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Review

Cardiac manifestations of primary mitochondrial disorders

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ABSTRACT

Objectives: One of the most frequently affected organs in mitochondrial disorders (MIDs), defined as hereditary diseases due to affection of the mitochondrial energy metabolism, is the heart. Cardiac involvement (CI) in MIDs has therapeutic and prognostic implications. This review aims at summarizing and discussing the various cardiac manifestations in MIDs.
Methods: Data for this review were identified by searches of MEDLINE, Current Contents, and PubMed using appropriate search terms.
Results: CI in MIDs may be classified according to various different criteria. In the present review cardiac abnormalities in MIDs are discussed according to their frequency with which they occur. CI in MIDs includes cardiomyopathy, arrhythmias, heart failure, pulmonary hypertension, dilation of the aortic root, pericardial effusion, coronary heart disease, autonomous nervous system dysfunction, congenital heart defects, or sudden cardiac death. The most frequent among the cardiomyopathies is hypertrophic cardiomyopathy, followed by dilated cardiomyopathy, and noncompaction.
Conclusions: CI in MID is more variable and prevalent than previously thought. All tissues of the heart may be variably affected. The most frequently affected tissue is the myocardium. MIDs should be included in the differential diagnoses of cardiac disease.

1. Introduction

Mitochondrial disorders (MIDs) are defined as hereditary or sporadic disorders due to impaired mitochondrial energy metabolism [1]. MIDs are multisystem diseases either already at onset of clinical manifestations or later during the disease course [1]. Though cardiac involvement (CI) in MIDs is increasingly recognized, practicing cardiologists are still under-informed and frequently do not raise the suspicion of a mitochondrial background of cardiac disease. This is most likely the reason why the prevalence of CI in MIDs is still underestimated [2]. The incidence of MIDs, however, was estimated as 1:5000–1:8500 in 2000 and 2005 respectively. In 2008 the incidence of "at risk" carriers of mtDNA mutations in the UK was estimated at 1:10,000 adults. Detection of CI in MIDs is important since the prognosis may be better the earlier it is detected and treated. Previous studies have shown that the survival of MID patients decreases drastically when there is CI in MIDs [3]. Since the heart, as well as the brain and the muscle, is mainly dependent on aerobic respiration for its energy requirement [4,5], the heart is one of the organs most frequently affected in MIDs [6,7]. Generally, tissues with high aerobic metabolism demand are more frequently affected in MIDs than tissues with low aerobic energy demand [8]. Though cardiomyocytes differ from myocytes in many ways, cardiac mitochondria have also some similarities with mitochondria of other organs. Particularly, the continuously beating heart has different energetic requirements than the skeletal muscle, as reflected by variable respiratory control ratios [9]. This review aims at summarizing and discussing cardiac manifestations in MIDs and to sensitize the clinical cardiologist for a possible mitochondrial background of common cardiologic abnormalities. It will not cover pathogenetic, diagnostic, or therapeutic issues.

2. Methods

Data for this review were identified by searches of MEDLINE and Current Contents and references from relevant articles using the search terms "mitochondrial disorder", "metabolic myopathy", "mitochondrial cytopathy", "mitochondriopathy" in combination with

Abbreviations: AFIB, Atrial fibrillation; AFLU, Atrial flutter; AV, Atrio-ventricular; CI, Cardiac involvement; CMP, Cardiomyopathy; CPEO, Chronic progressive external ophthalmoplegia; dCMP, Dilated CMP; hCMP, Hypertrophic CMP; HUPRA, Pulmonary hypertension, renal failure in infancy and alkalosis syndrome; KSS, Kearns–Sayre syndrome; LAH, Left anterior hemiblock; LBBB, Left bundle branch block; LGE, Late gadolinium enhancement; LHON, Leber's hereditary optic neuropathy; LVHT, Left ventricular hypertrabeculation/noncompaction; MDS, Mitochondrial depletion syndrome; MELAS, Mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes; MERRF, Myoclonic epilepsy with ragged-red fibers; MID, Mitochondrial disorder; MLASA, Mitochondrial myopathy, lactic acidosis, and sideroblastic anemia; MRI, Magnetic resonance imaging; mtDNA, Mitochondrial DNA; NARP, Neuropathy, ataxia, retinitis pigmentosa syndrome; nDNA, Nuclear DNA; PAH, Pulmonary artery hypertension; RBBB, Right bundle branch block; RCC, Respiratory chain complex; rCMP, Restrictive CMP; rRNA, Ribosomal RNA; tRNA, Transfer RNA; TTS, Takotsubo syndrome; VT, Ventricular tachycardia; WPW, Wolff–Parkinson–White syndrome.

