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# Mitochondrial Cardiomyopathy

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## Abstract

Mitochondrial diseases are multisystem disorders, resulting from mitochondrial electron transport chain dysfunction and oxidative phosphorylation due to pathogenic variants in mitochondrial or nuclear DNA. The clinical presentations are variable in the age of onset, symptoms, and range and severity of organ involvement. Diagnosis requires a multidisciplinary approach and is based on clinical symptoms, laboratory tests, histopathological findings, and genetic analysis. Due to the multi-organ involvement, the evaluation of mitochondrial diseases should include a systemic screening for all targeted organs, including neuroimaging, ophthalmology, and hearing examinations. Cardiac involvement should be evaluated at the time of diagnosis, as cardiac involvement is an independent predictor of morbidity and early mortality, even in asymptomatic cases. Hypertrophic cardiomyopathy is the most common cardiac manifestation; however, mitochondrial cardiomyopathy might also present as left ventricular non-compaction (LVNC) or as dilated, histiocytoid, or restrictive cardiomyopathy. The precise evaluation of cardiac involvement is of clinical use in predicting future cardiac events and prognosis. Despite advancements in molecular biology, no satisfactory treatments for mitochondrial diseases exist. Treatment remains largely symptomatic and does not significantly alter disease progression.

**Keywords:** mitochondrial disease, electron transport chain dysfunction, genetic variants, cardiomyopathy, multimodality imaging

## 1. Introduction

Disruption of the mitochondrial respiratory chain results in a diverse and variable group of multisystem disorders, known as mitochondrial diseases, which are progressive in nature. Since mitochondrial diseases comprise multi-organ system disorders, the clinical

manifestations are nonspecific. The varied and nonspecific nature of the early symptoms often renders the diagnosis of mitochondrial diseases difficult for physicians. Furthermore, the myocardium is one of the most affected tissues in mitochondrial cardiomyopathy because of its high energy demand. As cardiac involvement can be life-threatening and cause sudden death, cardiac assessment at diagnosis is necessary, even in asymptomatic cases.

Herein, we review the etiology and clinical manifestations of mitochondrial diseases, with a focus on cardiac symptoms. In addition, we review the evaluation modalities for cardiac involvement and treatment options.

## 2. Etiology

Mitochondria are rod-shaped organelles found in nearly all eukaryotic cells. Mitochondria play multiple roles in cellular processes, including calcium signaling, the generation of reactive oxygen species (ROS), and apoptosis [1–3]. The principal function of mitochondria is adenosine triphosphate (ATP) synthesis via aerobic metabolism. Mitochondria are responsible for the production of energy through the breakdown of carbohydrates and fatty acids via oxidative phosphorylation (OXPHOS). OXPHOS generates energy by coupling electron transport (complexes I, II, and IV) with ATP synthesis (complex V) through the electrochemical gradient [1–6]. Alterations in mitochondrial structure and function can impair OXPHOS, which in turn can reduce energy production, alter the cellular redox state, increase the ROS production, and dysregulate $Ca^{2+}$ homeostasis, and apoptosis [1–6]. OXPHOS disturbance can destabilize the mitochondrial DNA (mtDNA), leading to a progressive accumulation of mtDNA mutations and deterioration of mitochondrial function [3, 6].

The transfer of electrons among respiratory chain enzyme complexes I–IV drives proton transfer across the inner mitochondrial membrane, forming an electrochemical gradient utilized by complex V to generate ATP. The mitochondrial genome encodes all of the ribosomal RNAs (mt-rRNAs), and most of the transfer RNAs (mt-tRNAs), needed for the translation of these protein-coding sequences within the mitochondria. The majority of mitochondria proteins is encoded in the nuclear DNA (nDNA), thought to have been transferred to the nucleus from the ancestral mitochondrial genome. However, the mtDNA encodes 13 polypeptides that are critical components of the OXPHOS enzyme complexes, 2 rRNAs (16S and 12S), and 22 tRNAs, which are required for the translation of the proteins encoded by the organelle genome [3, 6].

Mitochondria have their own genetic system, as mitochondria are thought to have evolved from bacteria. Mitochondrial genomes are usually circular DNA molecules, like those of bacteria, which are present in multiple copies per organelle. Since almost all of the mtDNA in fertilized eggs are contributed by the oocyte rather than by the sperm, germline mutations in the mtDNA are transmitted to the next generation in the maternal line [3, 6]. Although mtDNA mutations are exclusively maternally inherited, nuclear mutations may be transmitted as autosomal dominant, autosomal recessive, or X-linked traits [3, 6]. Approximately, 15% of mitochondrial diseases are caused by a mutation in the mtDNA; most mitochondrial diseases are caused by mutations in the nDNA.

The multi-copy nature of mtDNA gives rise to heteroplasmy, a unique aspect of mtDNA-associated genetics, which occurs when there is coexistence of mutant and wild-type mtDNA molecules. The mtDNA in cells can be identical (homoplasmy) or a mixture of variable copies (heteroplasmy) [3]. Heteroplasmic mutations often engender variable mutation thresholds (i.e., the level to which the cell can tolerate defective mtDNA mutations). Furthermore, the threshold level varies among different organs and tissues, depending on their energy requirements. Quality control can occur by fission/fusion, allowing the segregation of damaged mitochondria, mitophagy for the removal of damaged mitochondria, and, ultimately, cell death when the damage is too severe [7]. Thus, phenotypic variability is, at least in part, due to heteroplasmy, with varying proportions of mutant and wild-type mtDNA in different tissues. In addition, the tissue-specific mtDNA mutation load and threshold may affect the onset and extent of the clinical manifestations. Moreover, some nuclear genetic mutations can result in clinical phenotypes that are similar to those due to mtDNA variants.

## 3. Mitochondrial diseases associated with cardiomyopathy

Mitochondrial diseases comprise a clinically heterogeneous group of disorders that arise as a result of mitochondrial respiratory chain dysfunction. The clinical presentations are variable in terms of the age of onset, symptoms, and range and severity of organ involvement. While some mitochondrial disorders only affect a single organ, multiple organ systems are generally involved. High-energy-demanding tissues, such as the cardiac muscles, kidneys, liver, and central nervous system, are the most commonly affected tissues. Cardiomyopathies associated with defects in the electron transport chain (ETC) complex subunits and their assembly factors, mt-tRNAs, mt-rRNAs, ribosomal proteins, translation factors, mtDNA maintenance factors, and CoQ10 synthesis frequently manifest in mitochondrial diseases, as reviewed below (**Table 1**).

