Mitochondrial disorders with cardiac dysfunction: an under-reported aetiology with phenotypic heterogeneity

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This editorial refers to ‘Long-term cardiac prognosis and risk stratification in 260 adults presenting with mitochondrial diseases†, by K. Wahbi et al., on page 2886.

Reports of cardiac involvement in mitochondrial diseases in the past often referred to only small series of patients describing a wide variety of presentations, including conduction system diseases, left ventricular (LV) myocardial non-compaction, heart failure (HF), or hypertrophic and dilated cardiomyopathy (for reviews, see Myers et al., Limongelli et al., and Bates et al.). In contrast to these studies, Wahbi et al. have designed a survival analysis not only to measure the prevalence of cardiac involvement, but also to determine long-term cardiac prognosis and to identify predictors of major adverse cardiac events.

Mitochondrial diseases caused by either mitochondrial or nuclear DNA defects include various clinical disorders as a result of an impaired energy metabolism due to a dysfunctional cellular oxidative phosphorylation. Mitochondrial DNA (mtDNA) disease appears to be more common than previously expected, causing disease in ~1 in 5000–10 000 individuals. The m.3243A>G mutation, for example, is present in 1 in 300 individuals of the general population, but most often is asymptomatic, while many individuals possess low levels of mutation (<1%). This results from the fact that in the case of pathogenic mtDNA mutations, two or more distinct mitochondrial genomes exist within the same cell or tissue at different percentages (heteroplasmy induced by random mitotic segregation). Typically, maternally inherited mtDNA mutations become of clinical relevance if the proportion of mutated mtDNA exceeds a threshold level of typically 60–90%. For that reason, mtDNA mutation load and threshold may affect the onset and extent of clinical disease.

In contrast to other published reports by Limongelli et al. or Malfatti et al. with 32 and 41 patients reported, respectively, a large number of patients (260 individuals) were included in this long-term follow-up with a median duration of 7 years and a total duration of 14 years. A total of 464 patients strongly suspected to suffer from mitochondrial disease were investigated, and 260 patients (60% women) from 230 families with identified pathogenic mutations in mitochondrial or nuclear DNA were included in the study. For the first time, the aim was to determine the long-term cardiac prognosis of patients with known pathogenic mutations in mitochondrial or nuclear DNA and to identify predictors of major adverse cardiac events.

Prevalence of mitochondrial DNA mutations

The most often detected mutations in this population were single, large-scale mtDNA deletions in 109 (41%) and the MT-TL1 m.3243A>G ‘MELAS’ (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) mutation in 64 (24%) patients.

Cardiac involvement was present at baseline in 31% (81) of patients, and patients presenting with single large-scale mtDNA deletions or the m.3243A>G mutation had the highest prevalence of cardiac abnormalities. This includes conduction system disease in 26 patients (10%), premature ventricular complexes (PVCs) in 17 patients, non-sustained ventricular tachycardia in a single patient, paroxysmal atrial fibrillation in 5, and permanent atrial fibrillation in 1 patient. Hypertrophic cardiomyopathy was present in 48 patients (18%), mostly in carriers of the m.3243A>G mutation.

First of all, the results with regard to the prevalence of mitochondrial mutations are in concordance with other investigations, where it has been shown that, on the one hand, specific mtDNA mutations may present with different cardiac phenotypes and, on the other hand, specific cardiac involvement can occur in patients

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with different mtDNA mutations, suggesting distinct patterns of cardiac involvement. This was summarized in 2012, with hypertrophic cardiomyopathy more frequently associated with mt-tRNA mutations than dilated cardiomyopathy, and atrioventricular (AV) block as a feature of Kearns–Sayre syndrome (KKS) most often induced by large-scale mtDNA mutations.

**Major adverse cardiac events in patients with mitochondrial DNA mutations**

As the endpoint of the survival analysis reported here, the incidence of a first MACE (major adverse cardiac event), which included sudden death, resuscitated cardiac arrest, death due to HF, third-degree atrioventricular (AV) block, type II second-degree AV block, sinus node dysfunction, cardiac transplantation, and hospitalization for HF was identified. During the medium follow-up of 7 years, 25 patients (10%) suffered from a MACE and 48 patients died, including 8 from HF. The subgroup analyses showed that the wide variability in cardiac abnormalities as well as nearly all MACEs observed in the entire sample were present in each genetic subgroup. The large-scale mtDNA deletions and the ‘MELAS’ m.3243A>G mutation in MT-TL1 were associated with the most predictable cardiac abnormalities and with the highest risk of a MACE. Patients with large-scale mtDNA deletions had the highest prevalence of conduction system disease, and were at high risk of complete AV block and sudden death, LV systolic dysfunction, and end-stage HF. Patients with the m.3243A>G mutation presented mainly with progressive concentric, hypertrophic cardiomyopathy, often complicated by advanced congestive HF.

In contrast, a previous follow-up investigation reported a 5-year event-free survival of 67% in 32 patients with mtDNA diseases. It was summarized that a high prevalence of cardiovascular involvement in adults with mtDNA disease was demonstrated, with ECG abnormalities representing the most common abnormality. Nevertheless, cardiac arrhythmias in this study including AV block and progressive systolic dysfunction occurred only in a minority. On the other hand, by review of the published literature, a prevalence of conduction system disease of 84% for patients with KKS was established. For that reason, AV block forms part of the diagnostic criteria of KKS. Conduction system disease occurs commonly (5–10%) in patients with mtDNA disease, especially in patients with neuromuscular disease, where progression to high-grade AV block often needs consideration of early intervention.