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"cardiac", "myocardium", "heart", "cardiomyopathy", "coronary arteries", "pulmonary hypertension", "systolic dysfunction", "diastolic dysfunction", "arrhythmias", "heart failure", "late enhancement", "myocardial fibrosis", "pericardial effusion", "valvulopathy", "murmurs", and "sudden cardiac death". Randomized (blinded or open label) clinical trials, longitudinal studies, case series, and case reports were considered. Only articles about humans and published in English between 1966 and 2013 were considered. All age groups and both sexes were considered. Included were only reports about patients with definite MID (genetically or biochemically confirmed). Syndromic as well as non-syndromic MIDs were considered. Excluded were abstracts and reports about meetings (Table 1). Papers matching these criteria were studied and discussed for their suitability to be included in this review.

3. Results

Cardiac manifestations of MIDs may be classified as structural, functional, or both. Structural lesions affect the myocardium, the coronary arteries, the pericardium, or the aortic root. In addition to structural abnormalities, CI may manifest with functional abnormalities such as impulse generation or conduction abnormalities, systolic dysfunction, heart failure, pulmonary hypertension, or dysfunction of autonomic fibers supplying the cardiac conduction system. Structural abnormalities, however, are frequently associated with functional abnormalities and both categories may overlap. Structural involvement frequently leads to functional abnormalities and most of the functional abnormalities, such as arrhythmias or systolic dysfunction, are secondary to structural involvement. CI may be also classified according to whether the heart is primarily or secondarily affected. CI is classified as secondary if it is the consequence of a non-cardiac manifestation of the MID (e.g. diabetes, epilepsy (SUDEP-syndrome)). Secondary cardiac disease in MID will not be covered by this review. Furthermore, cardiac abnormalities in MIDs may be categorized according to the underlying mutation located in either a nuclear DNA or mtDNA located gene. Description and discussion of CI in MIDs in this review simply follow the frequency with which cardiac abnormalities occur in MIDs.

3.1. Myocardial abnormalities

The most frequent cardiac manifestation of a MID is cardiomyopathy (CMP). It may manifest as hypertrophic CMP (hCMP), dilated CMP (dCMP), restrictive CMP (rCMP), histiocytoid CMP, or unclassified CMP (left ventricular hypertrabeculation/noncompaction (LVHT) or Takotsubo syndrome (TTS)). Myocardial fibrosis and late enhancement (LGE) can be found in various cardiomyopathies.

3.1.1. hCMP

hCMP is the most frequent cardiac manifestation in MIDs (Table 2) [10,11]. hCMP has been described in a number of different syndromic and non-syndromic MIDs (Table 2). Syndromic MIDs associated with hCMP include MELAS, MERRF, CPEO, Leigh-syndrome, and NARP (Table 2) [12,13]. hCMP may be the only manifestation of a MID or may be a part of a multisystem disease (Table 2). hCMP is a frequent finding in MELAS syndrome and may present already in the neonatal period [14]. Severity of CI in MELAS directly correlates with the mutation load [15]. There are a number of studies showing the highly variable prevalence of hCMP in MIDs [3,16,17]. In a study of 113 pediatric MID patients, 40% had developed cardiac disease on echocardiography [17]. Among the latter 58% manifested with hCMP [17]. In a study of 41 MELAS patients carrying the m.3243A > G mutation, left ventricular hypertrophy was found in 16 patients (39%) [18]. In a study of 24 children with a MID undergoing heart transplantation, 20% had hCMP [10]. In a study of 89 pediatric MID patients hCMP was found in 5 (5.6%) [3]. In a study of 90 adult Chinese MID patients, the prevalence of CMP was 5.6% but only 2.2% had hCMP [16]. hCMP can be detected as early as in the antenatal period. Rarely, obstructive hCMP has been reported in MIDs. hCMP frequently develops into systolic dysfunction followed by decompensation and dilatation of the left ventricle (Fig. 1). Thus, usually hCMP turns into dCMP in due course of time [19].

