Cardiomyopathies

Mitochondrial cardiomyopathy is characterized by abnormal myocardial structure and function due to genetically determined abnormalities in the mitochondrial respiratory chain without concomitant coronary artery disease, hypertension or valvular heart disease [15]. The phenotype and course of cardiomyopathy may vary.

The most common type of mitochondrial cardiomyopathy manifests with left ventricular hypertrophy (LVH) but dilated cardiomyopathy (DCM), restrictive cardiomyopathy, left ventricular noncompaction cardiomyopathy (LVNC), takotsubo cardiomyopathy and histiocytoid cardiomyopathy were also reported [13]. The exact prevalence of mitochondrial cardiomyopathy is unknown but it has been estimated to occur in 20–40% of children [14] and more than 20% adults with MD [6], and the prevalence in the general population may be at least 1/10,000–15,000 [5].

The spectrum of clinical manifestations is very wide, from absent symptoms to life-threatening conditions such as HF, ventricular tachyarrhythmia, and sudden cardiac death. Symptoms usually become worse during metabolic stress caused by physiological stressors (e.g., fever) or surgery, which may lead to acute HF [15]. Drugs that impair mitochondrial respiratory chain function (Table 2) may...
also contribute to metabolic stress [15]. Manifestations of mitochondrial cardiomyopathy are frequently accompanied by symptoms from many other organ systems (Figure 1) but mitochondrial cardiomyopathy may also be the initial or sole manifestation of MD [14].

The form presenting with LVH may occur in as many as 20% of patients [6, 12, 17] and is usually seen in subjects with the m.3243A>G mutation, of whom more than half may be affected with LVH [12, 18]. In these cases, LVH is usually concentric [6, 18], and left ventricular (LV) outflow obstruction is rare [6, 17]. LV systolic dysfunction tends to progress with time [6]. The LVH form may imitate hypertrophic cardiomyopathy (HCM) which is caused by cardiac sarcomere protein gene mutations in 60% of adult patients but up to 10% of cases are due to other genetic disorders including MD [19]. A maternal inheritance pattern and some characteristic symptoms and signs, such as sensorineural deafness, particularly with concomitant diabetes, vision disturbances, ptosis, and muscle weakness, should suggest a likely underlying mitochondrial defect.

Another more rare form is DCM. It is usually observed due to progression of preexisting LVH with development of systolic dysfunction, LV dilation, and LV wall thinning, but it may also be the initial cardiac manifestation in patients with MD [20]. In patients with the m.8344A>G mutation, the rate of DCM is more than 20% [21] but it is much lower, less than 5%, in patients with other mutations [6, 22].

Left ventricular noncompaction cardiomyopathy has been reported in many MD, including MELAS, Kearns-Sayre syndrome (KSS), Leigh syndrome [23], and Leber’s hereditary optic neuropathy (LHON) [24], but also in patients with nonspecific mitochondrial multiorgan disorder syndromes [25]. LVNC is present in a small subset of adult patients with MD (about 3%) [6] but due to the fact that MD are the most common genetic disorders associated with LVNC [25], MD should be suspected in every patient with the diagnosis of LVNC.

A very rare form of arrhythmogenic cardiomyopathy associated with MD is histiocytoid cardiomyopathy or Purkinje fibre dysplasia, characterized by the presence of abnormal cardiomyocytes and histiocyte-like Purkinje cells [12]. It usually affects children, more commonly girls, but it was also reported in adults [26]. It may manifest with arrhythmia and sudden cardiac death [27] and it may coexist with LVNC [26, 27].

### Arrhythmias and conduction disturbances

An abnormal electrocardiogram (ECG) is seen in as many as 70% of patients with MD [6], most commonly in those with the m.3243A>G mutation and MELAS [10], more frequent in the paediatric population [10]. Arrhythmia or syncope necessitating implantation of a cardiac device or invasive treatment was observed in more than 12% of patients [6].