### 3.1. Deficiencies in the ETC complexes

ETC complex I deficiency accounts for approximately 30% of all cases of childhood-onset mitochondrial diseases and is clinically and genetically heterogeneous [8]. ETC complex I deficiency can present with hypertrophic cardiomyopathy, which might be isolated or associated with multi-organ disease [8]. ETC complex II is entirely nuclear-encoded and functions within the OXPHOS chain [9]. Hypertrophic and dilated cardiomyopathies, and left ventricular non-compaction, have been reported in patients with ETC complex II deficiency [9]. ETC complex III deficiency is one of the least common respiratory chain defects and is generally caused by mutations in the nDNA encoding the *BCS1L*, *UQCRB*, and *UQCRQ* genes and the mtDNA encoding the *MTCYB* gene, which encodes cytochrome b [9, 10]. Mutations in cytochrome b are associated with histiocytoid cardiomyopathy [10]. Mitochondrial complex III deficiency can be fatal in childhood; however, individuals with mild signs and symptoms can survive into adulthood [10]. ETC complex IV, or cytochrome c oxidase (COX), is the terminal enzyme of the respiratory chain and catalyzes the transfer of the reducing equivalents from cytochrome c to molecular oxygen. COX deficiency often leads to early-onset severe neuromuscular disease, and hypertrophic cardiomyopathy is the most common cardiomyopathy.

| Syndrome | Clinical feature | Cardiac manifestation | DNA mutation, Mode of inheritance |
|---|---|---|---|
| MELAS | Myopathy, Encephalopathy, Lactic acidosis, Stroke-like episodes, Diabetes mellitus, Short stature, Sensorineural hearing loss | Hypertrophic cardiomyopathy, bundle branch block | t-RNA gene mutation (m.3243A>G), Maternal inheritance |
| MERRF | Myoclonus, Epilepsy, Ataxia, Muscle weakness, Sensorineural hearing loss, Short stature, Lactic acidosis | Dilated and histyocitoid cardiomyopathy, WPW syndrome | t-RNA gene mutation (m.8344A>G), Maternal inheritance |
| Coenzyme Q10 deficiency | Encephalopathy, Myopathy, Ataxia, Nephrotic syndrome | Hypertrophic cardiomyopathy | Mutations in gene involved in CoQ10 biosynthesis (CoQ2,4,6 etc) |
| Kearns-Sayre syndrome | External opthalmoplegia, Pigmentary retinopathy | Conduction defects, Dilated cardiomyopathy | single, large-scale mtDNA deletions |
| Friedreich ataxia | Ataxia, Dysarthria, Peripheral sensory neuropathy, Diabetes Mellitus | Hypertrophic cardiomyopathy | Defects in iron-sulfur cluster (FXN), Autosomal recessive inheritance |
| Barth syndrome | Myopathy, Growth retardation, Neutropenia | Non-compaction and dilated cardiomyopathies, supraventricular and ventricular tachycardia | 3-Methylglutaconic aciduria type 2(TAZ), X-linked |

MELAS: mitochondrial encephalopathy, lactic acidosis and stroke-like episodes
MERRF: Myoclonic epilepsy and ragged-red fiber

**Table 1.** Mitochondrial diseases associated with cardiomyopathy.

Mitochondrial mutations in the $MT\text{-}CO_2$ and $MT\text{-}CO_3$ genes, which encode complex IV, have been reported in dilated cardiomyopathy [11]. In addition, multiple OXPHOS complex deficiencies can result in mitochondrial dysfunction. Mutations in mt-tRNAs, mitochondrial ribosomes, and posttranscriptional modifications of mt-tRNAs may result in mitochondrial translation defects and multiple OXPHOS deficiencies [2, 4].

### 3.2. Mt-tRNA genes

Mutations in several mt-tRNA genes (e.g., *MTCK* and *MTTL1*) have been reported to cause mitochondrial diseases or isolated cardiomyopathies [12–17]. Cardiomyopathies associated with variants in genes encoding mt-tRNAs are usually hypertrophic but can also be dilated or histiocytoid [12–17].

Mitochondrial encephalopathy, lactic acidosis, and stroke-like episode (MELAS) is a multi-system syndrome that is often devastating. The syndrome is genetically heterogeneous; however, approximately 80% of patients with MELAS syndrome harbor a heteroplasmic A-to-G transition in the tRNALeu-encoding gene at base pair 3243 in the mtDNA (3243A > G) [12, 13]. The signs and symptoms of MELAS most often appear during childhood, and early symptoms may include muscle weakness and pain, recurrent headaches, loss of appetite, vomiting, and seizures. [18–20]. Most affected individuals experience stroke-like episodes before the age of 40 years [18–20]. These episodes often involve temporary muscle weakness on one side of the body, altered consciousness, vision abnormalities, seizures, and severe headaches, resembling migraines. Repeated stroke-like episodes can progressively damage the brain, leading to vision loss, movement problems, and loss of intellectual function [18–20]. Most patients with MELAS have a buildup of lactic acid in their bodies, known as lactic acidosis. Increased

acidity in the blood can lead to vomiting, abdominal pain, extreme tiredness, muscle weakness, and difficulty breathing [14, 15].

Myoclonic epilepsy and ragged-red fibers (MERRF) is a multisystem disorder characterized by myoclonus (often the first symptom), followed by generalized epilepsy, ataxia, weakness, and dementia [16, 17]. Common findings include hearing loss, short stature, optic atrophy, and cardiomyopathy with Wolff-Parkinson-White (WPW) syndrome. Pigmentary retinopathy and lipomatosis are occasionally observed. The mtDNA gene, *MT-TK*, which encodes tRNALys, is the gene most commonly associated with MERRF. The most common pathogenic variant (present in 80% of affected individuals) is an A-to-G transition at nucleotide 8344 (m.8344A > G). Pathogenic variants in *MT-TF*, *MT-TL1*, *MT-TI*, and *MT-TP* genes have also been described in a subset of patients with MERRF [3, 6].