Myocardial fibrosis may be a late stage of cardiomyopathy and may manifest as LGE on cardiac MRI. LGE may be a rare finding in MIDs due to the low frequency of systematic cardiac investigations of MID patients or due to unawareness of CI in MIDs. Myocardial fibrosis is usually diagnosed on cardiac MRI. Myocardial fibrosis has been rarely reported in MELAS patients [20] as focal with disarray of myofibrils resembling the histological features of idiopathic hCMP [20]. Myocardial fibrosis was also found in a single patient with KSS [21]. In a cardiac MRI study of 37 patients with various MIDs LGE was observed in patients with CPEO, KSS, and MELAS [22]. In this study, diffuse, intramural late gadolinium enhancement in the inferolateral segments of the left ventricle was regarded as pathognomonic for CPEO and KSS [22]. Non-ischemic LGE of the septal wall extending like a streak through the complete septum and also affecting the basal parts of the subepicardial inferolateral wall was reported in a MELAS patient with hCMP [23]. Diffuse LGE was also found in other MELAS patients [22]. LGE in MELAS patients may also concern the subepicardial layer of the inferior and lateral left ventricular segments [24]. Definitively, more studies on this matter are warranted.

3.1.2. dCMP

dCMP may be primary or secondary following hCMP. Primary dCMP may be associated with KSS, MELAS, MERRF, or Leigh syndrome

Table 1
Criteria of a publication which needed to be fulfilled to be included in the review.

Article language:	English
Publication date	Between 1966 and 2014
Subjects	Humans
Age	All ages
Sex	Both sexes
Phenotype	Syndromic or non-syndromic MIDs
Diagnostic significance	Definite MIDs (genetically or biochemically confirmed)

Table 2
Mutated genes associated with MID and hypertrophic cardiomyopathy.

Gene/biochemical defect	Phenotype	Reference
mtDNA		
tRNALeu (MT-TL1)	hCMP, infantile CMP	[93,95]
tRNA (m.4797C > M, m.8728 T > Y)	hCMP	[96]
tRNAGlu	Infantile CMP	[97,98]
tRNALys	NS, various	[10,99]
tRNAVal	Various	[2]
rRNA	hCMP	[100]
12 s RNA	Various	[2]
ND5	Leigh syndrome, hCMP	[70,100,101]
ND1	Various	[101,102]
ATP8	Neuropathy	[103]
nDNA		
MRPL3	CMP	[104]
MRPL44	Infantile CMP	[105]
NDUFV2	Early-onset hCMP	[106]
NDUFAF1	Infantile hCMP	[107]
AARS2 (alanyl tRNA synthetase)	Infantile CMP	[108]
ATPase8	Infatile CMP	[109]
MTO1	hCMP, lactic acidosis	[110]
ANT1	CMP, myopathy	[111]
mtDNA depletion	MDS	[112]
MRPS22	NS, encephalocardiopathy	[113,114]
NDUFS2	Leigh syndrome	[115]
SCO1	Infantile enceohalopathy	[116]
SCO2	Cardioencephalomyopathy	[117,118]
YARS2	MLASA	[119]
BSCL2	Generalized lipodystrophy	[83]
NFU1	Infantile encephalopathy	[120]
TMEM70	Encephalocardiomyopathy	[121,122]
COX3	Various	[2]
COX2	Various	[2]
RCC1 mutation	Syndromic MIDs, NS	[123]
ATP synthetase	Encephalocardiomyopathy	[124]

NS: non-syndromic, MLASA: Myopathy, lactic acidosis, sideroblastic anemia, MDS: mitochondrial depletion syndrome.