Conduction disturbances are quite common in MD (about 10%) [6, 18, 28] and their prevalence increases with age, similarly to the general population [5]. The highest risk group are patients with KSS [15] in whom conduction

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### Table 2. Drugs with potentially adverse effects in mitochondrial diseases (based on [15, 16])

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Potential adverse effects</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>Myopathy, rhabdomyolysis</td>
<td>Avoid simvastatin, atorvastatin preferred, use with caution and monitor creatine kinase level</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>May worsen symptoms of MD</td>
<td>No clear evidence that beta-blockers should be avoided</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Muscle damage</td>
<td>Use with caution and monitor symptoms and lactate and creatine kinase levels</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Muscle damage, lactic acidosis</td>
<td></td>
</tr>
<tr>
<td>Amiloride</td>
<td>Muscle damage, lactic acidosis</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Muscle damage</td>
<td></td>
</tr>
<tr>
<td>Prostaglandin inhibitors</td>
<td>Muscle damage, lactic acidosis</td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>Lactic acidosis</td>
<td>Use with caution and monitor lactate level</td>
</tr>
<tr>
<td>Valproate</td>
<td>Liver failure, status epilepticus</td>
<td>Avoid</td>
</tr>
<tr>
<td>Propofol</td>
<td>Propofol infusion syndrome</td>
<td>Short-term use seems safe, avoid long-term use and large doses</td>
</tr>
<tr>
<td>Antibiotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td>Lactic acidosis</td>
<td>Avoid, particularly in patients with MELAS</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Acute hepatitis, blood dyscrasias</td>
<td>Low risk of adverse effects but use of alternative drugs preferred if possible</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Hearing loss</td>
<td>Avoid</td>
</tr>
</tbody>
</table>

MELAS — mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes

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Disturbances are the most common manifestation of cardiac involvement, present in more than 60% of patients [29], and they may rapidly progress to complete atrioventricular (AV) block [29, 30] or bradycardia-related polymorphic ventricular tachycardia [31].

Preexcitation and Wolff-Parkinson-White syndrome (WPW) are present in 15–20% of patients [6, 21, 28] and are most commonly associated with the m.8344A>G and m.3243A>G mutations (responsible for most cases of MERRF and MELAS, respectively) [6, 21, 28] but were also reported in patients with chronic progressive external ophthalmoplegia (CPEO), neuropathy, ataxia and retinitis pigmentosa (NARP) [6], LHON [24] and KSS [29], and in patients with nonspecific mitochondrial multiorgan disorder syndromes [6]. In patients with LHON, WPW may coexist with LVNC [24].

The most common supraventricular arrhythmia in MD is atrial fibrillation, while atrial flutter has been rarely reported [13]. Ventricular tachyarrhythmias in patients with MD occur mostly in the paediatric population and in patients with cardiomyopathies [5]. Torsade de pointes has been frequently reported in KSS. It may be associated with QT interval prolongation and syncope, with progression to AV block and cardiac arrest [13].

**Cardiac biomarkers**

Elevated cardiac troponin levels have been reported in patients with MD. In 43% of 42 patients in our centre, high-sensitive troponin T (hsTnT) was moderately elevated and stable, up to 0.045 ng/mL. Further studies are needed to determine whether elevated troponin levels seen in patients with MD are a marker of cardiac damage or, similarly to other patients with neuromuscular disease [32], they may result from muscle damage.

**Natural history and prognosis**

Cardiac involvement in patients with MD is common, progressive [6] and is associated with worse outcomes and increased mortality due to HF [17, 21]. The major factor affecting the natural history and severity of the phenotype is age at diagnosis [11, 21]. Among 113 paediatric patients with MD, survival until 16 years of age in patients with or without cardiomyopathy was 18% and 95%, respectively [33]. It seems that cardiomyopathy in adults has a milder course and is associated with better prognosis [6, 22]. During a 7-year follow-up of 260 patients, a study endpoint (sudden death, death due to HF, resuscitated cardiac arrest, third degree AV block, sinus node dysfunction, cardiac transplantation, or hospitalization due to HF) occurred in 10%. Independent predictors of the study endpoint included intraventricular conduction disturbances, diabetes, ventricular premature beats and LVH, and the rate of major adverse cardiac events (MACE) in patients with no, 1, 2 or more risk factors were 1%, 7%, 15%, and 42%, respectively [17]. LVH was the only variable associated with the study endpoint in multivariable analysis in patients with the m.3243A>G mutation, and during the follow-up ranging from 3 to 9 years (median 5 years), 25% of patients died, including 7% due to HF, and life-threatening cardiovascular events (hospitalization due to severe HF and resuscitated cardiac arrest) were noted in 17% [28].