### 3.3. CoQ10 deficiency

Coenzyme Q10 (CoQ10) shuttles electrons from complexes I and II to complex III. CoQ10 is also an antioxidant and is involved in the regulation of apoptosis and pyrimidine synthesis [21–26]. Defects in CoQ10 biosynthesis result in primary CoQ10 deficiency, which is a phenotypically and genetically heterogeneous condition with various clinical presentations, including encephalomyopathy, isolated myopathy, cerebellar ataxia, nephrotic syndrome, and infantile multisystem mitochondrial disease [21–26]. Hypertrophic cardiomyopathy has been reported with mutations in genes involved in CoQ10 biosynthesis (*COQ2*, *COQ4*, and *COQ9*) [21–26]. Although the response is variable, primary CoQ10 deficiency is treatable with CoQ10 supplementation.

### 3.4. Kearns-Sayre syndrome (KSS)

KSS is most commonly due to a 1.1–10 kb mtDNA deletion [26–28]. The KSS triad comprises external ophthalmoplegia, pigmentary retinopathy, and cardiac conduction defects [26–28]. KSS usually presents before the age of 20 years. Approximately 60% of patients with KSS have cardiac involvement, including recurrent syncope, bundle branch block, and fascicular block [26–28].

### 3.5. Friedreich ataxia

Friedreich ataxia is an autosomal recessively inherited disease caused by triplet expansion in FXN gene which encodes frataxin [29–31]. Exact function of frataxin has not been determined; however, previous studies showed frataxin is involved in the biosynthesis of Fe-S clusters [29–31]. Patients typically develop progressive ataxia at childhood [29–31]. Cardiac involvement is also frequently seen in patients with Friedreich ataxia and hypertrophic type of cardiomyopathy is most frequently observed [29–31].

### 3.6. Barth syndrome

Barth syndrome is an X-linked disorder characterized by cardiomyopathy, with skeletal myopathy, growth retardation, neutropenia, and urinary excretion of 3-methylglutaconic acid [32–34]. Barth syndrome is caused by mutations in the *TAZ* gene at Xq28, which encodes tafazzin, a phospholipid transacylase in the mitochondrial membrane [32–34]. Cardiac

manifestation is most common [35, 36]. Left ventricular non-compaction (LVNC) and dilated cardiomyopathies are common, while hypertrophic cardiomyopathy is rarely observed [35, 36]. Other cardiac manifestations of Barth syndrome include ventricular tachycardia and sudden death [35, 36]. Barth should be considered for male patients with severe cardiac failure. However, the prognosis after 5 years of age is favorable because cardiac function gradually recovers during infancy.

## 4. Diagnosis

Mitochondrial diseases constitute a broad spectrum of disorders that affect multiple organs. A maternal inheritance pattern or the presence of extra-cardiac features may raise suspicions regarding the diagnosis. Although extra-cardiac manifestations include common or nonspecific features, the particular pattern of organ involvement should alert the physician to the possibility of mitochondrial disease. Due to the multi-organ involvement, the evaluation of mitochondrial diseases should include a systemic screening of all targeted organs, including neuroimaging, hearing and ophthalmologic examinations, laboratory tests, histopathological analysis, and genetic testing (**Table 2**) [37, 38].

### 4.1. Laboratory tests

Laboratory tests should include serum creatine kinase (CK), serum fasting glucose, and hemoglobin A1c. Serum CK may be normal or mildly elevated in mitochondrial diseases. Patients with very high values in the thousands should first be evaluated for other types of myopathies like polymyositis. Diabetes mellitus is common in patients with mitochondrial diseases.

Lactic acidosis is the most recognized laboratory abnormality. The measurement of plasma or cerebrospinal fluid (CSF) lactate concentration is indicated in individuals with features of myopathy or central nervous system involvement. Markedly, elevated levels of lactate (>3 mm/L in blood or > 1.5 mm/L in cerebrospinal fluid) support a diagnosis of mitochondrial disease [39]. It is important to note that the elevated lactate level in plasma and/or CSF is neither specific nor sensitive [40, 41]. Thus, it is important to exclude other causes of lactic acidosis, such as ischemic stroke and seizures.

### 4.2. Neuroimaging

The brain is one of the most affected organs in mitochondrial diseases. In mitochondrial encephalopathy, central nervous system structures are affected differentially in their distribution and severity [42, 43]. Gray matter lesions are prevalent in MERFF and MELAS (**Figure 1A**, **B**), while white matter involvement is typically observed in KSS. Computed tomography may show basal ganglia calcification and diffuse atrophy of the cortex or cerebellum. Magnetic resonance (MR) imaging may show focal atrophy of the cortex or cerebellum, or high-intensity

| | Symptoms | Examination |
|---|---|---|
| **Systemic** | | |
| | short stature | Laboratory test: lactic acidosis |
| | fatigue | Genetic testing: mtDNA or nDNA mutation |
| | vomiting | Genetists examination |
| | growth failure | |
| | lactic acidosis | |
| **Brain and nerve** | | |
| | | CT and MRI: basal ganglia calcification, atrophy of cortex and cerebellum , ischemic lesion, lactate peak in MR sepectroscopy |
| | developmental delays | |
| | mental retardation | |
| | dementia | |
| | seizures | |
| | stroke-like episodes | |
| | migraines | |
| | ataxia | |
| | spasticity | |
| **Muscles** | | |
| | weakness | Skeletal muscle biopsy: ragged-red fibers, COX/SDH staining |
| | cramping | Neurologists examination |
| | hypotonia | |
| **Ears and Eyes** | | |
| | visual loss and blindness | Visual assessment by opthalmologist |
| | ptosis | Hearing assessment by nasopharygiologists |
| | visual field defects | |
| | opthalmoplegia | |
| | hearing loss | |
| **Heart** | | |
| | heart failure | Chest X-ray: cardiac enlargement, congestive heart failure |
| | conduction problems | Electrocardiogram: AV block, WPW syndrome |
| | ventricular pre-exciation | Echocradiography: various types of cardiomyopathy (hypertrophic is the most common type) |
| | | CMR: late gadolium enhancement |
| | | $^{99m}$Tc-MIBI, $^{123}$I-BMIPP: perfusion and metabolic abnormality |
| **Gastrointestinal** | | |
| | | Laboratory tests: hepatic dysfunction, hypoglycemia |
| | constipation | |
| | dysphagia | |
| | pseudo-obstruction | |
| **Endocrine** | | |
| | diabetes mellitus | Laboratory tests: Fasting glucose, HbA1c, Ca, PTH,FSH, LH, PRL |
| | hypoparathyroidism | |
| | gonadal failure | |
| **kidney** | | |
| | renal tubular acidosis | Laboratory tests: renal impairment |
| | proximal tubule nephropathy | |