**Predictors of major adverse cardiac events**

Factors associated with a MACE by single variable analysis identified by Whabi et al. included retinopathy, renal insufficiency, diabetes, first-degree AV block, intraventricular conduction block, PVCs, atrial fibrillation, and LV hypertrophy. In the multiple variable Cox regression model, intraventricular conduction block, diabetes, PVCs, and LV hypertrophy were identified as independent predictors of a MACE, which might facilitate the identification of patients at the highest risk. Diabetes, a common manifestation of mitochondrial disease, may represent either an additional form of injury to the myocardium or a global marker of the severity of mitochondrial disease, in contrast to the three other risk factors, which reflect early myocardial or electrical system involvement. In patients with the m.3243A>G mutation, diabetes has been previously associated with a more prominent LV hypertrophy.

At 10% in the entire group of patients, the incidence of MACES ranged from 1.7% in the subgroup of patients with zero risk factors, to 15% in the subgroup with one, and to 42% in the subgroup with ≥2 risk factors. The authors stated that, despite the complexity and heterogeneity of cardiac involvement in mitochondrial diseases, relatively simple investigations, including clinical examination, 12-lead and 24-h ambulatory ECG, and a standard transthoracic echocardiogram, can effectively stratify the risk. This evaluation should be offered to all patients at the time of diagnosis and during follow-up, at intervals depending on their risk profile.

In summary, the prevalence of cardiac involvement in this population with mtDNA mutations was high and had a prominent impact on the long-term outcome, as 10% of the patients either died from cardiac death or sustained a life-threatening MACE. Secondly, the genetic subgroup which would benefit the most from the above-mentioned strategy are patients presenting with single large-scale mtDNA deletions, who were at highest risk of complete AV block and sudden death.

The most important implication arising from the data published by Whabi et al. is that cardiac involvement in mtDNA disease is progressive and, together with additional risk factors such as intraventricular conduction block, diabetes, PVCs, and LV hypertrophy, is an independent predictor of morbidity and early mortality.

For that reason, the definite diagnosis of mtDNA disease in patients presenting with oligosymptomatic states to complex syndromes involving neurological, cardiological, ophthalmological, endocrine, or gastroenterological features (for more details see Figure 1) should be made as soon as possible. To promote the multidisciplinary care of patients, cardiologists should refer patients with suspicion of mtDNA disease to a geneticist or mitochondrial specialist to obtain a definite diagnosis. Suspicion should be higher if there is a presence of additional symptoms, which need urgent collaboration with other departments to make the accurate diagnosis and arrange the appropriate care.

**Achieving the diagnosis is most often complex and requires a multidisciplinary approach**

All patients under suspicion of having mtDNA disease should be seen by a cardiologist with understanding of the condition. Cardiologists should be familiar with the unique non-Mendelian inheritance pattern and the distinct pathophysiology of this disease complex.

Additionally, we should bear in mind that a relevant proportion of patients are presenting first with neurological symptoms. For that reason, according to the guidelines of the German Society of Neurology, patients with neurological symptoms should be seen by a neurologist with understanding of mtDNA disease, who should
immediately consult a cardiologist to perform 12-lead ECG and echocardiography in almost all patients.

Recently, a detailed clinical update with algorithms for the assessment of mtDNA disease using blood or urine DNA or, most importantly, tissue from the affected organ was published in the *European Heart Journal*. In the same paper, a very useful clinical algorithm for cardiac screening and management of patients with mtDNA diseases was proposed. This algorithm includes suggestions for an early therapy especially in patients with rhythm disturbances according to the international guidelines, as well as suggestions for clinical long-term follow-up including annual clinical examination, 12-lead ECG, and echocardiography for these patients.

Only by using a comprehensive clinical algorithm in a multidisciplinary approach it will hopefully be possible to diagnose patients with mtDNA mutations correctly as soon as possible and to treat patient under high risk appropriately. As disease-specific treatment options are so far not on the horizon, clinicians should be aware of all established supportive strategies.

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**References**


Left ventricular free wall rupture contained by an apical pseudo-aneurysm

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A 76-year-old male patient was admitted for exertional shortness of breath for the last month. Physical examination showed bipulmonary hypventilation and fine crackles. The electrocardiogram was compatible with sequelae of anterior myocardial infarction, with borderline troponin-T levels, and no elevation of creatinine-kinase. Trans thoracic echocardiography confirmed a large anterior myocardial infarction with a dilated left ventricle (LV) and a large antero-septo-apical akin esia, connected with an apical pseudo-aneurysm (asterisk) (Panels A and B) through an apical free wall rupture (arrow) (Panels A and B). Left ventricle ejection fraction (EF) was 20–25% with a preserved right ventricular function. Computed tomographic angiography confirmed an LV apical aneurysmal dilatation connected through an apical rupture (arrow) with a pseudo-aneurysm (asterisk) (Panels D and E). His coronary angiography showed single vessel disease with total occlusion of the proximal left anterior descending coronary artery without patent distal lumen (arrow) (Panel C).

The patient underwent urgent open heart surgery. After opening the chest, it was observed that the LV was dilated with a free wall rupture (dotted arrow) of the apex, which was contained by a pseudo-aneurysm formation (solid arrow) (Panel G). The Dor technique was used for endo-exclusion of the aneurysm by a patch (arrow) (Panel H) and closure of the LV apical free wall rupture (arrows) (Panel I). Intra-operative transoesophageal echocardiography showed normal LV size without intra-cavitary thrombus, and the excluded apical aneurysm (asterisk) by endopatch (arrow) (Panel F). His exercise capacity increased within 6 months after surgery, with an LVEF of 40%.

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