**Diagnostic workup**

Guidelines [34] indicate that screening for cardiomyopathy and cardiac arrhythmia should be a part of the standard management in patients with MD, in particular those with MELAS and MERRF [10] who require monitoring for LVH and DCM [13] due to a higher prevalence of these conditions and a higher risk of sudden cardiac death [28]. Annual follow-up with ECG and TTE is recommended, also in the presymptomatic phase when standard ECG is normal [3, 34, 35], as cardiac involvement may remain asymptomatic even until an advanced disease stage is reached [36], often due to a limited patient mobility.

Myocardial strain analysis by speckle tracking in TTE seems a promising modality to identify subclinical cardiac damage in patients with MD [36]. A reduced global longitudinal strain and longitudinal strain in two-chamber view was shown compared to the control group despite the fact that systolic function was within limits at conventional TTE examination [37]. Holter monitoring is recommended in patients at high risk of preexcitation and/or conduction disturbances (even if asymptomatic), severe LV systolic dysfunction, and frequent paroxysmal symptoms suggesting cardiac involvement [34, 35]. Cardiovascular magnetic resonance (CMR) may be useful in patients with suboptimal imaging by TTE and those in whom more precise assessment is required before therapeutic decisions are made [35, 36]. CMR reveals cardiac involvement in more than 50% of patients with MD [37, 38], and the most frequent finding is late gadolinium enhancement (LGE) of non-ischaemic aetiology. In patients with CPEO/KSS, LGE is located intramurally in the basal inferolateral LV segments [38, 39], and patients with MELAS show concentric LVH with diffuse intramurally LGE areas [38]. Overall, assessment using ECG, TTE, CMR, and myocardial strain analysis in patients with MD showed cardiac involvement in as many as 80% of patients [37].

**Patient care**

All patients with MD and cardiac involvement, also those asymptomatic, should be referred to a cardiologist with an expertise in the management of such patients [34, 35].
Patients with HF due to mitochondrial cardiomyopathy should be managed according to the current HF management guidelines as their LV function was noted to improve significantly following standard therapy [20]. In symptomatic patients with cardiomyopathy and LVH, it seems reasonable to follow the recommendations for the management of HCM [19] but due to a progressive nature of this form of cardiomyopathy, some authors recommend initiating a beta-blocker or a calcium antagonist and an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker in all patients, including those who are asymptomatic [5, 35].

Due to the risk of a rapid progression of conduction disturbances in patients with neuromuscular disease including MD, in particular in those with KSS, it is necessary to identify any AV block (including first degree block) early and consider pacemaker implantation [3, 34, 35]. In patients with third degree or advanced second degree AV block, pacemaker implantation is recommended regardless of the anatomical location of the block [3]. In patients with preexcitation, an electrophysiological study is recommended and catheter ablation of accessory pathways should be considered [35]. Patients with MD and ventricular arrhythmia should be managed similarly to those without neuromuscular disease [3].

Management

No specific therapy of MD is available yet and symptomatic treatment remains the only therapeutic option. Much hope is vested in a new drug elamipretide, tetrapeptide that binds cardiolipin in the inner mitochondrial membrane, which improved the walking distance by on average 64.5 metres after 5 days of intravenous administration in a study in 36 patients [40]. A phase III trial [MMPOWER-3 study (A Phase 3 Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Daily Subcutaneous Injections of Elamipretide in Subjects with Primary Mitochondrial Myopathy Followed by an Open-Label Treatment Extension-GB)] is currently underway to evaluate its safety and efficacy.

Summary

Cardiac involvement in patients with MD is common, progressive and is associated with worse outcomes and increased mortality. In addition, it may remain asymptomatic until an advanced disease stage due to a limited patient mobility. Screening for cardiomyopathy and cardiac arrhythmia should be a part of the standard management in patients with MD. Further studies are needed to allow the detection of preclinical cardiac involvement, early diagnosis, and timely initiation of therapy to improve outcomes in this patient group.

Conflict of interests

The authors declare no conflict of interests.

References