CT: computed tomography, MR: magnetic resonance, CMR: cardiac magnetic resonance
$^{99m}$Tc-MIBI: $^{99m}$Tc-sestamibi, $^{123}$I-BMIPP: $^{123}$I-labeled 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid

**Table 2.** Clinical symptoms and examination to diagnose mitochondrial diseases.

signals on T2-weighted scans, particularly in the occipital cortex. Cerebellar atrophy is also a prominent feature. MR spectroscopy may also be of use for the detection of an elevated lactate level (**Figure 1C**) [44]. Elevated central nervous system signals on MR spectroscopy may be detected, which is associated with a shorter survival duration [45].

### 4.3. Visual and hearing assessments

Various eye signs may accompany mitochondrial disease, including bilateral optic atrophy, chronic progressive ophthalmoplegia, pigmentary retinopathy, and loss of vision [46]. Bilateral optic atrophy is typically seen in Leber's hereditary optic neuropathy (LHON) [47]. Chronic progressive external ophthalmoplegia (CPEO) is the most common ocular manifestation in mitochondrial diseases. Acute or subacute vision loss typically occurs in early adult life. Pigmentary retinopathy occurs in MELAS, Leigh syndrome, and CPEO. Retrochiasmal visual pathway and visual cortex impairments can cause homonymous hemianopia and cortical blindness. Visual loss due to retrochiasmal visual pathway impairment is most frequently seen in MELAS.

Hearing impairment is common in patients with mitochondrial disorders, affecting half of the cases over the course of the disease [38]. Hearing assessments using audiograms or brainstem auditory-evoked potentials are necessary when hearing symptoms are present. Hearing impairment is usually peripheral, with cochlear or auditory nerve dysfunction; however, the central auditory system, including the brainstem and auditory cortex, can also be affected. Peripheral hearing loss typically affects high frequencies first, followed by intermediate frequencies. The preferential involvement of high frequencies may be related to the high-energy requirements of the basal cochlea.

### 4.4. Muscle biopsy

As discussed above, the laboratory investigation of suspected mitochondrial disease is complex. Although mitochondrial disorders are characterized by a wide spectrum of clinical presentations, skeletal muscles are one of the frequently affected tissues. Whenever possible, the presence of mitochondrial disease should be assessed in the affected tissues, such as the liver, heart, or skeletal muscle. However, in vivo access to these tissues is often not possible, and muscle biopsies must serve as an alternative, even when there is no evidence of myopathy.

The histology of the affected muscles typically shows ragged-red fibers (**Figure 2A**, **B**), which can be demonstrated using modified Gomori trichrome stains, and contains a peripheral and intermyofibrillar accumulation of abnormal mitochondria. Electron microscopy can sometimes reveal subsarcolemmal and enlarged, swollen mitochondria, with irregular cristae and paracrystalline inclusions (**Figure 2C**). The histochemical analysis of COX and succinate dehydrogenase is standard for assessing mitochondrial respiratory chain function in muscle samples [48, 49].

Establishing a biochemical phenotype is not only important for candidate gene selection but also provides important information required to interpret the genetic test results. The biochemical examination of a muscle biopsy to evaluate the functional state of the mitochondria
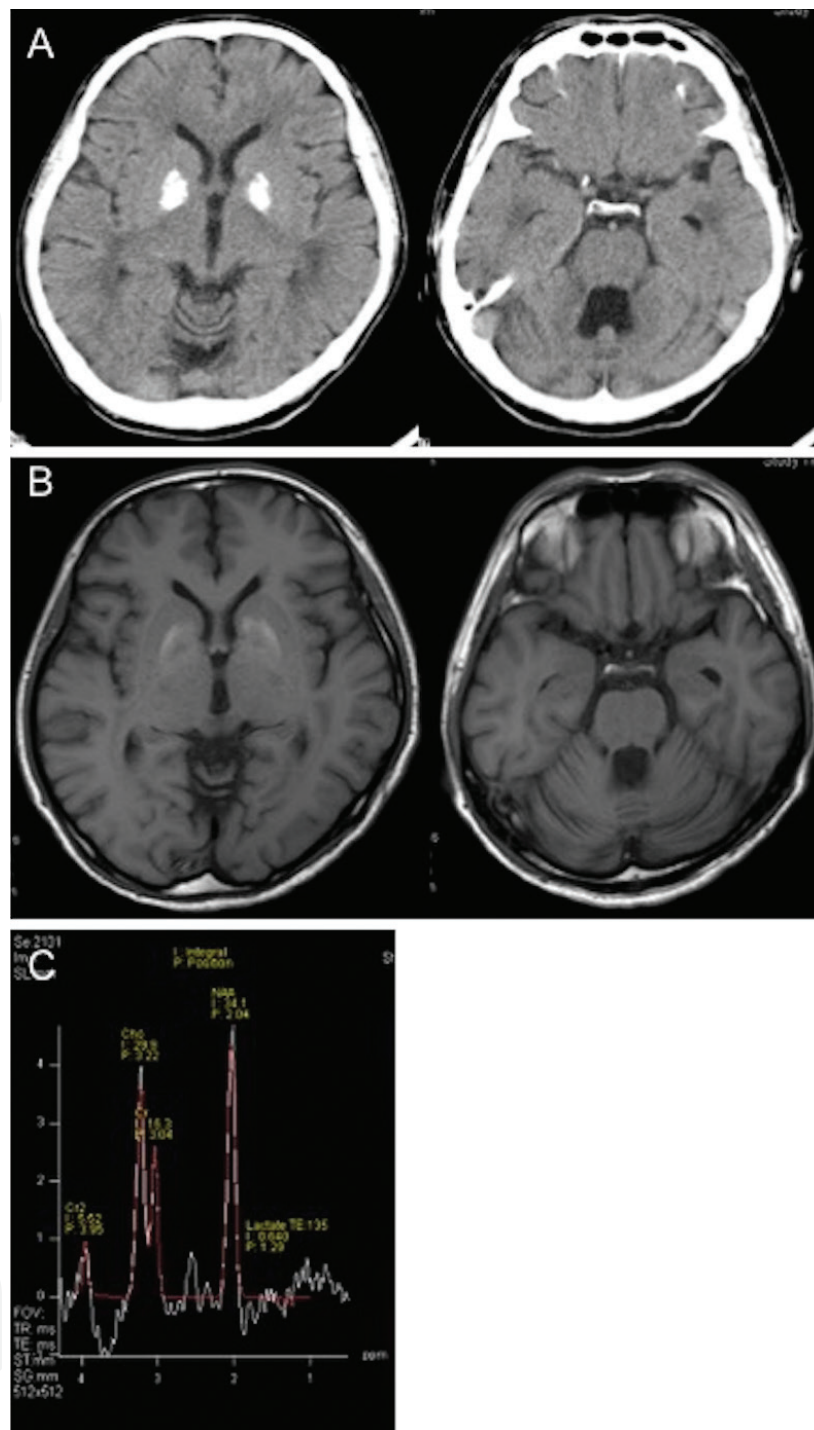
**Figure 1.** Neuroimaging: Brain computed tomography (A) and T1-weighted magnetic resonance imaging (B) show calcification in the bilateral basal ganglia and cerebellar atrophy. There is no lactate peak on magnetic resonance spectroscopy in this case (C).

is still regarded as a critical examination for patients with mitochondrial diseases. Activity measurements of oxidative phosphorylation enzymes and analyses of mitochondrial respiration, substrate oxidation, and ATP production can unveil an aberrant mitochondrial energy-generating system [50].
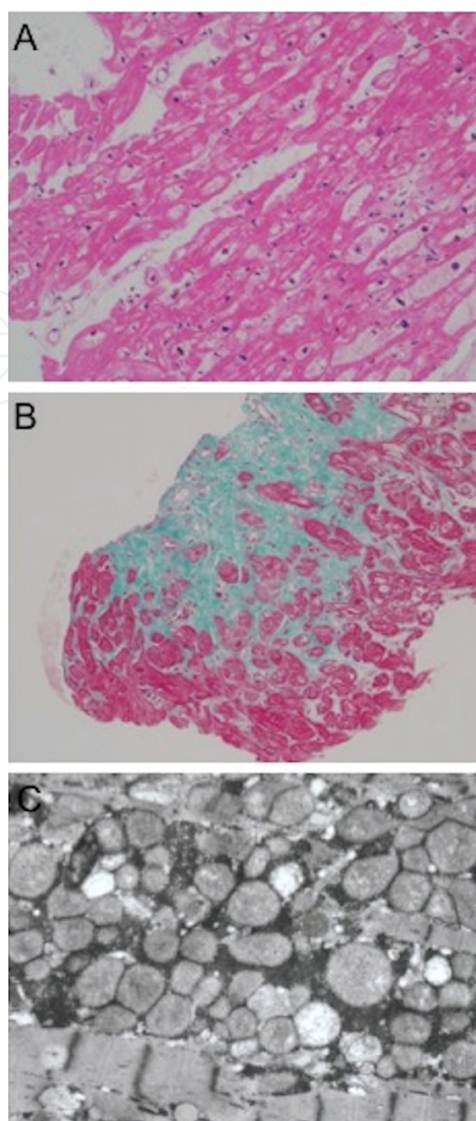
**Figure 2.** Histopathological findings: A myocardial biopsy from the endometrium of the right ventricles was performed. Hematoxylin-eosin staining shows a loss of cardiomyocytes and the enlargement of the remaining cardiomyocytes, with vacuoles (A). Elastica-Masson staining shows interstitial fibrosis (B). Electron microscope shows an increased number of mitochondria, with variable size and shape (C).

## 4.5. Molecular genetic analysis

A three-generation family history can suggest the mode of transmission, aid in the diagnosis, and direct the molecular genetic testing. Many individuals with mtDNA mutations display a cluster of clinical features that fall into a specific clinical syndrome, such as MELAS or MERRF [12]. When the presentation is classic for a maternally inherited mitochondrial syndrome, such as MELAS and MERRF, mtDNA studies should be obtained first. However, there is often considerable clinical variability, and many affected individuals do not fit into one particular category. Genotype-phenotype correlations are often obscure, and genetic analyses are frequently required for a definite diagnosis. Molecular genetic testing may be carried out on genomic DNA extracted from the blood or muscle. The ordering of molecular genetic tests and the interpretation of results require the support of an experienced clinical geneticist.

## 5. Cardiac manifestations

Because cardiac muscles are a high-energy-demanding tissue, cardiac involvement occurs in a large proportion of cases of mitochondrial diseases. Natural history studies have demonstrated that cardiac involvement is an independent predictor of morbidity and early mortality in mitochondrial diseases [2, 4, 51]. When mitochondrial disease is known or suspected, the cardiac examination should be directed toward eliciting signs of heart failure, including cardiac enlargement, elevated jugular venous pressure, auscultation of gallop, bilateral lung crackles, pitting edema, and hepatomegaly. Mitochondrial cardiomyopathies can vary in severity, from asymptomatic to severe manifestations, including heart failure, arrhythmias, and sudden cardiac death.

Patients with MELAS are particularly prone to cardiomyopathy [4, 52–54]. Hypertrophic cardiomyopathy is the most common cardiac manifestation, occurring in approximately 40% of cases [4]. However, mitochondrial cardiomyopathies might also present as LVNC or as dilated, histiocytoid, or restrictive cardiomyopathy [2, 4, 51]. In addition, the conduction system can be affected.

### 5.1. Hypertrophic remodeling

Hypertrophic remodeling is the most common form of cardiomyopathy and can mimic hypertrophic cardiomyopathy (HCM) [2, 4, 51]. Patients diagnosed as HCM may include those with mitochondrial abnormalities, especially in cases of atypical HCM. There are some differences between HCM and hypertrophic remodeling in mitochondrial cardiomyopathy. Left ventricular outflow tract obstruction is rarely observed in mitochondrial cardiomyopathy, while a progression to ventricular dilation and heart failure is more frequent than HCM [2]. A longitudinal study demonstrated that the degree of left ventricular hypertrophy (LVH) is correlated positively with left ventricular end-diastolic volume and negatively with ejection fraction in patients with MELAS [53]. These findings are unique in mitochondrial cardiomyopathy, not seen in hypertrophic cardiomyopathy due to mutations in sarcomeric proteins.

### 5.2. Dilated remodeling

Dilated remodeling, leading to heart failure, has also been occasionally reported in patients with mitochondrial diseases; however, it is less common [54]. Dilated remodeling is reported in KSS, MELAS, MERRF, and Light encephalomyopathy [54–56]; however, most of the dilated remodeling in mitochondrial diseases represents the progression from hypertrophic remodeling accompanying chamber dilation and systolic dysfunction.

### 5.3. Rare types of remodeling

LVNC is a rare finding in mitochondrial cardiomyopathy. However, among patients with LVNC, mitochondrial diseases are highly prevalent [57, 58]. Research using next-generation sequencing has revealed that mtDNA mutations, with subsequent mitochondrial dysfunction, may be key players in the etiology of LVNC. Furthermore, recent research has demonstrated

that a loss of mitochondrial intermediate presequence proteases results in LVNC [59]. LVNC is generally more frequent in male patients and tends to develop during pregnancy in female patients. Occasionally, it may disappear during the disease time course in some patients with mitochondrial diseases.

Histiocytoid remodeling is histologically characterized by morphological and functional abnormalities of the cardiomyocytes and Purkinje cells, with a cytoplasm similar to that in histiocytoid foam cells, containing glycogen and lipids [60]. This type of remodeling has been reported exclusively in mitochondrial diseases.

### 5.4. Conduction system abnormalities

Conduction system dysfunction commonly occurs in patients with mitochondrial diseases. The diagnostic criteria for KSS include atrioventricular block, given its high prevalence rate in KSS [61–64]. Conduction system disease occurs, albeit less commonly, in 5–10% of patients with other forms of mtDNA disease, with atrioventricular or intraventricular conduction disturbances reported in association with m.3243A > G and m.8344A > G mutations [2, 4, 51–53, 65].

In patients with mitochondrial diseases, progression to lethal atrioventricular block is often unpredictable, which requires the recognition of any conduction system abnormalities and consideration of intervention at early phase. Early deaths in patients with KSS may be attributable to infranodal heart block. Furthermore, WPW syndrome and conduction block are common in patients with mitochondrial diseases [66].

### 5.5. Rare manifestations

Pulmonary artery syndrome has been observed in patients with MELAS syndrome, as well as in patients with hyperuricemia, pulmonary hypertension, renal failure in infancy, and alkalosis (HUPRA) syndrome. HUPRA syndrome is associated with mutations in *SARS*, which encodes mitochondrial seryl-tRNA synthetase [66]. Furthermore, congenital cardiac abnormalities are observed in microphthalmia with linear skin lesions, which is associated with holocytochrome-c-type synthetase and *COX7B* mutations [67].

## 6. Evaluation of the cardiac manifestation severity

Multiple imaging modalities exist for differentiating viable myocardium from scar tissue in territories with contractile dysfunction [67]. Cardiac involvement should be evaluated at the diagnosis in all patients with mitochondrial diseases, irrespective of their symptoms, as the cardiomyopathy can remain asymptomatic until reaching an advanced stage. Because of the heterogeneous and variable manifestation of mitochondrial cardiomyopathies, the evaluation of the extent and severity of the cardiac damage is rather difficult. However, the evaluation and follow-up of cardiac involvement are quite important, as cardiac involvement is the major cause of death in mitochondrial diseases. Below, we review here the current status of each relevant imaging modality for the assessment of mitochondrial cardiomyopathy.

### 6.1. Cardiac MR (CMR) imaging

With tissue characterization using late gadolinium enhancement (LGE) and T1 and T2 mapping, the underlying etiology of the heart failure can be readily established [68, 69]. Gadolinium is extracellular and resides in the interstitial space. LGE refers to the discrimination of regions of scar tissue, necrosis, and/or inflammation from normal tissue by the prolonged retention of gadolinium-based contrast agents (**Figure 3A, B**) [69, 70]. CMR is a noninvasive tool that accurately identifies and quantifies myocardial fibrosis. Nonischemic cardiomyopathy can be distinguished from ischemic cardiomyopathy, as a subendocardial or transmural LGE pattern concordant with the coronary artery supply is indicative of ischemic cardiomyopathy (necrosis begins in the subendocardium and progresses toward the epicardial area). However, nonischemic cardiomyopathies, including sarcoidosis, amyloidosis, and Fabry's disease, show various LGE patterns [71–74]. Extensive amounts of LGE can be predictive of subsequent remodeling and an evolution toward the end stage [75, 76]. In addition, the presence and extent of LGE in cardiomyopathies are associated with adverse cardiovascular outcomes and a poor response to standard medical and interventional therapies [75, 76]. Furthermore, abnormal myocardial perfusion reserve and fibrosis occur before cardiac damage becomes symptomatic in patients with Friedreich ataxia [77]. Thus, CMR may be useful in detecting trivial myocardial damage in the early stages of mitochondrial cardiomyopathy and in evaluating the extent of cardiac damage and assessing the prognosis in cardiomyopathies.

### 6.2. $^{99m}$Tc-MIBI cardiac scintigraphy

$^{99m}$Tc-sestamibi (MIBI) is a lipophilic cation. Myocardial uptake and the retention of $^{99m}$Tc-MIBI involve passive diffusion across the plasma and mitochondrial membranes. Cellular influx of the tracer is driven by the inside negative plasma and mitochondrial inner membrane potentials, which concentrate the tracer within the cytosol and mitochondria [78, 79]. The retention of $^{99m}$Tc-MIBI in the mitochondria is related to mitochondrial function (**Figure 3C**). The washout rate of $^{99m}$Tc-MIBI is calculated from the segmental counts in the early and delayed images. Recent human studies on patients with congestive heart failure have shown that the myocardial washout rate of $^{99m}$Tc-MIBI is a novel marker for the diagnosis of myocardial damage or dysfunction, providing prognostic information [80, 81]. $^{99m}$Tc-MIBI is commonly used as a myocardial perfusion imaging tracer for the detection of significant coronary artery disease. Furthermore, an impaired $^{99m}$Tc-MIBI washout may predict mitochondrial dysfunction, and the impairment of myocardial contractile and relaxation reserves during dobutamine stress in patients with HCM or dilated cardiomyopathy [81]. In patients with MELAS, decreased $^{99m}$Tc-MIBI uptake and increased MIBI washout are observed, which correlate inversely with the left ventricular ejection fraction [82–88]. Thus, the $^{99m}$Tc-MIBI washout rate and a disturbed uptake of $^{99m}$Tc-MIBI are indicators of the severity of mitochondrial damage in mitochondrial cardiomyopathy.

### 6.3. $^{123}$I-BMIPP scintigraphy

As free fatty acids are the main energy source of the heart under aerobic conditions, the evaluation of myocardial fatty acid metabolism is useful in understanding the pathophysiological
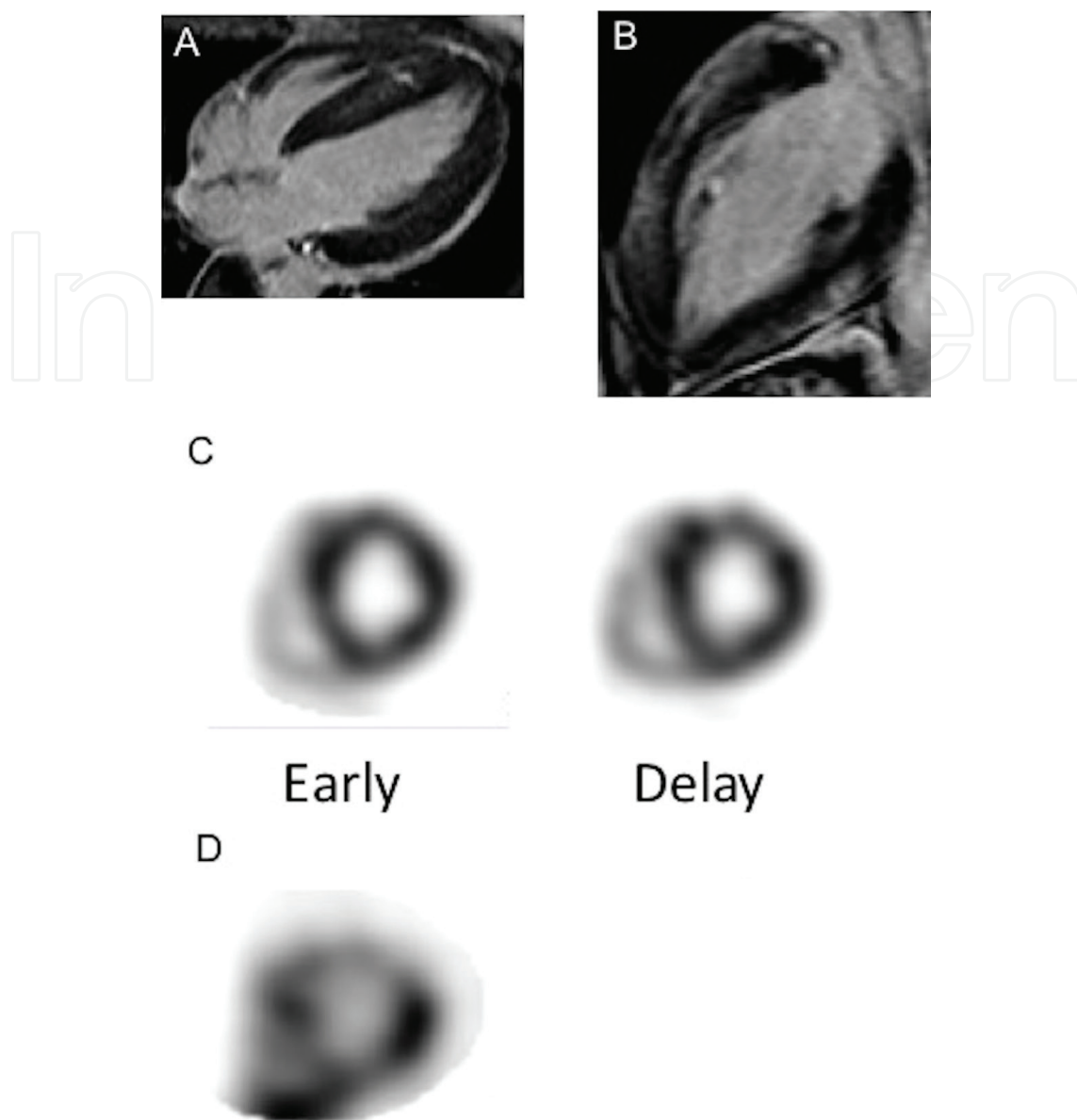
**Figure 3.** Multimodality imaging: Cardiac magnetic resonance reveals regional wall motion abnormalities, with thickening of both the left and right ventricular walls (A). Late gadolinium enhancement is observed in the middle layers of the anterior and interventricular septum and inferior walls, partially extending into the epicardium (B). Decreased uptake of ^{123}I-labeled 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid (^{123}I-BMIPP) is observed in the anterior and interventricular septum and inferior walls (C). Preserved uptake of ^{99m}Tc-sestamibi (MIBI) in the early phase is shown (D). Global ^{99m}Tc-MIBI washout rate is increased, which is one of characteristic features of mitochondrial cardiomyopathy (24.74% vs. control 11 ± 5%).

conditions of various heart diseases [85]. ^{123}I-labeled 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP) is a radiolabeled fatty acid tracer that can be used with single photon emission tomography (SPECT) to evaluate fatty acid metabolism [86–88]. Areas of the myocardium with reduced BMIPP uptake, relative to that for myocardial perfusion following revascularization for acute myocardial infarctions, suggest the presence of metabolically dysfunctional myocardium, which may indicate a lower likelihood of functional recovery [89–92].

Myocardial metabolism abnormalities on $^{123}$I-BMIPP scintigraphy are related to the severity of heart failure. $^{123}$I-BMIPP scintigraphy can detect minor metabolic abnormalities, even when echocardiography fails to show any abnormality (**Figure 3D**) [93]. Many previous case reports have demonstrated that increased uptake of $^{123}$I-BMIPP in mitochondrial cardiomyopathy is a consequence of suppressed fatty acid metabolism due to enhanced glucose utilization.

### 6.4. Multimodality evaluations

Current imaging methods focus on the evaluation of myocardial anatomy and function. However, the detection of perfusion and metabolic abnormalities using SPECT may aid in understanding the extent and severity of the myocardial damage.

Although previous case reports suggest that a decreased uptake of $^{99m}$Tc-MIBI and increased uptake of $^{123}$I-BMIPP are characteristic patterns in mitochondrial cardiomyopathies [82, 83], our group reported a unique case demonstrating a non-decreased $^{99m}$Tc-MIBI/$^{123}$I-BMIPP mismatch pattern [84]. In this previous report, we also compared the findings on scintigraphy, CMR imaging, and histopathology. Inhomogeneous LGE intensity reflects scattered viable myocytes and surrounding fibrosis, while preserved uptake of $^{99m}$Tc-MIBI may reflect preserved blood flow and a volume effect of the left ventricular wall from the histopathological investigation. Although the $^{99m}$Tc-MIBI/$^{123}$I-BMIPP mismatch pattern in our case may reflect a nonspecific phenomenon in patients with dilated cardiomyopathy, the diverse patterns of myocardial damage may reflect different stages or diverse manifestations of mitochondrial cardiomyopathies.

Multimodality studies with cardiac scintigraphy, CMR imaging, and histopathology may unveil the current status of metabolic and perfusion abnormalities, myocyte damage, and the severity and future progression of mitochondrial cardiomyopathies. Comparisons between imaging modalities and histopathological findings may also aid in the understanding of the underlying etiology; however, further studies and an accumulation of data are required. Furthermore, molecular imaging might provide a perspective on the investigation of mitochondrial function of the myocardium in vivo, noninvasively and quantitatively, in the near future. Moreover, the response to therapeutic interventions could be monitored using these methods.

## 7. Treatments

Currently, there are no satisfactory therapies available for mitochondrial diseases. Treatment remains largely symptomatic and does not significantly alter the progression of the disease [94–96].

Exercise can be helpful for patients with mitochondrial disease. In healthy individuals, a lack of exercise leads to an overall reduction in mitochondrial ETC activity, whereas endurance training can improve ETC activity, and resistance training can stimulate the incorporation of satellite cells into existing muscle fibers. Resistance training might also improve

mitochondrial function. Although no specific dietary manipulation has shown a consistent benefit for individuals with mitochondrial diseases, pharmacologic strategies include the use of various dietary supplements. Therapeutic strategies for mitochondrial diseases include the use of agents that enhance ETC function and mitochondrial biogenesis, agents that act as an energy buffer, antioxidants, and gene therapy [78, 79, 97]. However, most attempted strategies have turned out to be failures [98–100]. CoQ10 and its synthetic analogues are the only agents which have shown therapeutic benefits for mitochondrial diseases with CoQ10 deficiency [101–103]. Oral CoQ10 supplementation may alleviate the progression of encephalopathy.

Gene therapy has shown promising results in treating LHON. Approximately, 70% of individuals with LHON have pathogenic variants in the mtDNA gene encoding subunit 4 of complex IV (*MT-ND4*). The adeno-associated virus (AAV) can carry the mitochondrial and mitochondrial targeting genes, and the viral capsid, VP2, can be fused with an AAV mitochondrial-targeting sequence to the mitochondria, achieving ND4 expression. Wild-type ND4 expression in cells with an ND4 mutation leads to the restoration of defective ATP synthesis [104]. In addition, clinical studies have shown an improvement in the average acuity for patients with LHON and bilateral vision loss with the use of this therapy [105].

It is usually difficult to improve cardiac function once deterioration in cardiac function occurs. In patients with cardiomyopathy, early intervention with beta-blockers and an angiotensin-converting enzyme (ACE) inhibitor is thought to delay cardiomyopathy progression, as it does in other causes of heart failure. Recommendations for the management of hypertrophic remodeling in mtDNA diseases are reliant on clinical studies in HCM and LVH. Calcium channel antagonists and beta-blockers are recommended in symptomatic patients or in those with symptomatic LVH and HCM. Beta-blockers, ACE inhibitors, and angiotensin receptor blockers have been demonstrated to reduce LVH in the general population [106]. Given the progressive nature of hypertrophic remodeling in mitochondrial diseases, these drugs are often started with the first appreciation of LVH in mitochondrial cardiomyopathy.

American and European guidelines recommend permanent pacemaker implantation at an early stage of conduction system dysfunction in patients with mitochondrial diseases, due to its unpredictable progression. Rarely, heart transplantations have been performed in patients with mitochondrial cardiomyopathy when the clinical manifestation was limited to the myocardium and extra-cardiac manifestations were relatively mild and nonprogressive [107–119].

## 8. Conclusion

Myocardium is one of the most frequently affected tissues in mitochondrial diseases because of its high energy demand. The clinical presentations are variable in terms of the age of onset, symptoms, and range and severity of organ involvement. Since cardiac involvement is an independent predictor of morbidity and early mortality, careful and accurate examination of cardiac damage is required. Current imaging methods focus on the evaluation of myocardial anatomy and function; however, the detection of perfusion and metabolic abnormalities using SPECT may aid in understanding the extent and severity of the myocardial damage in each patient.

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## Conflict of interest

The authors have no conflicts of interest to declare.

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